Departamento de Patología y Cirugía

Evaluación Farmacocinética del Oxaliplatino Intraperitoneal Hipertérmico en Rata Wistar

Tesis Doctoral

María Isabel Mas Fuster

Directores

Amelia Ramón López

Ricardo Nalda Molina

Francisco Javier Lacueva Gómez

Alicante, 2017

UNIVERSITAS
Miguel
Hernández

UNIVERSIDAD MIGUEL HERNÁNDEZ

FACULTAD DE MEDICINA

DEPARTAMENTO DE PATOLOGÍA Y CIRUGÍA

EVALUACIÓN FARMACOCINÉTICA DEL OXALIPLATINO INTRAPERITONEAL HIPERTÉRMICO EN RATA WISTAR

TESIS DOCTORAL

María Isabel Mas Fuster

Alicante, 2017

UNIVERSITAS
Miguel
Hernández

Los que suscriben, **Dra. Amelia Ramón López**, Profesora Contratada Doctora del Área de Farmacia y Tecnología Farmacéutica; **Dr. Ricardo Nalda Molina**, Profesor Contratado Doctor del Área de Farmacia y Tecnología Farmacéutica y **Dr. Francisco Javier Lacueva Gómez,** Profesor Titular Universidad, Subdirector del Departamento de Patología y Cirugía.

CERTIFICAN:

que la investigación incluida en esta Memoria para optar al Grado de Doctor, titulada:

"EVALUACIÓN FARMACOCINÉTICA DEL OXALIPLATINO INTRAPERITONEAL HIPERTÉRMICO EN RATA WISTAR"

ha sido realizada por Dña. María Isabel Mas Fuster, bajo su dirección y supervisión en el Área de Farmacia y Tecnología Farmacéutica del Departamento de Ingeniería de la Universidad Miguel Hernández de Elche, reuniendo las condiciones necesarias para que pueda aspirar con este trabajo a la obtención del Grado de Doctor.

Para que así conste, firman el presente certificado a 29 de Mayo de 2017

Fdo. Dra. Amelia Ramón López **Fdo. Dr. Ricardo Nalda Molina**

Fdo. Dr. F. Javier Lacueva Gómez

UNIVERSITAS
Miguel
Hernández

FACULTAD DE MEDICINA
DEPARTAMENTO DE PATOLOGÍA Y CIRUGÍA

Dra. **María Susana Jiménez Moreno**, Directora del Departamento de Patología y Cirugía de la Universidad Miguel Hernández de Elche,

CERTIFICA:

que Dña. María Isabel Mas Fuster ha realizado bajo la coordinación de este Departamento su Memoria de Tesis doctoral, titulada:

"EVALUACIÓN FARMACOCINÉTICA DEL OXALIPLATINO INTRAPERITONEAL HIPERTÉRMICO EN RATA WISTAR"

cumpliendo todos los objetivos previstos, finalizando su trabajo en forma satisfactoria para su defensa pública y capacitándole para optar al Grado de Doctor.

Lo que certifico en San Juan de Alicante, a 29 de Mayo de 2017.

Fdo. Dra. María Susana Jiménez Moreno

UNIVERSITAS
Miguel
Hernández

PRODUCCIÓN CIENTÍFICA DEL DOCTORANDO

Las publicaciones científicas generadas por Dña. María Isabel Mas Fuster durante su doctorado y directamente asociadas a la presente Memoria de Tesis Doctoral de la Universidad Miguel Hernández son las siguientes:

- **María Isabel Mas Fuster**, Amelia Ramón López, Ricardo Nalda Molina. *Importance of standardizing the dose in hyperthermic intraperitoneal chemotherapy (HIPEC): a pharmacodynamic point of view*. Cancer Chemother Pharmacol 2013; 72: 273-4. doi: 10.1007/s00280-013-2204-z

- **María Isabel Mas Fuster**, Amelia Ramón López, Javier Lacueva, Antonio Compañ, Patricio Más Serrano, Ricardo Nalda Molina. *Impact of Laparotomy and Intraperitoneal Hyperthermic Instillation (LIHI) on the oxaliplatin pharmacokinetics after intravenous administration in Wistar rats*. Cancer Chemother Pharmacol 2017; 79: 621-627. doi: 10.1007/s00280-017-3244-6

- **María Isabel Mas Fuster,** Amelia Ramón López, Javier Lacueva, Antonio Compañ, Patricio Más Serrano, Ricardo Nalda Molina. *Population Pharmacokinetics of Oxaliplatin after Intraperitoneal Administration with Hyperthermia in Wistar Rats*. Submitted to AAPS J.

- **María Isabel Mas Fuster**, Amelia Ramón López, Javier Lacueva, Patricio Más Serrano, Ricardo Nalda Molina. *Suitability of the AUC ratio as an Indicator of the Pharmacokinetic Advantage in HIPEC.* Submitted to Cancer Chemother Pharmacol.

Además, la producción científica anterior se complementa con el siguiente número de presentaciones realizadas en congresos de carácter nacional e internacional durante la realización de la presente Tesis Doctoral:

- **María Isabel Mas Fuster**, Amelia Ramón López, Javier Lacueva, Patricio Más Serrano, Rafael Calpena, Ricardo Nalda Molina. (Póster). *Impact of the surgical procedure involved in HIPEC on the intravenous oxaliplatin pharmacokinetics in Wistar rat.* IV Congreso Nacional SEOQ V Reunión GECOP 2015 (Sociedad Española de Oncología Quirúrgica y la VI Reunión GECOP - Grupo Español de Cirugía Oncología Peritoneal); 2015 Nov 19-20; Madrid. Comunicación premiada como mejor póster.

- **María Isabel Mas Fuster**, Amelia Ramón López, Javier Lacueva, Patricio Más Serrano, Rafael Calpena, Ricardo Nalda Molina. (Póster). *Suitability of the AUC-ratio as an indicator of the pharmacokinetic advantage in HIPEC. Regarding platinum drugs.* IV Congreso Nacional SEOQ V Reunión GECOP 2015 (Sociedad Española de Oncología Quirúrgica y la VI

Reunión GECOP - Grupo Español de Cirugía Oncología Peritoneal); 2015 Nov 19-20; Madrid.

- **María Isabel Mas Fuster**, Clara Siscar Peretó, Amelia Ramón López, Javier Lacueva, Patricio Más Serrano, Ricardo Nalda Molina. (Póster). *Modelo experimental en rata para la administración intraperiotoneal con hipertermia (HIPEC) en técnica abierta. Validación, puesta a punto y primeros resultados.* V Jornadas de Modelización y Simulación en Biomedicina; 2013 Nov 20-22; Colmenar Viejo (Madrid).

- **María Isabel Mas Fuster**, Clara Siscar Peretó, Amelia Ramón López, Javier Lacueva, Patricio Más Serrano, Ricardo Nalda Molina. (Póster). *Estudio comparativo de las concentraciones plasmáticas de oxaliplatino tras HIPEC en rata frente a humanos. Importancia de la concentración del líquido de instilación.* III Congreso Nacional SEOQ V Reunión GECOP 2013 (Sociedad Española de Oncología Quirúrgica y la V Reunión GECOP - Grupo Español de Cirugía Oncología Peritoneal); 2013 Oct 3-4. Alicante.

- **María Isabel Mas Fuster**, Clara Siscar Peretó, Amelia Ramón López, Javier Lacueva, Patricio Más Serrano, Ricardo Nalda Molina. (Presentación oral). *Diseño de un modelo experimental animal en rata Wistar para HIPEC.* IX CEFA (Congreso Nacional de Estudiantes de Farmacia); 2013 Oct 23-25; San Juan de Alicante (Alicante).

AYUDAS A LA INVESTIGACIÓN DE FINANCIACIÓN PÚBLICA Y PRIVADA

La presente Tesis Doctoral ha sido financiada por las siguientes ayudas a la investigación de financiación pública y privada:

1. Ayudas a la investigación de financiación pública y privada:
Proyecto concedido por la Fundación Bancaja-Universidad Miguel Hernández en su convocatoria 2012, titulado "Estudio farmacocinético de oxaliplatino tras la administración intraperitoneal con hipertermia (HIPEC) en rata", cuyo Investigador Principal es la Dra. Amelia Ramón López.

2. Ayudas a la investigación de financiación privada:
Proyecto concedido por la Fundación Bienvenida Navarro-Luciano Tripodi en su convocatoria 2014-2015, titulado "Estudio de la absorción de oxaliplatino en rata Wistar tras su administración mediante quimioterapia intraperitoneal con hipertermia (HIPEC)", cuyo Investigador Principal es el Dr. Francisco Javier Lacueva Gómez.

Por otro lado, la investigación científica presentada en esta Tesis Doctoral ha sido financiada por las siguientes ayudas concedidas a Dña. María Isabel Mas Fuster:

1. Beca de Fomento de la Investigación en los Departamentos, concedida por la Universidad Miguel Hernández, en su convocatoria 2013.

2. Beca por las Actividades de Apoyo en el Servicio de Experimentación Animal, concedida por el Servicio de Experimentación Animal-Universidad Miguel Hernández, en su convocatoria 2013.

3. Beca de Colaboración asociada a proyecto de colaboración avalado, concedida por el Ministerio de Educación, Cultura y Deporte, en su resolución del 2 de agosto de 2012.

UNIVERSITAS
Miguel
Hernández

A mis padres
A mi hermano
A Javi

UNIVERSITAS
Miguel
Hernández

“Un camino de mil millas
comienza con un paso”

Benjamin Franklin

UNIVERSITAS
Miguel
Hernández

AGRADECIMIENTOS

Durante mi etapa de doctoranda he tenido la suerte de contar con tres directores de tesis que para mí han constituido un ejemplo a seguir, tanto en el terreno académico y teórico, como en el humano. En gran parte gracias a ellos mi paso por la universidad como doctoranda se ha convertido en mi mejor etapa formativa y de ellos me llevo la impresión de que la profesión académica y la investigadora son dedicaciones nobles y apasionantes.

Quiero agradecer de manera especial a la Dra. Amelia Ramón López, su apoyo diario, comprensión y confianza en mi trabajo. Conservaré con un cariño especial las primeras clases en las que me dio a conocer NONMEM. La puerta de su despacho siempre ha estado abierta para atender todas mis dudas. También quiero reconocer públicamente su implicación en que yo pudiese aprovechar cualquier oportunidad que me abriese un camino en la investigación y su ejemplo de un buen trabajo en equipo. Su profesionalidad y pasión por la docencia universitaria me han hecho ver esta profesión con un inmenso cariño e interés.

Quiero expresar igualmente mi honda gratitud al Dr. Ricardo Nalda Molina, codirector de tesis, por abrirme las puertas a su grupo de investigación y por ser mi primer mentor en el campo experimental. Su capacidad para guiar mis ideas ha sido incalculable, no solo en el trabajo desarrollado en esta tesis, sino durante mi formación investigadora. Debo destacar también su permanente disponibilidad para ayudarme a entender conceptos de esta rama de la ciencia, bella y a la vez compleja, así como todas esas charlas más informales sobre ciencia que, desde otro ángulo, han despertado en mí el pensamiento crítico.

Asimismo, manifiesto mi profundo reconocimiento al Dr. Javier Lacueva Gómez por su interés e implicación en mi trabajo, por guiarme en los aspectos más clínicos de esta tesis doctoral, y por su apoyo en la búsqueda de proyectos que contribuyeran a mi formación investigadora. Le agradezco igualmente el haberme facilitado siempre los medios suficientes para llevar a cabo parte de las actividades propuestas durante el desarrollo de esta tesis.

A los tres codirectores, muchas gracias por confiar en mí.

Igualmente, quiero agradecer a la unidad de Farmacocinética Clínica del Hospital General Universitario de Alicante, en especial a Patricio, su ayuda y contribución a este trabajo. Por darme la oportunidad de conocer la aplicación que el campo de la farmacocinética poblacional tiene en la clínica.

Asimismo, quiero agradecer al Servicio de Experimentación Animal del campus de San Juan de la Universidad Miguel Hernández, en especial a José Antonio, su predisposición y disponibilidad constante, toda su ayuda en la parte experimental de esta tesis y por brindarme cualquier oportunidad que contribuyese a formarme en la investigación.

A la Dra. Elsa López Pintor, por haber confiado en mi trabajo y haberme permitido conocer más de cerca cómo es la gestión docente.

A Mayte y a Celia, por haber compartido el reto de convertirnos en Doctoras y por haber comprendido inquietudes y dudas que en ocasiones sólo otro doctorando puede entender. A Clara y a Juan, porque han sido unos buenos compañeros de viaje, por su aportación y ayuda durante los experimentos y por los buenos ratos compartidos.

También me gustaría agradecer a todas mis compañeras de oficina de farmacia su apoyo y su interés en este proyecto. En especial a María, Claudia y Maripaz por ayudarme a dar los primeros pasos en el mundo de la botica.

A mis padres, porque nunca les voy a poder pagar todo el esfuerzo que han hecho para que yo hoy pueda estar aquí escribiendo este trabajo. Por apoyarme en todas las decisiones que he ido tomando y por darme las fuerzas y los medios suficientes para poder desarrollarme moral e intelectualmente.

A mi padre, por ser el ejemplo personificado de la perseverancia, por inculcarme la capacidad de esfuerzo desde pequeña y por tener siempre una palabra de tranquilidad cuando el camino se volvía tortuoso.

A mi madre, por inculcar en mí la madurez para conseguir estos objetivos y mirar al futuro con fuerza. Por doblar esfuerzos para que yo pudiese dedicarme en exclusiva a la tesis en algunos momentos. Por mostrarme su valentía para superar los miedos. Por hacer fácil lo difícil.

A mi hermano, porque parte de esta tesis también es suya. Por su calor humano, sus bromas y deseos de que todo salga bien. Y porque él también se encuentra persiguiendo su propio sueño.

A Javi, por su paciencia y comprensión incondicional. Por haberme ayudado a enfrentar los enemigos más prosaicos y a la vez inesperados que una tesis puede tener preparados para un doctorando. Por darme la mano cuando parecía que el camino terminaba. Porque han sido tiempos de sacrificio y lucha por los sueños que teníamos y porque hoy ya estamos un paso más cerca de haberlos conseguido juntos.

ÍNDICE

UNIVERSITAS
Miguel
Hernández

ÍNDICE DE ILUSTRACIONES Y FIGURAS

ÍNDICE DE TABLAS

LISTA DE ABREVIATURAS

AUC	Área Bajo la Curva de Concentración del Fármaco
AUC_{per}	Área Bajo la Curva de Concentraciones Peritoneales
AUC_{pla}	Área Bajo la Curva de Concentraciones Plasmáticas
$AUC_{pla\ 0-\infty}$	Área Bajo la Curva de Concentraciones Plasmáticas desde tiempo 0 a infinito
BSA	Área de Superficie Corporal
CC	Índice de Citorreducción Conseguido
CC-0	Cirugía Citorreductora de Exéresis Completa
CC-1	Cirugía Citorreductora de Exéresis casi Completa
CCR	Cirugía Citorreductora
CI	Intervalo de Confianza
CL	Aclaramiento del Fármaco
C_{max}	Concentración Máxima de Fármaco
CP	Carcinomatosis Peritoneal
CPCR	Carcinomatosis Peritoneal de Origen Colorrectal
CRS	Cirugía Citorreductora
CV	Coeficiente de Variación
CWRES	Residuales Ponderados Poblacionales Condicionales
df	Grados de Libertad
EBE	Estimación Bayesiana Empírica de los Parámetros del Modelo
F	Biodisponibilidad
FIGO	Federación de Ginecología y Obstetricia
FOCE	Estimación Condicional de Primer Orden
GOF	Bondad de Ajuste
HIPEC	Quimioterapia Intraperitoneal Hipertérmica
HIPEO	Oxaliplatino Intraperitoneal Hipertérmico
ID	Número de Identificación del Sujeto
IIV	Variabilidad Interindividual

ip	Intraperitoneal
IPRED	Predicción Individual
iv	Intravenoso
k_{23}	Microconstante Intercompartimental desde el Compartimento 2 al 3
k_{32}	Microconstante Intercompartimental desde el Compartimento 2 al 2
k_a	Constante de absorción
k_{a_app}	Constante de Absorción Aparente
k_{el}	Constante de eliminación
L	Litro
LIHI	Laparotomía + Instilación Intraperitoneal Hipertérmica
mg	Miligramo
min	Minutos
mL	Mililitro
MOFV	Valor de la Función Mínimo Objetivo
ΔMOFV	Cambio en el Valor de la Función Mínimo Objetivo
η_i	Variabilidad Interindividual
NPBS	Bootstrap No Paramétrico
NPDE	Errores de Distribución No Predichos
NONMEM	Modelos no Lineales de Efectos Mixtos
P	Parámetro Farmacocinético
PCI	Índice de Carcinomatosis Peritoneal
pcVPC	Predicción Corregida de la Evaluación Predictiva Visual
PET	Tomografía Emisora de Positrones
PK	Farmacocinética
PKA	Ventaja Farmacocinética
PM	Metástasis Peritoneal
PRED	Predicción Poblacional del Modelo
Q/ Q_1	Aclaramiento Intercompartimental entre el Compartimento Central y el Peritoneal

Q_2	Aclaramiento Intercompartimental entre el Compartimento Central y el Periférico
RM	Resonancia Magnética
RSE	Error Estándar Relativo
SD	Desviación Estándar
SIG	Factor de Sigmoidicidad
$t_{1/2\beta}$	Semivida beta
$t_{1/2per}$	Semivida peritoneal
T_{50}	Estimación Poblacional del Punto de Inflexión
TAC	Tomografía Axial Computerizada
TNM	Método de Estadiaje de Neoplasias de la American Joint Committee on Cancer: Tumor primario (T); Ganglios Linfáticos Regionales (N); Metástasis Distante (M)
V_1	Volumen de Distribución en Peritoneo
V_2	Volumen de Distribución en el Compartimento Central
V_3	Volumen de Distribución en el Compartimento Periférico
X^2	Test Chi-cuadrado

CAPÍTULO I. INTRODUCCIÓN Y OBJETIVOS

UNIVERSITAS
Miguel
Hernández

1. INTRODUCCIÓN

1.1. CARCINOMATOSIS PERITONEAL. CONCEPTO E HISTORIA NATURAL

La carcinomatosis peritoneal (CP) se caracteriza por la aparición de nódulos tumorales de distinto tamaño, número y distribución sobre la superficie peritoneal. Puede originarse a partir de las propias células peritoneales, constituyendo una forma primaria rara de tumor maligno, como el mesotelioma peritoneal y el carcinoma papilar seroso de la superficie peritoneal (1,2). Sin embargo, su causa más frecuente es la diseminación de tumores primarios de origen gastrointestinal como los carcinomas colorrectal, apendicular o gástrico, y de origen ginecológico como el carcinoma de ovario. En los carcinomas digestivos supone siempre la extensión a distancia del tumor (estadio IV de la clasificación TNM), con la excepción del carcinoma ovárico (estadio IIIC de la clasificación de la FIGO). En las CP de origen digestivo se asocia a una pérdida rápida de la calidad de vida y su pronóstico es infausto, siendo que la quimioterapia sistémica solo consigue mejoras discretas en la supervivencia media, pero no logra su curación. El 80% de los pacientes fallece en un término promedio de 6 meses y sin que ningún caso sobreviva más allá de dos años (3).

En el caso del carcinoma colorrectal, el peritoneo constituye la segunda localización más frecuente de metástasis después del hígado (4). La CP de origen colorrectal (CPCR) se detecta de forma sincrónica en un 10-15% de los aproximadamente 400.000 nuevos pacientes diagnosticados en Europa cada año con este cáncer (5) y, en un 10-35% de aquéllos que recidivan después del tratamiento del tumor colorrectal, la localización de la metástasis es exclusivamente peritoneal (6). El tratamiento mediante cirugía citorreductora (CCR) y quimioterapia intraperitoneal (ip) hipertérmica (HIPEC) seguido de quimioterapia adyuvante ha cambiado la evolución de la enfermedad en pacientes seleccionados (7-9).

El pseudomixoma peritoneal se caracteriza por la presencia de depósitos mucinosos y la acumulación de mucina intraperitoneal (ascitis mucinosa) producida por una neoplasia mucosecretora. En la mayoría de las ocasiones procede de una neoplasia del apéndice que puede ser de bajo grado o adenocarcinomas (alto grado). En estas neoplasias la CCR y HIPEC se ha convertido en el tratamiento de elección, consiguiendo una supervivencia libre de enfermedad a los 5 años en la mitad de los casos (10).

La CP aparece en aproximadamente la mitad de los pacientes con carcinoma gástrico que afectan la serosa y que han sido previamente tratados quirúrgicamente y ya está presente en el momento del diagnóstico hasta en el 20% de los pacientes (11). El tratamiento mediante

CCR y HIPEC puede aumentar la supervivencia en algunos pacientes seleccionados con una afectación peritoneal muy limitada (12).

En el cáncer de ovario, la CP aparece frecuentemente en el momento del diagnóstico y permanece confinada a la cavidad peritoneal durante gran parte de su historia natural (13,14). Algunos estudios muestran que el tratamiento mediante CCR y quimioterapia intraperitoneal seguido de quimioterapia sistémica puede aumentar la supervivencia, aunque la indicación sigue estando muy cuestionada (15,16).

1.2. CARCINOMATOSIS PERITONEAL. FISIOPATOLOGÍA

El peritoneo es la membrana serosa más grande y compleja del cuerpo humano (17). El peritoneo visceral, que se encuentra cubriendo los órganos intra-abdominales y los mesenterios, forma una capa continua junto con el peritoneo parietal, que une la pared abdominal y las cavidades pélvicas. El peritoneo se compone de una monocapa de células mesoteliales, sujetas por una membrana base que descansa sobre una capa de tejido conectivo, también llamado submesotelio (Ilustración I-1) (18). La superficie luminal de las células mesoteliales tiene numerosos microvilli, que difieren en tamaño, forma y densidad. La membrana base consiste en una red laminar que contiene colágeno, proteoglicanos y glicoproteínas. El submesotelio está formado por una compleja red de matriz extracelular, constituida también por colágeno, proteoglicanos y glicoproteínas, así como capilares sanguíneos, linfáticos y varios tipos de células (fibroblastos, macrófagos y mastocitos).

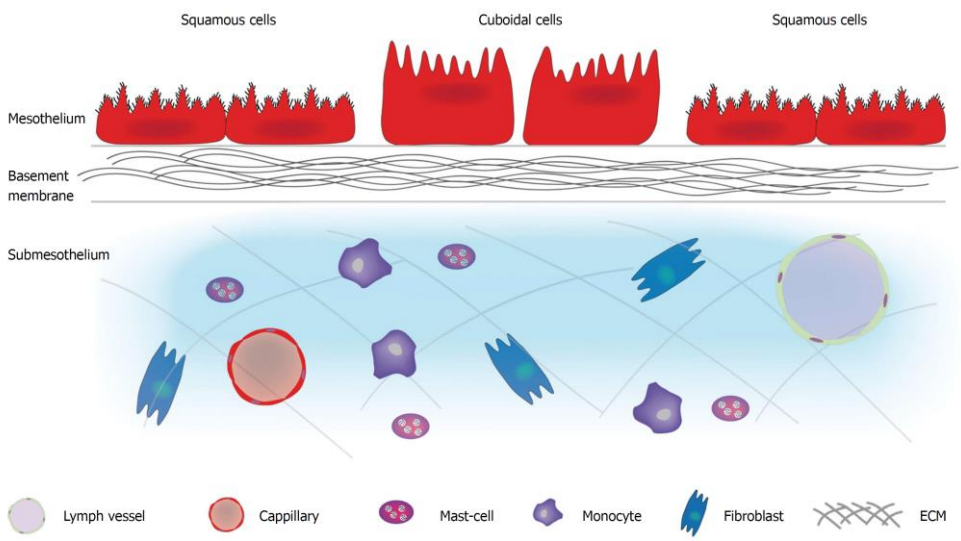


Ilustración I-1. Estructura del peritoneo. Tomada de Lemoine et al. (18).

La aparición de la CP es el resultado de la interacción entre células tumorales y elementos huésped del peritoneo, comprendiendo distintos pasos bien diferenciados. Las células o los agregados de las mismas que se desprenden a la cavidad abdominal desde la superficie serosa del tumor primario pueden alcanzar la cavidad peritoneal (Ilustración I-2). La exfoliación espontánea de las células tumorales del tumor primario puede estar causada por la baja regulación de la E-cadherina, una presión aumentada del fluido intersticial o de forma iatrogénica durante la cirugía, como la perforación o la manipulación tumoral. Las células tumorales desprendidas se vuelven susceptibles al transporte peritoneal regular. Éstas siguen rutas predecibles que, obedeciendo a movimientos hidrodinámicos de la respiración y a la gravedad, o a movimientos peristálticos del intestino, explican el predominio de implantes en determinadas zonas, como la superficie del hemidiafragma derecho, el saco de Douglas o la fosa retrohepática y las partes fijas del intestino delgado como el ángulo de Treitz y segmento ileocólico (19). La adhesión al peritoneo distante de estas células circulantes puede ocurrir por dos vías, denominadas metástasis transmesoteliales y translinfáticas. Tras evadir el sistema inmunitario, las células invaden el submesotelio, en el que desarrollan angiogénesis y proliferación. Por otro lado, dada la función defensiva asociada al peritoneo, una rotura en su estructura también estimula esta invasión de células tumorales en la superficie del abdomen y la pelvis (20).

Esta diseminación de la enfermedad podría permanecer confinada a la cavidad abdominal durante un tiempo antes de continuar su expansión y desarrollar metástasis distantes, constituyendo una manifestación neoplásica de carácter locorregional y no una enfermedad sistémica.

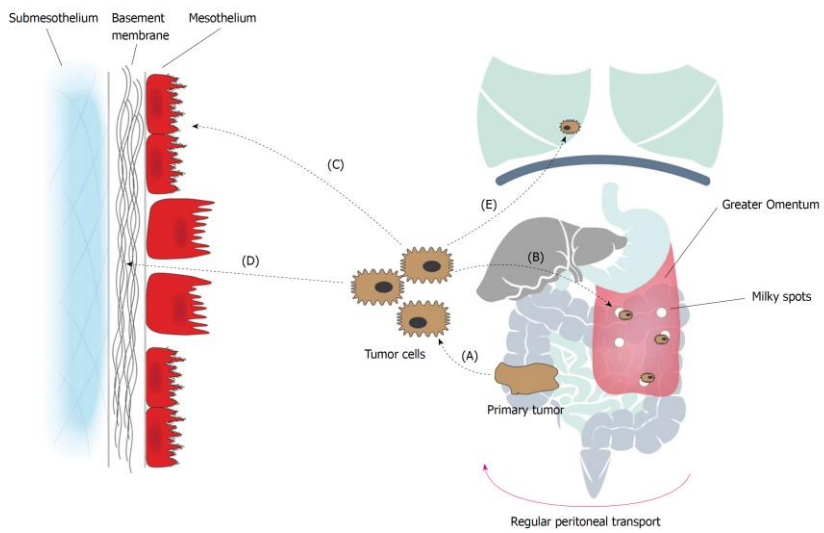


Ilustración I-2. Fisiopatología de la carcinomatosis peritoneal colorrectal: la cascada metastásica peritoneal. Tomada de Lemoine et al. (18).

1.3. METODOS DE DIAGNÓSTICO POR IMAGEN

La tomografía axial computerizada (TAC) es capaz de diagnosticar signos de CP avanzada como el engrosamiento del omento mayor ("omental cake") y nódulos peritoneales de alrededor de 1 cm, con una sensibilidad muy baja, que puede ser <20% en los mesos y asas de yeyuno e ileon (21). En consecuencia, esta técnica de imagen infraestima el volumen de afectación peritoneal, aunque continúa siendo el estudio complementario de imagen estándar para evaluar su extensión (PCI), que en ocasiones puede suplementarse con la realización de una tomografía emisora de positrones (PET) (22).

Recientemente, están apareciendo estudios que muestran que la realización de resonancia magnética (RM) con consecución de secuencias rápidas de imagen y resolución con alto contraste puede evaluar mejor el PCI, especialmente en tumores mucinosos y aumentar la sensibilidad en la detección de enfermedad en el intestino delgado (23).

La utilización de la laparoscopia exploradora ha sido especialmente preconizada en la estadificación de los carcinomas de ovario donde la CP micronodular es frecuente y se realiza de forma sistemática para la evaluación del PCI en los carcinomas de ovario avanzados. Sin embargo, no hay unanimidad en su indicación y existe un estudio aleatorizado multicéntrico (LapOvCa-trial) en marcha para evaluar si puede prevenir la realización de cirugía subóptima (24).

1.4. TRATAMIENTO MULTIDISCIPLINAR

En línea con la hipótesis de que la CP podría caracterizarse por ser una enfermedad locorregional y siguiendo la propuesta de Sugarbaker (25), la circunscripción de la enfermedad al peritoneo en una fase inicial permitiría definir un tratamiento de intensificación terapéutica regional, basado en la realización de una CCR de exéresis completa (CC-0) o casi completa (CC-1) dejando implantes < 2.5 mm, seguida de una instilación de HIPEC, un enfoque multidisciplinar con intención curativa. Aunque aún no se trata de una técnica consolidada, este tratamiento multimodal es el de referencia para pseudomixoma peritoneal y mesotelioma maligno peritoneal. La literatura demuestra resultados alentadores derivados de estudios Fase I y Fase II para cáncer colorrectal (26,27), ovárico (28) y gástrico (29). Para la CPCR en concreto, tratada con oxaliplatino ip hipertérmico (HIPEO), la supervivencia mediana ha pasado de 24 meses a 62,7 meses en un grupo seleccionado de pacientes (30), con índices de curación del 22% (31). La estricta selección de pacientes que ha exigido la técnica HIPEC se fundamenta principalmente en el elevado carácter invasivo de la técnica y la elevada morbimortalidad asociada al procedimiento reportada hace unos años (32,33). Sin embargo, actualmente se están consiguiendo reducciones sustanciales de estos índices de morbimortalidad desde

centros especializados en este tratamiento multimodal, del mismo modo que se ha destacado el papel fundamental de la curva de aprendizaje del equipo de trabajo en la reducción de dichos índices (34,35).

1.4.1. Cirugía Citorreductora

En una primera fase, el objetivo de la CCR es reducir todo lo posible la carga tumoral en la cavidad abdominal. El PCI cuantifica la extensión tumoral inicial, teniendo en cuenta el tamaño de la lesión y su localización en la cavidad abdominal. La presencia de la enfermedad se evalúa en 13 regiones abdominales diferenciadas. En cada una de ellas, se mide el nódulo de mayor tamaño y se clasifica como LS 0, cuando la enfermedad no es visible; LS 1 cuando el mayor nódulo localizado mide hasta 0,5 cm; LS 2, si el tamaño se encuentra entre 0,5 cm y 5 cm y LS 3 cuando el tamaño del nódulo es superior a 5 cm. La suma del grado de LS obtenido en cada región constituye el PCI, siendo 39 la máxima puntuación posible (36). Tras las resecciones y peritonectomías necesarias, se evalúa el índice de citorreducción conseguido (CC). La citorreducción ha sido completa cuando no han quedado implantes residuales macroscópicos (CC-0). En el caso de no conseguirlo, la lesión remanente se clasifica en función de su tamaño: CC-1 si el implante es menor de 0,25 cm o CC-2, si es mayor de 0,25 cm (37). Tanto la extensión tumoral, evaluada a través del PCI, como la resección completa se consideran factores pronóstico en los pacientes con CP (38).

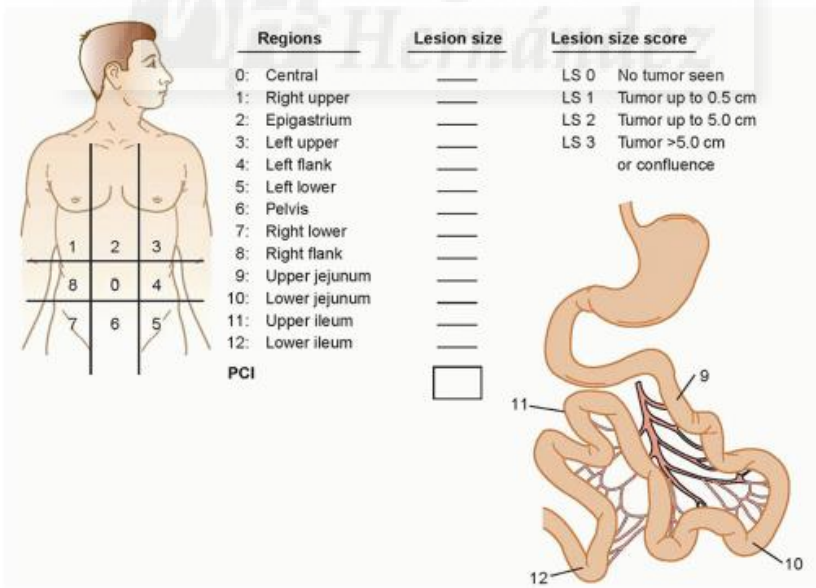


Ilustración I-3. Valoración de la carga tumoral. Imagen tomada de http://oncohemakey.com.

1.4.2. Fármacos para la Quimioterapia Intraperitoneal

El efecto citotóxico esperado en el tratamiento, derivado de la administración local, puede potenciarse con la adecuada selección y dosificación del agente citostático. Actualmente, la selección de fármacos en HIPEC se basa, en parte, en los datos existentes sobre la actividad sistémica probada de los mismos. Desde un punto de vista farmacocinético, el perfil del agente idóneo para HIPEC pasa por un elevado carácter hidrofílico y alto peso molecular, de forma que pueda mantenerse en la biofase a concentraciones elevadas el mayor tiempo posible, limitándose así su toxicidad sistémica. Del mismo modo, fármacos con elevados aclaramientos plasmáticos ayudarían a reducir el tiempo de exposición sistémica de los mismos. Otra de las características deseadas en los compuestos adecuados para HIPEC es un elevado ratio del área bajo la curva de concentraciones (AUC) peritoneales (AUC_{per}) y plasmáticas (AUC_{pla}). Sin embargo, esta propiedad presentaría algunas desventajas que limitarían su uso en la elección del mejor agente para HIPEC, como se discute en el Capítulo V de este estudio.

Por otro lado, el fármaco debe presentar un efecto sinérgico en presencia de hipertermia, un mecanismo de acción que no dependa de la fase del ciclo celular de las células tumorales y un adecuado grado de penetración en el tumor.

Los fármacos actualmente más empleados en HIPEC son mitomicina, compuestos derivados del platino, sobre todo cisplatino y oxaliplatino y algunos compuestos pertenecientes al grupo de los taxanos y de las antraciclinas, principalmente placlitaxel y doxorrubicina, respectivamente (39). La elección de uno u otro depende, entre otros factores, de las características del tumor primario y de la experiencia previa de cada grupo de trabajo, por lo que el fármaco o la combinación de los mismos más eficaz no han sido claramente establecidos en la literatura (40). Para la CPCR los dos fármacos más utilizados basan su mecanismo de acción en la inhibición de la síntesis de ADN y son mitomicina, administrada a una dosis de 15 mg/m^2 durante 90 minutos (41) y oxaliplatino, administrado a una dosis de 460 mg/m^2 durante 30 minutos (42), ambos en condiciones de hipertermia (43).

1.4.3. Hipertermia

Una de las variables que quedan definidas en última instancia por cada grupo de trabajo y que presenta conclusiones dispares en literatura es si el fármaco se debe administrar en condiciones de hipertermia o no y, en caso afirmativo, a qué temperatura.

El calor, por un lado, actúa sobre la propia célula, induciendo la apoptosis celular, la desnaturalización de proteínas, la síntesis de proteínas de choque térmico y provocando efectos relacionados con el metabolismo oxidativo y el sistema inmunológico, entre otros. Estudios *in vitro* han demostrado que esta citotoxicidad es selectiva para las células tumorales,

que sufrirían una disminución del flujo sanguíneo, llegando a la estasis vascular, a los 41ºC, temperatura inferior que la que provoca estos efectos en las células sanas (44). Por otro lado, la hipertermia *per se* sobre las células malignas se ve reforzada en HIPEC por la potenciación del efecto del fármaco, mediante un aumento de su capacidad de penetración en el nódulo tumoral (45,46). No obstante, la temperatura, al igual que el fármaco, tiene un grado limitado de penetración en el tejido (47).

En el caso concreto del oxaliplatino, el efecto sinérgico en presencia de hipertermia se ha probado in vitro (46) y en modelos animales en rata (48), aunque en este último caso las diferencias de concentración tisular de fármaco en presencia de hipertermia no fueron significativas respecto a las condiciones normotérmicas. Dado que la estabilidad del oxaliplatino no se ve comprometida hasta los 49ºC (49), la temperatura máxima la definiría la tolerancia clínica, concretamente la del intestino delgado, que ha demostrado lesiones por efecto directo del calor a los 43ºC (50,51).

En la clínica, se han observado incrementos significativos de la supervivencia global y del período libre de enfermedad en pacientes cuya perfusión ip de cisplatino alcanzó al menos los 40ºC (52).

1.4.4. Quimioterapia Intraperitoneal Hipertérmica

Tras eliminar el tumor visible confinado a la cavidad abdominal en la fase de CCR, el objetivo posterior es la consolidación de la resección quirúrgica mediante la administración locorregional de quimioterapia, ya que las células tumorales residuales serían las causantes de las recidivas peritoneales (19).

Brevemente, para la aplicación de HIPEC bajo la modalidad abierta, también conocida como técnica “Coliseo” (25), se realiza una laparotomía desde la sínfisis púbica hasta el cartílago xifoides, de manera que la cavidad abdominal permanece completamente expuesta y sujeta por sus paredes a una estructura retractora, resultando en un coliseo capaz de albergar el volumen de solución quimioterápica que se administre. Gracias a una bomba perfusora, el fármaco se administra a una determinada velocidad, constituyendo un circuito cerrado. La colocación de varios catéteres en la cavidad abdominal permite tanto la entrada como salida del fluido hipertérmico transportador del fármaco durante el tiempo que dure la instilación. Del mismo modo, la técnica abierta permite la colocación de termómetros en varios puntos de la cavidad que permitan la monitorización de la temperatura en cada región. Durante la perfusión del fármaco se recomienda uniformizar la hipertermia en todo el volumen capaz de albergar la cavidad peritoneal mediante masajes manuales en el abdomen, de forma que el efecto sinérgico de la temperatura con el fármaco alcance todas las regiones (25). Existen otras modalidades como la técnica cerrada o la semiabierta.

La capacidad de penetración tisular en el tiempo en el que el fármaco está en contacto con las células malignas residuales mediante la instilación hipertérmica, es función de las características físico-químicas de la propia molécula, del tiempo de contacto con el tejido y de que presente un efecto sinérgico con la hipertermia. Dado que se ha demostrado experimentalmente que la capacidad de penetración del fármaco en tejido es limitada, los nódulos remanentes tras la citorreducción no deben exceder un tamaño máximo de diámetro, aproximadamente de 0,25 cm (53). Por el mismo motivo, la aplicación de esta quimioterapia debe producirse inmediatamente a continuación de la CCR, evitando que las células tumorales puedan quedar atrapadas en adhesiones de fibrina en la fase de cicatrización postquirúrgica, formando los llamados santuarios neoplásicos.

Aunque se ha establecido que uno de los principales factores pronóstico es el CC conseguido (38), a día de hoy permanece el debate sobre el papel que los dos componentes de este tratamiento multimodal, CCR y HIPEC, desempeñan por separado en cuanto a la mejora de la supervivencia (54). Del mismo modo, ciertos aspectos técnicos de HIPEC como la elección del fármaco, la duración de la instilación o la forma de dosificación siguen siendo objeto de debate, indicando la falta de consenso parcial en la práctica clínica (40). La respuesta de los implantes carcinomatosos a la quimioterapia ip se ha considerado un proceso multifactorial, sobre el que se han propuesto diferentes variables evaluables, como son la dosis del agente citostático, la duración de la instilación, la temperatura, el tipo de tumor primario, la presión intraabdominal, el uso de agentes vasoactivos, el tamaño de la lesión o el ratio de exposición peritoneo:plasma de cada fármaco.

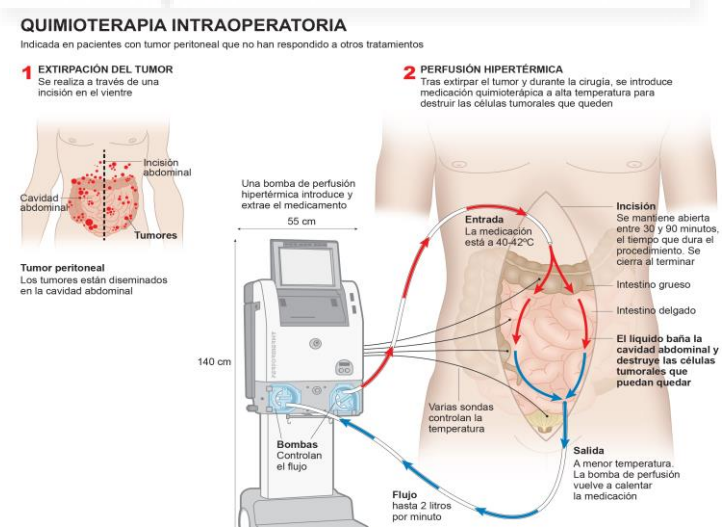


Ilustración I-4- Esquema del tratamiento de CCR seguido de HIPEC en la práctica clínica. ©Clínica Universidad de Navarra 2012.

1.4.4.1. Farmacocinética y Barrera Peritoneo-Plasma

La administración ip del fármaco permite que las células tumorales residuales se expongan a elevadas concentraciones del mismo, a la vez que se minimiza la exposición sistémica y, por tanto, la toxicidad. La barrera peritoneo-plasma constituye la base para esta administración locorregional del citostático a elevadas dosis (55). Esta barrera fisiológica, que aloja un gran espacio denominado cavidad peritoneal, retrasa el aclaramiento peritoneal del fármaco, aumentando su permanencia en la biofase, es decir, la cavidad peritoneal y limitando su acceso a la circulación sanguínea (13).

Esta ventaja farmacocinética también se ha demostrado para administraciones intravenosas (iv) de 5-fluorouracilo durante una instilación ip hipertérmica de doxorrubicina y mitomicina (56). La rápida distribución de este fármaco a la cavidad peritoneal, junto con un proceso limitado de difusión desde cavidad peritoneal a plasma, permitiría esta diferencia de concentraciones entre compartimentos. Este fenómeno farmacológico ha sido denominado "efecto sink", y ha servido para justificar la quimioterapia intraoperatoria bidireccional. La administración iv de 5-fluorouracilo durante el HIPEC con otros agentes simularía las condiciones de ascitis que presentan algunos de los pacientes con CP, referidas a un compartimento peritoneal expandido con solución ausente de fármaco que permite el paso del fármaco desde el compartimento plasmático hacia la cavidad peritoneal.

La ventaja farmacocinética derivada de este tipo de administración ha sido comúnmente definida mediante el ratio de AUC del fármaco en la cavidad peritoneal frente al de plasma (AUC_{per}:AUC_{pla}). Un ratio elevado reflejaría una mayor ventaja farmacocinética, siendo una de las características propuestas para la elección de los fármacos en HIPEC (39,57). Habitualmente, el ratio AUC se ha considerado que dependía únicamente de las características físico-químicas del fármaco, como el peso molecular, que influirían en su capacidad de paso a través del peritoneo a circulación sistémica (58). Con esa premisa, el AUC ratio debería ser una característica exclusiva de cada fármaco sin estar influenciado por otros factores ajenos al proceso de absorción sistémica. Sin embargo, otros aspectos relacionados con las características farmacocinéticas del fármaco o de la propia técnica HIPEC, podrían hacer variar el AUC ratio de un mismo fármaco, tal y como se expone en el trabajo presentado en el Capítulo V de este estudio. Estos factores no se tienen en cuenta cuando se calcula dicha ventaja farmacocinética, pudiendo constituir un sesgo en la optimización de la administración de fármacos ip.

1.4.4.2. Oxaliplatino y Dosificación en HIPEC

Aunque no existe un consenso total respecto a los fármacos ideales en HIPEC, el oxaliplatino, un complejo de platino de tercera generación, ha mostrado resultados muy positivos en el tratamiento de la CPCR (42). Este fármaco presenta sinergia con el calor (42,59,60), una buena difusión en el tumor peritoneal (42) y una citotoxicidad no específica del ciclo celular (61). Sin embargo, su exposición sistémica incrementa el riesgo de toxicidad hematológica y de neuropatía periférica, constituyendo las toxicidades limitantes de dosis (62-64). En este sentido, la administración ip a elevadas dosis de oxaliplatino ayudaría a reducir dicha exposición y, por tanto, a reducir el riesgo de toxicidad. Sin embargo, su administración peritoneal ocasiona una predisposición a otras complicaciones, asociadas principalmente a sangrado y toxicidad hepática (65-67).

En la literatura, la administración de HIPEO se realiza generalmente mediante la modalidad abierta, a una dosis de 460 mg/m^2 en 2 L/m^2 de dextrosa al 5%, resultando en un volumen total de rango 2,5 a 6 L. El tiempo de instilación es de 30 minutos en la mayoría de los estudios, así como la temperatura objetivo generalmente se establece en 42ºC. Sin embargo, otros grupos de trabajo realizan esta administración en diferentes condiciones, como puede ser el empleo de un volumen fijo de solución transportadora, independiente por tanto de las características antropométricas de los pacientes, o un tiempo de instilación más prolongado, tal y como refleja la Tabla I-1.

Tabla I-1. Características de los esquemas de tratamiento de la CP con HIPEO en la literatura.

Estudio	Técnica	Dosis mg/m²	Volumen instilado (L)	Solución	Tiempo de instilación (min)	Temperatura (ºC)
Löffler et al (68)	Abierta	300	5-6	Dextrosa 5%	30	42
Mehta et al (69)	Abierta	260	2 L/m²	Dianeal PD4 dextrosa 1.36%	30	42
Leung et al (70)	Abierta	350	3	Dextrosa 5%	30	42
Pérez-Ruixo et al (71)	Abierta	365-411	3.7-3.9	Dextrosa 5% o Icodextrina 4%	30	42
Marcotte et al (72)	Abierta	460	2 L/m²	Dextrosa 5%	30	42-44
Glockzin et al (73)	Cerrada	300	3	Cloruro sódico 0.9%	30	41-43
du Rieu et al (74)	Abierta	360 ó 460	2 L/m²	Dextrosa 5%	30	42-43
Shimizu et al (75)	Abierta	90-130	5	Cloruro sódico	30	42-43
Hompes et al (76)	Abierta	460	ND	Dextrosa 5%	30	41-42
Gervais et al (77)	Abierta	460	2 L/m²	Dextrosa 5%	30	42-44
Gouy et al (78)	Abierta	360 ó 460	2 L/m²	Dextrosa 5%	30	41-43
Wu XJ et al (79)	Abierta	460	3-4	Dextrosa 5%	60	42,5-43,5
Hompes et al (80)	Abierta	460	2 L/m²	Dextrosa 5%	30	41-42
Elias et al (42)	Abierta	460	2 L/m²	Dextrosa 5%	30	41-42
Ferron et al (81)	Abierta	360 ó 460	2 L/m²	Dextrosa 5%	30	42-43
Valenzuela et al (82)	Abierta	360	2,5-6	Icodextrina 4%	30	42-43
Stewart et al (83)	Cerrada	200-250	3	Dextrosa 5%	120	40-42,5
Mahteme et al (84)	Abierta	427	2 L/m²	Dextrosa 5%	30	41,5-43

El volumen de la solución transportadora del citostático, calculado comúnmente en función de la superficie corporal del paciente, al igual que la dosis, es el otro pilar relevante en la dosificación ip. El área de la superficie de contacto del fármaco con el tejido es crucial en los pacientes que reciben quimioterapia ip. Ya que los implantes de la CP pueden aparecer en cualquier punto de la cavidad abdominal, ésta en su totalidad es la diana terapéutica. Por tanto, el volumen en el que se diluya el citostático debe ser aquél que garantice dicha totalidad. Este hecho, junto a la premisa farmacológica de que una misma concentración produce un efecto y toxicidad similares, ha conducido a proponer una dosificación en HIPEC basada en concentraciones. De esta forma, la dosis de citostático y el volumen de solución transportadora dejarían de fundamentarse en parámetros antropométricos, garantizando una exposición completa y homogénea durante la totalidad de la duración de la instilación, tal y como se expone en el trabajo presentado en el Capítulo II de estudio.

Por otro lado, las características físico-químicas de la solución transportadora podrían desempeñar un papel importante en el paso del fármaco desde la cavidad peritoneal a la sangre. Una solución que contribuya a la permanencia del fármaco en la biofase aumentaría el tiempo de exposición del fármaco al tumor a concentraciones más elevadas, evitando su paso a la circulación sanguínea y reduciendo potencialmente su toxicidad sistémica. Con esta finalidad, se han probado soluciones transportadoras isotónicas de elevado peso molecular, como la icodextrina al 4% en tratamientos con HIPEO. Sin embargo, su uso no ha demostrado afectar de forma clínicamente significativa a la velocidad y extensión de la absorción del citostático respecto a otras soluciones transportadoras como la dextrosa al 5% (71).

1.4.4.3. Tiempo de Instilación

La duración de la instilación es una de las variables implicadas en la eficacia de este tratamiento. En el caso del oxaliplatino, como se ha mencionado anteriormente, el esquema de dosificación más común en la clínica para HIPEC es de 460 mg/m^2 en 2L/m^2 de dextrosa al 5%, instilado durante un tiempo de 30 minutos. Otros estudios han encontrado una mejor tolerancia al tratamiento cuando este fármaco se administra a una dosis de 200 mg/m^2 durante 2 horas (83). A pesar de que los estudios en literatura son homogéneos en cuanto a la duración de la instilación para cada fármaco, los parámetros farmacológicos que determinan este tiempo no han sido bien establecidos. El parámetro determinante empleado actualmente, bajo una justificación más bien empírica, es la semivida peritoneal del fármaco ($t_{1/2\ per}$) (85). Bajo este enfoque, el oxaliplatino se considera uno de los fármacos idóneos para HIPEC, dado que registra una de las menores $t_{1/2\ per}$, estimada aproximadamente en 40 minutos (86).

1.5. MODELOS EXPERIMENTALES EN ANIMALES

A pesar de que el tratamiento multimodal con HIPEC haya sido considerado como el referente en un grupo seleccionado de pacientes, aún no se trata de un protocolo estandarizado. La complejidad de la técnica contribuye a la falta de consenso actual y complica la implementación de guías definitivas (40). Además, la dificultad en la homogeneización de los grupos de pacientes dificulta la realización de estudios prospectivos controlados que permitan la evaluación aislada de cada una de las variables del procedimiento. La ausencia de dichos estudios, unida a la agresividad del tratamiento, son dos de los motivos de escepticismo en una parte de la comunidad científica (87). Sin embargo, los buenos resultados en cuanto a supervivencia y calidad de vida, nunca antes conseguidos con otros tratamientos, plantean la necesidad de seguir investigando mediante estudios correctamente diseñados (1,30).

Uno de los aspectos clave para evaluar el procedimiento HIPEC es la toxicidad derivada de la absorción sistémica del fármaco. La absorción a través de la barrera peritoneal no es un proceso trivial, y puede estar influido por distintas variables propias del procedimiento HIPEC. Conocer el impacto que tienen dichas variables en dicha absorción, y por lo tanto, en la exposición sistémica final permitiría, en un siguiente paso, modificar e individualizar la estrategia terapéutica si dichas variables están asociadas significativamente a una respuesta clínica.

El rápido paso del procedimiento HIPEC a la clínica, auspiciado por los buenos resultados conseguidos, deja un campo de trabajo pendiente en la investigación preclínica, donde el desarrollo de modelos animales adecuados contribuya a la evaluación del impacto de los múltiples componentes en HIPEC por separado y proporcione recomendaciones para futuras investigaciones en la clínica. La posibilidad de realizar una exhaustiva toma de muestras así como el análisis de covariables son dos de los puntos clave de la caracterización farmacocinética poblacional en modelos animales (88).

En el caso del HIPEO en concreto, se han realizado estudios tanto a nivel preclínico como clínico. En la clínica, varios estudios farmacocinéticos, algunos de carácter poblacional, han evaluado el impacto de componentes como el tipo de solución transportadora, el procedimiento de administración del fármaco o el tipo de técnica, en el perfil de concentraciones peritoneales y plasmáticas (71,81,89). A nivel preclínico, se han desarrollado modelos animales HIPEC en rata y cerdo (90), a partir de los que se han estudiado aspectos farmacocinéticos, crecimiento tumoral y supervivencia con diferentes fármacos. Sin embargo, la ausencia de modelos farmacocinéticos poblacionales específicos para HIPEO en animales justifica el desarrollo del presente trabajo.

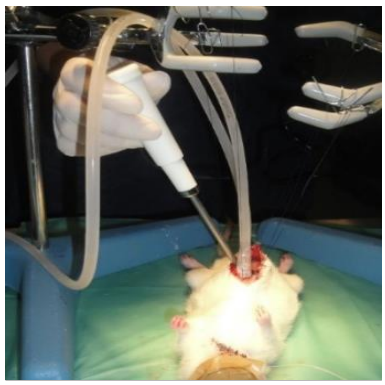


Ilustración I-5. Modelo animal para HIPEC en rata. Instilación del fármaco durante HIPEC y toma de temperatura.

1.6. MODELIZACIÓN FARMACOCINÉTICA DE OXALIPLATINO

Mediante distintos estudios Fase I se ha evaluado la farmacocinética de HIPEO en un rango de 200 a 460 mg/m^2, estableciéndose esta última como la dosis máxima tolerada. La literatura confirma que, tras la administración de 460 mg/m^2 mediante HIPEC, la concentración máxima (C_{max}) de oxaliplatino en la cavidad peritoneal supera significativamente la C_{max} en plasma alcanzada tras la administración iv del mismo fármaco a una dosis de 130 mg/m^2 (91,92), lo que demuestra una mayor exposición del fármaco a la biofase durante su administración locorregional.

El análisis farmacocinético de HIPEO basado en un enfoque poblacional fue descrito por primera vez en pacientes por Ferron et al. (81). Desde entonces, sucesivos estudios poblacionales han descrito la farmacocinética de HIPEO en la clínica mediante un modelo bicompartimental, con absorción lineal desde peritoneo a plasma y eliminación lineal desde el compartimento central (82,93). El decaimiento de las concentraciones de oxaliplatino en peritoneo se ha descrito de forma exponencial, registrando $t_{1/2\ per}$ en un rango de 29,5 a 40 minutos. La constante de absorción (k_a) se ha estimado en un valor aproximado de 1,4 h^{-1} (81), así como se ha sugerido que factores relacionados con el procedimiento quirúrgico o el analito pueden repercutir en su valor.

La concentración plasmática máxima se alcanza inmediatamente tras el fin de la perfusión, a partir del cual las concentraciones de oxaliplatino sufren un decaimiento biexponencial. El valor de aclaramiento (CL) aparente en literatura comprende un rango de 1.78 L/h a 5.47 L/h. Algunos estudios realizados en pacientes y en cerdos han descrito un aumento de la concentración plasmática de oxaliplatino a tiempos comprendidos entre las 6 y las 8 horas tras

finalizar la instilación, sugiriendo como posible causa una entrada tardía de parte de la dosis administrada, acumulada en el tejido peritoneal (81,89). El valor de la semivida beta ($t_{1/2\beta}$) difiere entre estudios, variabilidad que ha sido atribuida a la duración del tiempo de toma de muestras, de forma que esquemas de limitados a pocas horas tras la instilación podrían conducir a estimaciones imprecisas de este parámetro (82).

El ratio de distribución de oxaliplatino a los tejidos irrigados por la instilación frente a los no irrigados ha sido estimado en 17,8 (42), así como se han observado concentraciones del fármaco en tejido 25 a 32 veces superiores que las plasmáticas al final de la perfusión.

2. OBJETIVOS

De acuerdo con esta premisa, en la presente Memoria, realizada en base a los datos obtenidos tras la implementación de la técnica HIPEC en rata Wistar sana, desarrollada en el Servicio de Experimentación Animal de la Universidad Miguel Hernández de Elche, se han planteado los siguientes objetivos:

1. Establecimiento de la fundamentación teórica para la dosificación en HIPEC.

2. Desarrollo de un modelo farmacocinético poblacional para oxaliplatino tras su administración iv y evaluación del impacto de los factores quirúrgicos en la técnica abierta, entendidos como la realización de una laparotomía seguida de una instilación intraperitoneal hipertérmica de solución transportadora, en los parámetros farmacocinéticos de oxaliplatino.

3. Desarrollo de un modelo farmacocinético poblacional para oxaliplatino tras su administración ip en presencia de hipertermia y evaluación del impacto de las covariables asociadas al tratamiento dosis, temperatura y tiempo de instilación, en los parámetros farmacocinéticos de oxaliplatino.

4. Evaluación de la idoneidad del AUC ratio como parámetro indicador de la ventaja farmacocinética de un fármaco para su uso en HIPEC.

3. REFERENCIAS

1. Sugarbaker PH, Chang D. Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival. Eur J Surg Oncol. 2017; S0748-7983: 30059-8.

2. Tsujimura T, Takeda M, Terada N, Uramoto H. Two cases of peritoneal serous papillary adenocarcinoma. Acta Pathol Jpn. 1991; 41: 642–6.

3. Coccolini F, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, et al. Peritoneal carcinomatosis. World J Gastroenterol. 2013; 19: 6979–94.

4. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JWW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011; 128: 2717–25.

5. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013; 49: 1374–403.

6. Brodsky JT, Cohen AM: Peritoneal seeding following potentially curative resection of colonic carcinoma: Implications for adjuvant therapy. Dis Colon Rectum. 1991; 34: 723-727.

7. Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003; 21: 3737-3743.

8. Vallicelli C, Cavaliere D, Catena F, Coccolini F, Ansaloni L, Poiasina E, et al. Management of peritoneal carcinomatosis from colorectal cancer: review of the literature. Int J Colorectal Dis. 2014; 29: 895-898.

9. Elias D, Faron M, Iuga BS, Honore C, Dumont F, Bourgain DL, et al. Prognostic similarities and differences in optimally resected liver metastases and peritoneal metastases from colorectal cancers. Ann Surg. 2015; 26: 157-163.

10. Honore C, Caruso F, Dartigues P, Benhaim L, Chirica M, Goere D, et al. Strategies for preventing pseudomyxoma perotonei after resection of a mucinous neoplasm of the appendix. Anticancer Res. 2015; 35: 4943-4948.

11. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, et al. Extensive intraoperativa peritoneal lavage as a standard strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009; 250: 242-246.

12. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010; 17: 2370-2377.

13. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep. 1978; 62: 1-11.

14. Bakrin N, Classe JM, Pommel S, Gouy S, Chene G, Glehen O. Hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer. J Visc Surg. 2014: 151: 347-353.

15. Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, et al. Cytoreductive durgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015; 22: 1570-1575.

16. Markman M. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: where do we go from here? The Oncologist. 2016; 21: 529-531.

17. van der Wal JB, Jeekel J. Biology of the peritoneum in normal homeostasis and after surgical trauma. Colorectal Dis. 2007; Suppl 2: 9–13.

18. Lemoine L, Sugarbaker P, Van der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: Role of the peritoneum. World J Gastroenterol. 2016; 22: 7692–707.

19. Barrios P, Ramos I, Escayola C, Martin M. Implementación y desarrollo de un programa de tratamiento de la carcinomatosis peritoneal en Cataluña. Indicaciones y resultados clínicos con la técnica de Sugarbaker. Barcelona: Agència d'Avaluació de Tecnologia i Recerca Mèdiques. Servei Català de la Salut. Departament de Salut. Generalitat de Catalunya; 2009.

20. Oosterling SJ, Van der Bij GJ, Van Egmond M, Van der Sijp JR. Surgical trauma and peritoneal recurrence of colorectal carcinoma. Eur J Surg Oncol. 2005; 31: 29-37.

21. Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. Ann Surg Oncol. 2009; 16: 327-333.

22. Esquivel J, Chua TC, Stojadinovic A, Torres-Melero J, Levine EAGutman M, et al. Accuracy and clinical relevance of computed tomography scan interpretation of peritoneal cancer index in colorectal cancer peritoneal carcinomatosis: a multi-institutional study. J Surg Oncol. 2010; 102: 565-570.

23. Menassel B, Duclos A, Passot G, Dohan A, Payet C, Isaac s, et al. Preoperative CT and MRI prediction of non-resectability in patients treated for pseudomyxoma peritonei from mucinous appendiceal neoplasms. EJSO. 2016; 42: 558-566.

24. Rutten MJ, Gaarenstroom KN, van Gorp T, van Meus HS, Arts HJG, Bossuyt PM, et al. Laparoscopy to predict the result of primary cytoreductive surgery in advanced ovarian cancer patients (LapOvCa-trial): a multicentre randomized controlled study. BMC Cancer. 2012; 12: 31.

25. Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. Cancer Chem Pharmacol. 1999; 43(S): 15-25.

26. Glehen O, Mithieux F, Osinsky D, Beaujard AC, Freyer G, Guertsch P, et al. Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: A phase II study. J Clin Oncol. 2003; 21: 799-806.

27. Witkamp AJ, de Bree E, Kaag MM, Boot H,Beijnen JH, van Slooten GW, et al. Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin. Eur J Cancer. 2001; 37: 979–84.

28. Lentz SS, Miller BE, Kucera GL, Levine EA. Intraperitoneal hyperthermic chemotherapy using carboplatin: a phase I analysis in ovarian carcinoma. Gynecol Oncol. 2007; 106: 207–10.

29. Fujimura T, Yonemura Y, Muraoka K, Takamura H, Hirono Y, Sahara H, et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. World J Surg. 1994; 18: 150–5.

30. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe J-M, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009; 27: 681–5.

31. Cashin PH, Dranichnikov F, Mahteme H. Cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy treatment of colorectal peritoneal metastases: cohort analysis of high volume disease and cure rate. J Surg Oncol. 2014; 110: 203–6.

32. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer. 2010; 116: 5608–18.

33. Chua TC, Saxena A, Schellekens JF, Liauw W, Yan TD, Fransi S, Zhao J, et al. Morbidity and mortality outcomes of cytoreductive surgery and perioperative intraperitoneal chemotherapy at a single tertiary institution: towards a new perspective of this treatment. Ann Surg. 2010; 251: 101–6.

34. Haslinger M, Francescutti V, Attwood K, McCart JA, Fakih M, Kane JM, et al. A contemporary analysis of morbidity and outcomes in cytoreduction/hyperthermic intraperitoneal chemoperfusion. Cancer Med. 2013; 2:334–42.

35. Mohamed F, Moran BJ. Morbidity and mortality with cytoreductive surgery and intraperitoneal chemotherapy: the importance of a learning curve. Cancer J. 2009; 15: 196–9.

36. Gilly FN, Cotte E, Brigand C, Monneuse O, Beaujard AC, Freyer G, et al. Quantitative prognostic indices in peritoneal carcinomatosis. Eur J Surg Oncol. 2006; 32: 597–601.

37. Sugarbaker PH. Peritonectomy procedures. Surg Oncol Clin North Am. 2003; 12: 703-27.

38. Glehen O, Kwiatkoski M, Sugarbaker PH, Elis D, Levine EA, Gilly FN, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer. A multi-institutional study. J Clin Oncol. 2004; 22: 3284-92.

39. Braam HJ, Schellens JH, Boot H, van Sandick JW, Knibbe CA, Boerma D, et al. Selection of chemotherapy for hyperthermic intraperitoneal use in gastric cancer. Crit Rew Oncol Hematol. 2015; 95: 282–96.

40. Kusamura S, Dominique E, Baratti D, Younan R, Deraco M. Drugs, carrier solutions and temperature in hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2008; 98: 247–52.

41. Van der Speeten K, Stuart OA, Chang D, Mahteme H, Sugarbaker PH. Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis. Cancer Chemother Pharmacol. 2011; 68: 147–56.

42. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, et al. Heated Intra-Operative Intraperitoneal Oxaliplatin after Complete Resection of Peritoneal Carcinomatosis: Pharmacokinetics and Tissue Distribution. Ann Oncol. 2002; 13: 267–72.

43. Cohen MS, Al-Kasspooles MF, Williamson SK, Henry D, Broward M, Roby KF. Combination intraperitoneal chemotherapy is superior to mitomycin C or oxaliplatin for colorectal carcinomatosis in vivo. Ann Surg Oncol. 2010; 17: 296–303.

44. Dudar TE, Jain RK. Differential response of normal and tumor microcirculation to hyperthermia. Cancer Res. 1984; 44: 605–12.

45. Koga S, Hamazoe R, Maeta M, Shimizu N, Kanayama H, Osaki Y. Treatment of implanted peritoneal cancer in rats by continuous hyperthermic peritoneal perfusion in combination with an anticancer drug. Cancer Res. 1984; 44: 1840–2.

46. Atallah D, Marsaud V, Radanyi C, Kornprobst M, Rouzier R, Elias D, et al. Thermal enhancement of oxaliplatin-induced inhibition of cell proliferation and cell cycle progression in human carcinoma cell lines. Int J Hyperthermia. 2004; 20: 405–419.

47. Van Ruth S, Verwaal VJ, Hart AA, van Slooten GW, Zoetmulder FA. Heat penetration in locally applied hyperthermia in the abdomen during intra-operative hyperthermic intraperitoneal chemotherapy. Anticancer Res. 2003; 23: 1501-8.

48. Pestieau SR, Belliveau JF, Griffin H, Stuart OA, Sugarbaker PH. Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies. J Surg Oncol. 2001; 76: 106–114.

49. Escudero-Ortiz V, Duart-Duart MJ, Pérez-Ruixo C, Pérez-Ruixo JJ, Valenzuela B. Estudio de estabilidad de oxaliplatino y doxorrubicina para su administración intraperitoneal con hipertermia. Farm Hosp. 2014; 38: 154–61.

50. Yonemura Y, Fujimura T, Nishimura G, FallaR null, Sawa T, Katayama K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery. 1996; 119: 437-44.

51. Elias D, Gilly F, Boutitie F, Quenet F, Bereder J-M, Mansvelt B, et al. Peritoneal Colorectal Carcinomatosis Treated With Surgery and Perioperative Intraperitoneal Chemotherapy: Retrospective Analysis of 523 Patients From a Multicentric French Study. J Clin Oncol. 2010; 28: 63–8.

52. Schaaf L, van der Kuip H, Zopf W, Winter S, Münch M, Mürdter TE, et al. A Temperature of 40 °C Appears to be a Critical Threshold for Potentiating Cytotoxic Chemotherapy In Vitro and in Peritoneal Carcinomatosis Patients Undergoing HIPEC. Ann Surg Oncol. 2015; 22 Suppl 3: S758–65.

53. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst. 1997; 89: 480–7.

54. Sugarbaker PH, Ryan DP. Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach? Lancet Oncol. 2012; 13: e362–9.

55. Flessner MF. The transport barrier in intraperitoneal therapy. Am J Physiol Renal Physiol. 2005; 288: F433–42.

56. Van der Speeten K, Stuart OA, Mahteme H, Sugarbaker PH. Pharmacology of perioperative 5-fluorouracil. J Surg Oncol. 2010; 102: 730–5.

57. de Bree E. Optimal drugs for HIPEC in different tumors. J BUON. 2015; 20 Suppl 1: S40–6.

58. Barrasa A, Van de Speeten K, Anthony Stuart O, Hendrick Sugarbaker P, Zappa L. Rationale for perioperative chemotherapy treatment in peritoneal carcinomatosis. Cir Esp. 2009; 85: 3–13.

59. Mohamed F, Marchettini P, Stuart OA, Urano M, Sugarbaker PH. Thermal Enhancement of New Chemotherapeutic Agents at Moderate Hyperthermia. Ann Surg Oncol. 2003; 10: 463–68.

60. Rietbroek RC, van der Vaart PJ, Haveman J, Blommaert FA, Geerdink A, et al. Hyperthermia Enhances the Cytotoxicity and Platinum-DNA Adduct Formation of Lobaplatin and Oxaliplatin in Cultured SW 1573 Cells. J Cancer Res Clin Oncol. 1997; 123: 6–12.

61. Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. Curr Oncol. 2011; 18: 18-25.

62. Stewart JH, Shen P, Levine EA. Intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: current status and future directions. Ann Surg Oncol. 2005; 12: 765–77.

63. Culy CR, Clemett D, Wiseman LR. Oxaliplatin. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. Drugs. 2000; 60: 895–924.

64. Votanopoulos K, Ihemelandu C, Shen P, Stewart J, Russell G, Levine EA. A comparison of hematologic toxicity profiles after heated intraperitoneal chemotherapy with oxaliplatin and mitomycin C. J Surg Res. 2013; 179: e133–9.

65. Pomel C, Ferron G, Lorimier G, Rey A, Lhomme C, Classe JM, et al. Hyperthermic intraperitoneal chemotherapy using oxaliplatin as consolidation therapy for advanced epithelial ovarian carcinoma. Results of a phase II prospective multicentre trial. CHIPOVAC study. Eur J Surg Oncol. 2010; 36: 589-93.

66. Elias D, El Otmany A, Bonnay M, Paci A, Ducreux M, Antoun S, et al. Human pharmacokinetic study of heated intraperitoneal oxaliplatin in increasingly hypotonic solutions after complete resection of peritoneal carcinomatosis. Oncology. 2002; 63: 346-52.

67. Delhorme J-B, Sattler L, Severac F, Triki E, Gross I, Romain B, et al. Prognostic factors of hemorrhagic complications after oxaliplatin-based hyperthermic intraperitoneal chemotherapy: Toward routine preoperative dosage of Von Willebrand factor? Eur J Surg Oncol. 2017; 2: S0748-7983.

68. Löffler MW, Schuster H, Zeck A, Quilitz N, Weinreich J, Tolios A, et al. Pharmacodynamics of Oxaliplatin-Derived Platinum Compounds During Hyperthermic Intraperitoneal Chemotherapy (HIPEC): An Emerging Aspect Supporting the Rational Design of Treatment Protocols. Ann Surg Oncol. 2017; 3: 1–8.

69. Mehta AM, Huitema ADR, Burger JWA, Brandt-Kerkhof ARM, Heuvel SF van den, Verwaal VJ. Standard Clinical Protocol for Bidirectional Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Systemic Leucovorin, 5-Fluorouracil, and Heated Intraperitoneal Oxaliplatin in a Chloride-Containing Carrier Solution. Ann Surg Oncol. 2017; 24: 990–7.

70. Leung V, Huo YR, Liauw W, Morris DL. Oxaliplatin versus Mitomycin C for HIPEC in colorectal cancer peritoneal carcinomatosis. Eur J Surg Oncol. 2017; 43: 144–9.

71. Pérez-Ruixo C, Peris JE, Escudero-Ortiz V, Bretcha-Boix P, Farré-Alegre J, Pérez-Ruixo JJ, et al. Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol. 2014; 73: 1009-20.

72. Marcotte E, Sideris L, Drolet P, Mitchell A, Frenette S, Leblanc G, et al. Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin for Peritoneal Carcinomatosis Arising from Appendix: Preliminary Results of a Survival Analysis. Ann Surg Oncol. 2008; 15: 2701–8.

73. Glockzin G, Gerken M, Lang SA, Klinkhammer-Schalke M, Piso P, Schlitt HJ. Oxaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastasis from appendiceal and colorectal cancer: a retrospective analysis. BMC Cancer. 2014; 14:807.

74. Chalret du Rieu Q, White-Koning M, Picaud L, Lochon I, Marsili S, Gladieff L, et al. Population pharmacokinetics of peritoneal, plasma ultrafiltrated and protein-bound oxaliplatin concentrations in patients with disseminated peritoneal cancer after intraperitoneal hyperthermic chemoperfusion of

oxaliplatin following cytoreductive surgery: correlation between oxaliplatin exposure and thrombocytopenia. Cancer Chemother Pharmacol. 2014; 74: 571–82.

75. Shimizu T, Sonoda H, Murata S, Takebayashi K, Ohta H, Miyake T, et al. Hyperthermic intraperitoneal chemotherapy using a combination of mitomycin C,5-fluorouracil, and oxaliplatin in patients at high risk of colorectal peritoneal metastasis: A Phase I clinical study. Eur J Surg Oncol. 2014; 40: 521–8.

76. Hompes D, D'Hoore A, Wolthuis A, Fieuws S, Mirck B, Bruin S, et al. The use of Oxaliplatin or Mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. J Surg Oncol. 2014; 109: 527–32.

77. Gervais M-K, Dubé P, McConnell Y, Drolet P, Mitchell A, Sideris L. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with oxaliplatin for peritoneal carcinomatosis arising from colorectal cancer. J Surg Oncol 2013. 108: 438–43.

78. Gouy S, Uzan C, Pautier P, Lhomme C, Duvillard P, Morice P. Results of oxaliplatin-based hyperthermic intraperitoneal chemotherapy in recurrent ovarian granulosa cell tumors. Eur J Obstet Gynecol Reprod Biol. 2013; 170: 464–7.

79. Wu X-J, Yuan P, Li Z-Y, Bu Z-D, Zhang L-H, Wu A-W, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves the survival of gastric cancer patients with ovarian metastasis and peritoneal dissemination. Tumor Biol. 2013; 34: 463–9.

80. Hompes D, D'Hoore A, Van Cutsem E, Fieuws S, Ceelen W, Peeters M, et al. The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. Ann Surg Oncol. 2012; 19: 2186–94.

81. Ferron G, Dattez S, Gladieff L, Delord JP, Pierre S, Lafont T, et al. Pharmacokinetics of Heated Intraperitoneal Oxaliplatin. Cancer Chemother Pharmacol. 2008; 62: 679–83.

82. Valenzuela B, Nalda-Molina R, Bretcha-Boix P, Escudero-Ortíz V, Duart MJ, Carbonell V, et al. Pharmacokinetic and pharmacodynamic analysis of hyperthermic intraperitoneal oxaliplatin-induced neutropenia in subjects with peritoneal carcinomatosis. AAPS J. 2011; 13: 72–82.

83. Stewart JH, Shen P, Russell G, Fenstermaker J, McWilliams L, Coldrun FM, et al. A phase I trial of oxaliplatin for intraperitoneal hyperthermic chemoperfusion for the treatment of peritoneal surface dissemination from colorectal and appendiceal cancers. Ann Surg Oncol. 2008; 15: 2137.

84. Mahteme H, Wallin I, Glimelius B, Påhlman L, Ehrsson H. Systemic exposure of the parent drug oxaliplatin during hyperthermic intraperitoneal perfusion. Eur J Clin Pharmacol. 2008; 64: 907–11.

85. Sugarbaker PH, Van der Speeten K. Surgical technology and pharmacology of hyperthermic perioperative chemotherapy. J Gastrointest Oncol. 2016; 7: 29–44.

86. Elias D, Raynard B, Bonnay M, Pocard M. Heated intraoperative intraperitoneal oxaliplatin alone and in combination with intraperitoneal irinotecan: Pharmacologic studies. Eur J Surg Oncol. 2006; 32: 607-13.

87. Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O, et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. Ann Surg Oncol. 2004; 11: 518–21.

88. Porzio S. Application of population pharmacokinetics for preclinical safety and efficacy studies. Bioanalysis. 2013; 5: 2053–69.

89. Gesson-Paute A, Ferron G, Thomas F. Pharmacokinetics of Oxaliplatin during Open versus Laparoscopically Assisted Heated Intraoperative Intraperitoneal Chemotherapy (HIPEC): An Experimental Study. Ann Surg Oncol. 2008; 15: 339–44.

90. Pelz JO, Doerfer J, Hohenberger W, Meyer T. A new survival model for hyperthermic intraperitoneal chemotherapy (HIPEC) in tumor-bearing rats in the treatment of peritoneal carcinomatosis. BMC Cancer. 2005; 5: 56.

91. Massari C, Brienza S, Rotarski M, et al. Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function. Cancer Chemother Pharmacol. 2000; 45: 157-64.

92. Elias D, Sideris L. Pharmacokinetics of heated intraoperative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis. Surg Oncol Clin North Am. 2003; 12: 755-69.

93. Pérez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farré-Alegre J, et al. Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery. Cancer Chemother Pharmacol. 2013; 71: 693–704.

UNIVERSITAS
Miguel
Hernández

CAPÍTULO II

UNIVERSITAS
Miguel
Hernández

CAPÍTULO II

Letter to the Editor

Importance of Standardizing the Dose in Hyperthermic Intraperitoneal Chemotherapy (HIPEC): a Pharmacodynamic Point of View

María Isabel Mas Fuster[1], Amelia Ramón López[1], Ricardo Nalda Molina[1]

1. Pharmacy and Pharmaceutics Division, Department of Engineering, Miguel Hernandez University, San Juan de Alicante, Alicante, Spain.

Cancer Chemother Pharmacol 2013; 72: 273-4

Impact Factor 2013	2,571
Oncology (Q3)	Rank: 111/213
Pharmacology and Pharmacy (Q2)	Rank: 89/255

1. Letter to the Editor

Peritoneal carcinomatosis is a severe disease progression in patients with intra-abdominal cancer, and it remains one of the most common causes of incurability in these cases. An aggressive strategy with cytoreductive surgery (CCR) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a therapeutic schedule focused on the local handling of this progression, with many studies showing a significant increase in the median overall survival compared to the systemic chemotherapy treatment. Examples of drugs used in this type of administration are oxaliplatin, carboplatin, cisplatin, mitomycin C, irinotecan, paclitaxel, docetaxel, doxorubicin and melphalan. Given that this protocol is a local treatment, with no systemic effect intention, and based on the premise that the same concentration produces a similar effect and toxicity, doses should be considered in terms of concentration instead of being defined by the body surface area (BSA). It should be kept in mind that, in HIPEC, the drug does not need to be distributed in order to reach the biophase (peritoneal cavity) and, therefore, homogenous concentrations should be achieved in the instillation solution.

However, in the reviewed literature, the doses in HIPEC were defined by the BSA. In some of the studies, the method for calculating the volume of instillation was not specified. Therefore, the volume may vary depending on the capacity of the abdominal cavity to hold liquid or may be fixed for all patients [1]. Consequently, the initial drug concentration is no longer constant, and it depends on the volume of the instilled solution. Other authors calculate both volume and dose from each patient's BSA [2, 3]. In these cases, the initial concentration was constant for all of them. Even though BSA may be helpful to calculate the volume of instillation needed to maintain a desired flow rate in the closed-technique HIPEC, in some cases this volume may be inappropriate. For instance, the abdominal capacity can be altered by individual pathophysiological characteristics or by the relatively frequent complications in these patients (as ascites). As a result, volumes based on the anthropometric characteristics could present a poor relationship with the abdominal cavity [4]. Thus, patients with small BSA and large abdominal cavities may have an insufficient volume to cover the entire peritoneum, and subsequent increases in volume to resolve it would change the concentration at baseline. This procedure takes us away from the initial homogenous drug concentration desired, increasing the variability in the systemic and tumor exposure to the drug. In fact, a previous study showed that the plasma drug concentrations were higher, the lower the volume was [5]. In conclusion, considering the HIPEC as a local administration, with no systemic intention, we recommend using fixed concentrations instead of dosing by BSA. Although many authors actually use homogeneous concentrations when normalizing both dose and volume by BSA, it would be more practical to define a fixed concentration independent of anthropometric characteristics.

Thus, the variability of the abdominal capacity would not influence the systemic and tumor exposure to the drug.

Conflict of interest: None.

2. REFERENCES

1. Glockzin G, von Breitenbuch P, Schlitt HJ, Piso P (2012) Treatment related morbidity and toxicity of CRS and oxaliplatin-based HIPEC compared to a mitomycin and doxorubicin-based HIPEC protocol in patients with peritoneal carcinomatosis: a matched-pair analysis. J Surg Oncol 107:574–578
2. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S et al (2002) Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 13:267–272.
3. Sugarbaker PH (1999) Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol 43(suppl):S15–S25
4. Duez A, Cotte E, Glehen O, Cotton F, Bakrin N (2009) Appraisal of peritoneal cavity's capacity in order to assess the pharmacology of liquid chemotherapy solution in hyperthermic intraperitoneal chemotherapy. Surg Radiol Anat 31:573–578.
5. Sugarbaker PH, Stuart OA, Carmignani CP (2006) Pharmacokinetic changes induced by the volume of chemotherapy solution in patients treated with hyperthermic intraperitoneal mitomycin C. Cancer Chemother Pharmacol 57:703–708

Anexo II-1. Reprint publicación original.

CAPÍTULO III

UNIVERSITAS
Miguel
Hernández

CAPÍTULO III

Short Communication

Impact of Laparotomy and Intraperitoneal Hyperthermic Instillation (LIHI) on the Oxaliplatin Pharmacokinetics after Intravenous Administration in Wistar Rats

María Isabel Mas Fuster[1], Amelia Ramón López[1], Javier Lacueva[2], Antonio Compañ[2], Patricio Más Serrano[1,3], Ricardo Nalda Molina[1]

1. Division of Pharmacy and Pharmaceutics, Department of Engineering, School of Pharmacy, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.
2. Department of Pathology and Surgery, School of Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.
3. Clinical Pharmacokinetics Unit, Pharmacy Department, Hospital General Universitario de Alicante, Alicante, Spain.

Cancer Chemother Pharmacol 2017; 79: 621-627

Impact Factor 2015	2,824
Oncology (Q3)	Rank: 111/213
Pharmacology and Pharmacy (Q2)	Rank: 89/255

UNIVERSITAS
Miguel
Hernández

1. ABSTRACT

Purpose: In peritoneal metastasis condition, the fact that most of the disease is limited to the peritoneal cavity laid the foundations for a surgical treatment, including intraperitoneal hyperthermic chemotherapy (HIPEC). The aim of this study was to evaluate the impact of the surgical procedures implied in open HIPEC technique, referred to laparotomy procedures followed by an intraperitoneal hyperthermic instillation (LIHI) on oxaliplatin tissue distribution and elimination. To delimit the influence of this procedure alone, oxaliplatin was administered as an intravenous (iv) bolus in both groups.

Methods: An experimental model in Wistar rats was employed, and LIHI was evaluated as a dichotomouscovariate by using a population pharmacokinetic (PK) approach. Rats were randomized in two groups receiving 1.5 mg iv oxaliplatin alone or 1.5 mg iv oxaliplatin under LIHI conditions, carrying out a hyperthermic 5% dextrose instillation. The oxaliplatin plasma concentrations were characterized by an open two-compartment PK model.

Results: Results concluded that surgical conditions affect the oxaliplatin elimination and distribution from blood to peripheral tissues, increasing the systemic drug exposure. Concretely, oxaliplatin peripheral volume of distribution, and clearance decreased by 48.6% and 55.3%, respectively, compared to the control group that resulted in a two-fold increase of the area under the concentration time curve.

Conclusions: Comparison in clinical practice of oxaliplatin PK parameters obtained after iv administrations with those obtained after HIPEC interventions must be done carefully. This would limit the use of iv PK parameters to simulate new scenarios for oxaliplatin in HIPEC.

Keywords

Population pharmacokinetics · Oxaliplatin · Hyperthermia · Intraperitoneal chemotherapy · Peritoneal Metastasis

2. INTRODUCTION

Multimodal therapy consisting of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) has shown a potential benefit in selected patients with peritoneal metastasis (PM) [1]. This procedure increases the efficacy of chemotherapy by exposing remaining microscopic tumor cells in peritoneal cavity directly to a high drug concentration while minimizing systemic drug exposure due to the peritoneum-plasma barrier [2]. To this purpose, drugs used in HIPEC must have specific characteristics, such as a high capacity of tumor penetration, a low capacity to diffuse into the subperitoneal tissues and capillaries, and a synergetic profile with hyperthermia. Oxaliplatin is one of the most used drugs in HIPEC for the PM treatment from colorectal origin [3], given that it fulfills the aforementioned characteristics as well as its cytotoxicity is not cell cycle specific [4]. Several pharmacokinetic (PK) studies have evaluated the impact of different variables involved in HIPEC on the oxaliplatin plasma concentration profile, such as the type of carrier solution, the oxaliplatin administration procedure, and the type of technique [5–7]. However, the impact of the surgical procedures implied in open HIPEC technique, referred to laparotomy procedures followed by an intraperitoneal hyperthermic instillation (LIHI), on the systemic oxaliplatin PK parameters has not been previously studied. It is worth mentioning that this factor is common during this treatment, regardless of other variables, and a significant impact on parameters, such as systemic clearance and volume of distribution, could affect drug plasma concentrations and thus toxicity of drug therapy. Ideally, one would expect that the PK parameters obtained after systemic administration were useful for simulation purposes (e.g., evaluation of new doses for HIPEC treatments). However, this assumption would require that these parameters were not affected by the surgical conditions that occur in HIPEC. Thus, this work has considered LIHI as an independent covariate and has evaluated its impact on the oxaliplatin tissue distribution and elimination through an experimental model in Wistar rats using a population PK approach.

3. MATERIALS AND METHODS

Experimental procedure

Animals

The technique was developed in 12 healthy male Wistar rats, weighing 250–300 grams, kept in the standard housing conditions with free access to water and a fasting day before surgery. Sample size was selected, after statistical evaluation, as minimally required while still being able to assess experimental variability. The development of the experimental model, previously validated in rat (unpublished work), was held at the Animal Experimentation Service

of San Juan de Alicante, associated with Miguel Hernández University of Elche (UMH). At the end of the procedure, rats were sacrificed. Care of the animals and drug administration was performed under veterinary control according to European Union Directive 2010/63/EU for animal experiments and with approval from the Ethics Committee of the UMH.

Experimental design

Anesthesia was induced by isoflurane (Isovet®) with oxygen vaporization. Intensity was regulated during the induction and maintenance phases (Fluovac®, Surgivet®). To avoid hypothermia induced by the anesthesia and by the opening of the abdominal cavity, rats were placed in the surgical area on a thermal blanket. To evaluate the impact of LIHI on the oxaliplatin PK parameters, rats were randomized into two groups. An oxaliplatin dose of 1.5 mg, calculated from previous experimental studies [8], was administered as an intravenous (iv) bolus to the rats of both groups through a permanent jugular vein catheterization. In the control group (group 1, n = 6), no surgery was performed. In the LIHI group (group 2, n = 6), a laparotomy followed by hyperthermic intraperitoneal 5% dextrose instillation was performed, simulating the conditions of the open HIPEC procedure [9], without adding any intraperitoneal drug. To perform recirculation of dextrose, an inlet and outlet drains were placed in the abdominal cavity. A total volume of 100 mL of dextrose solution was recirculated for 30 min at 50 mL/min using an infusion pump (Masterflex® L/S EasyLoad 77202-50). In this group, oxaliplatin was administered 5 min after the start of the hyperthermic intraperitoneal instillation. Temperature of the solution in the abdominal cavity was maintained to 40–42 °C using athermostatic bath (JpSelecta®). Once the instillation finalized, the volume remaining in the peritoneal cavity was drained and the abdominal cavity was closed. Buprenorphine (Buprex® 0.3 mg/mL) was administered as analgesic at a subcutaneous dose of 0.05 mg/kg after surgery. According to previous simulation studies, blood samples were taken after the iv bolus administration of oxaliplatin at times 1, 10, 20, 30, 45, 60, 90, 150, 270, and 510 min. To balance blood loss by the sampling schedule and to prevent the catheter obstruction, the catheter was rinsed with saline and filled with a 60% polyvinylpyrrolidone solution with heparinized saline (500 IU/mL) after each extraction. Samples were collected in heparin tubes and centrifuged at room temperature. Plasma was stored at −20°C until their analysis. Total oxaliplatin was measured by a validated graphite furnace atomic absorption spectrophotometry method [10]. The analytical technique employed has a limit of quantification of 0.06 mg/L of oxaliplatin.

Pharmacokinetic model development

Nonparametric area under the plasma concentration time curve from time zero to infinite ($AUC_{pla\ 0-\infty}$) was calculated in both groups. To characterize the time course of oxaliplatin

plasma concentrations, a population PK modeling was applied to the data. Data fitting was performed using the FOCE algorithm in the NONMEM 7.3 software package [11]. Postprocessing of results and diagnostic plots was performed using R Studio 0.99.486 [12] implemented with R 3.2.5 [13].

Structural model

Time course of iv oxaliplatin plasma concentrations decayed in a bi-exponential fashion (Fig. 1), indicating that the iv oxaliplatin PK is characterized by a two-compartment model, with linear elimination and nonspecific distribution to peripheral tissues, consistent with previous studies [5]. Thus, this model was parameterized in terms of clearance (CL), central volume of distribution (V_1), intercompartmental clearance (Q) and peripheral volume of distribution (V_2).

Statistical model

Taking into account the population model, variability of PK parameters between rats (interindividual variability, IIV) was assumed to follow a log-normal distribution. The unexplained or residual variability was assessed using an additive model after log-normal transformation of observedand model predicted oxaliplatin plasma concentrations. Magnitude of the residual and interindividual variability was expressed as coefficient of variation (CV). The shrinkage of the empirical Bayes estimate of the IIV was calculated as previously suggested [14]. Once the population PK model that best described the data was established, it was followed by covariate analysis and model validation.

Model selection criteria

The improvement of the fit obtained for each model was assessed by the likelihood ratio test for nested models (significance level, $p = 0.01$), the reduction in the IIV and residual variability, the precision and correlation in parameter estimates, and the examination of shrinkage, the goodness of fit plots (GOF) and the normalized prediction distribution errors (NPDE) [14].

Covariate analysis

Once the model was validated, the impact of LIHI on its parameters was evaluated as a dichotomous covariate. The NONMEM-generated objective function value (OFV) was used to perform the likelihood ratio test for nested models. The significance level was set to $p = 0.01$, which corresponds to a decrease in OFV of ≥6.635 points, after the inclusion of one parameter, assuming that the difference in minimum value of the OFV between two nested models is $\chi 2$ distributed.

Model validation

A nonparametric bootstrap (NPBS) and a prediction-corrected visual predictive check (pcVPC) [15] were used as internal evaluation methods to qualify the estimates of the PK model parameters. The NPBS was made after the generation of 1000 databases with resampling and replacement by using the software WINGS for NONMEM (N. Holford, Version 616, Auckland, New Zealand). The mean and the 95% confidence intervals (CI) of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset. To perform the pcVPC, the 5th, 50th and 95th percentiles of the observed values, and the 95% CI for the corresponding model-based predicted percentiles computed from 1000 replicates, obtained by simulating the design of the underlying dataset with the final model parameters, were calculated.

4. RESULTS

The technique was well tolerated in general, although death of one of the rats from LIHI group was recorded during surgery for unknown etiology.

Oxaliplatin plasma profiles

A total of 91 plasma samples were available for PK analysis, 49 of them corresponding to the control group and 42 to LIHI group. Differences between both groups were visually detected (Fig. 1), with the highest drug plasma concentrations corresponding to the group that suffered LIHI. The oxaliplatin average maximum plasma concentration and standard deviation (±SD) were 23.7 (6.9) mg/L in control group and 22.5 (2.5) mg/L in LIHI group, reached immediately after iv oxaliplatin bolus administration. The mean (±SD) $AUC_{pla\ 0-\infty}$ was 1375 (645) mg*min/L and 2766 (440) mg*min/L for control and LIHI groups, respectively, showing significant differences in the $AUC_{pla\ 0-\infty}$ in both groups ($p < 0.01$).

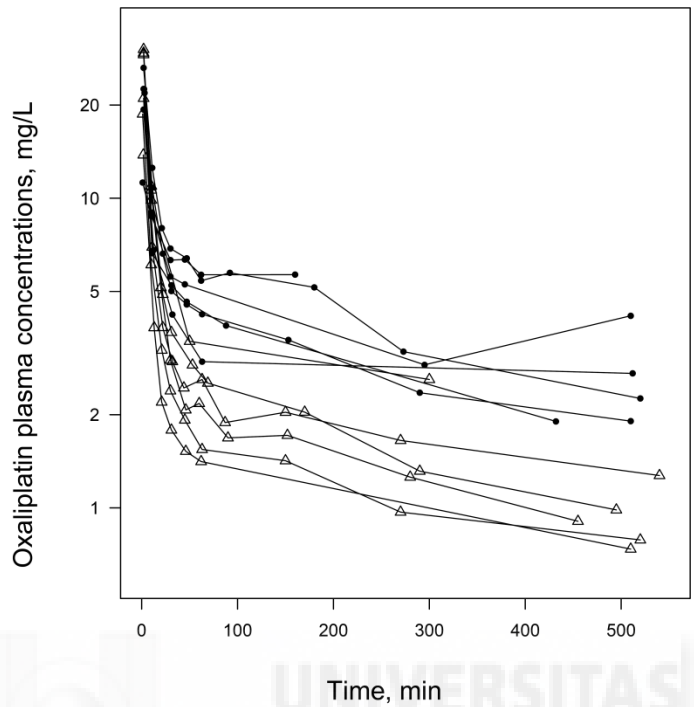


Fig 1. Oxaliplatin plasma concentration profile for control group (empty triangles) and LIHI group (black circles).

Pharmacokinetics

LIHI, considered as a dichotomous covariate, significantly improved the objective function value of the model when it was included in CL and V_2, with a decrease of 18.3 points ($p < 0.001$). Therefore, LIHI was included as a covariate of both parameters and this model was considered as the final model. Values of CL in control group and LIHI group were 0.94 (28.3) mL/min and 0.42 (14.0) mL/min, respectively. Values of V_2 in control group and LIHI group were 430 (12.3) mL and 221 (11.8) mL, respectively (Table 1). Upper panels in Fig. 2 show GOF for the population (panel A) and individual (panel B) oxaliplatin plasma predicted *vs* observed concentrations, indicating the absence of bias in the model. Panels C and D show the results of NPDE check, confirming a normal distribution around each individual observation within the predictions of the model. In fact, the mean (±SD) of the NPDE for plasma concentrations was 0.02 (95% CI −0.14:0.22) and 0.90 (95% CI 0.78:−1.06), respectively. These results confirmed that observations were accurately predicted by the model without bias. Panels of Fig. 3 show the pcVPC, evidencing that the model developed was appropriate to describe the time course of oxaliplatin and its variability in both groups. Final model estimates were similar to the

average of the NPBS replications and were included within the 95% CI (Table 1). The PK model described the data accurately, with an adequate IIV of less than 35% in all the PK parameters and a residual variability of less than 12%. Shrinkage values of IIV were estimated in less than 14%.

Table 1. Parameter estimates (Relative Standard Errors) and nonparametric bootstrap analysis of the oxaliplatin population pharmacokinetic model.

Model parameters	Original dataset	Nonparametric Bootstrap	
	Estimate (RSE %[a])	Mean (RSE %)	95% CI
Fixed effect parameters			
$CL_{Control\ Group}$ (mL/min)	0.94 (28.3)	0.94 (15.2)	0.67 - 1.20
$CL_{LIHI\ Group}$ (mL/min)	0.42 (14.0)	0.42 (19.4)	0.29 - 0.59
V_1 (mL)	53.2 (7.80)	53.4 (8.16)	46.7 - 62.4
Q (mL/min)	6.01 (9.58)	6.05 (9.92)	5.15 - 7.38
$V_{2\ Control\ Group}$ (mL)	430 (12.3)	436 (12.8)	350 - 557
$V_{2\ LIHI\ Group}$ (mL)	221 (11.8)	223 (13.4)	181 - 287
Interindividual variability (η)[b]			
η_{CL}	33.3 (24.7)	29.7 (31.9)	15.0- 49.0
η_{V}	20.6 (28.8)	17.7 (42.5)	0.20- 29.0
η_{Q}	28.8 (18.1)	26.7 (22.9)	16.6 - 37.7
η_{V2}	26.7(18.3)	22.7 (27.2)	11.7- 32.6
Residual variability[b]	11.5 (15.0)	11.4 (14.5)	8.90 - 14.9

Shrinkage values (%) of BSV in CL, V_1, Q and V_2 were estimated at 5.70, 13.2, 3.02 and 2.32.

[a]Relative Standard Error. [b]Expressed as CV (%).

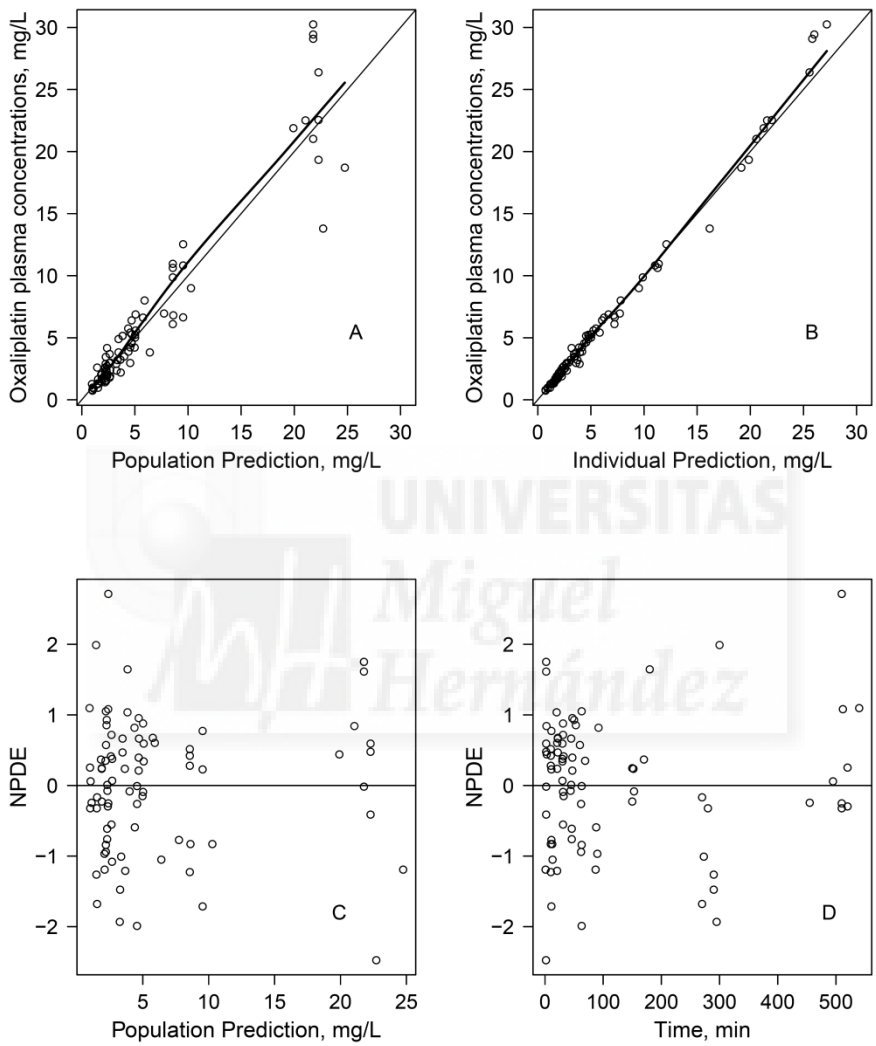


Fig 2. Diagnostic plots for the PK analysis. The upper panels represent the observed vs population (panel A) and individual (panel B) predicted concentrations. The lower panels represent the NPDE vs population predicted concentrations (panel C) and time.

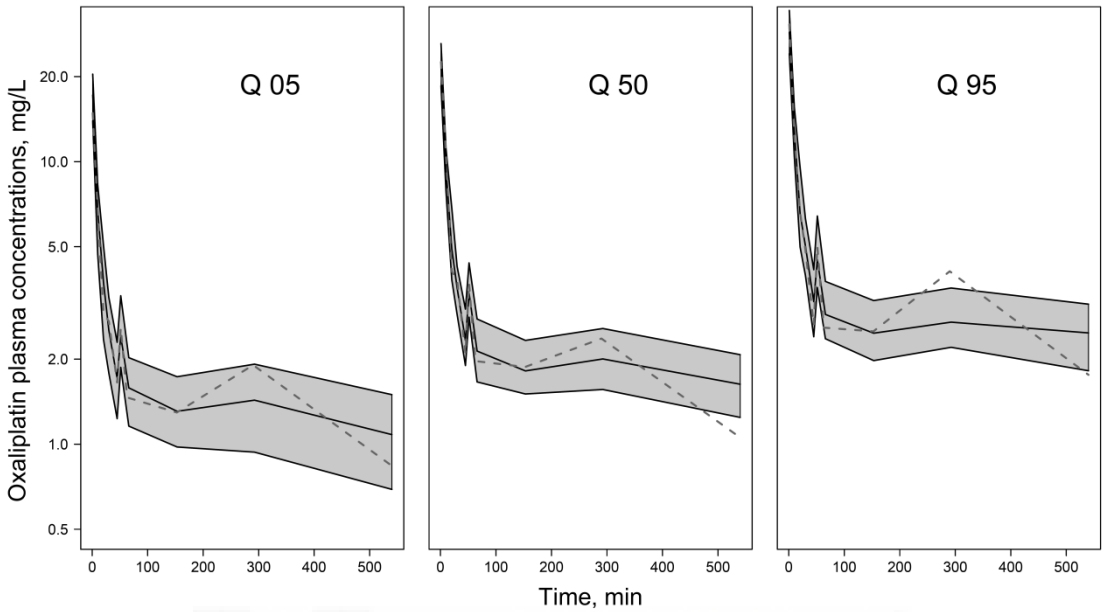


Fig 3. pcVPC, showing the 5th (Q05), 50th (Q50), and 95th (Q95) percentiles of the observed values (dashed lines), and the 95% confidence interval for the corresponding model-based predicted percentiles (solid lines).

5. DISCUSSION

The use of HIPEC in the clinical practice is increasing, supported by the advantageous results against more classic treatments based on systemic chemotherapy. There have been preclinical studies in HIPEC that considered the impact of different variables on the PK parameters of cytotoxic drugs [16]. However, influence of LIHI, despite being a process common to all experiments, has not been evaluated as a covariate that can modify the PK parameters of oxaliplatin. This experimental study evaluated the impact of the LIHI procedure, inherent in the open HIPEC technique, in Wistar rat. To delimit the influence of this procedure alone, it was decided to administer oxaliplatin as an iv bolus in both groups, resulting in two strictly equal groups, except from LIHI procedure. Therefore, this study evaluated only the impact of LIHI on the systemic drug distribution andelimination. Kinetics of oxaliplatin distribution and elimination after a single iv administration of 1.5 mg were determined, in the presence and absence of the conditions described above. A nonparametric analysis of the results revealed that the systemic exposure of the drug, $AUC_{pla\ 0-\infty}$ in the control group was significantly lower than the $AUC_{pla\ 0-\infty}$ obtained for LIHI group (1375 mg*min/L vs 2766 mg*min/L, respectively). In agreement with the literature [5], a structural two-compartment model described successfully the oxaliplatin plasma concentration profile. CL and V_2 decreased by 55.3% and 48.6%, respectively, when iv administration of oxaliplatin occurred in LIHI conditions, compared to the values achieved in the control group. CL value in control group is

consistent with other studies found in literature quantifying total oxaliplatin after iv administration [17]. One might have expected CL in LIHI group being higher than CL in control group, given that an openabdominal cavity filled with 5% dextrose solution could act as a sink [18], causing the distribution of oxaliplatin from blood to the peritoneal cavity, and therefore, increasing the apparent CL obtained. However, it has not been the result of this study. Given that platinum compounds are mainly excreted by the kidney, one possible hypothesis would be that the decrease in CL observed in LIHI group could have been caused by a change in renal function due to the surgical stress [19, 20]. This deterioration in renal function could have balanced out the "sink" effect, being even more determinant and thus, resulting in a final decrease of CL when rats are submitted to these conditions. This hypothesis would have been confirmed with greater robustness by taking peritoneal samples or by placing a bladder catheter. This would have allowed to determine oxaliplatin concentrations in the peritoneum or urine and the volume of urine excreted, respectively, and therefore to better explore the origin of the modification in CL value. Previous clinical studies showed that, although the peritoneum-plasma barrier limits the oxaliplatin access from peritoneum into the blood, the systemic exposure of oxaliplatin after HIPEC administration was similar to the systemic exposure after iv administration [5], even though the former would be expected to be lower than the latter. The results of our study suggested that this fact could be due to the decrease in CL due to the surgical stress in patients administered by HIPEC technique. A limitation of this study is that it has been conducted in healthy rats, with no peritonectomy performed. Therefore, actual conditions of cytoreduction were not completely recreated. Even though no changes in the PK have been reported based on the extent of peritonectomy [21], the impact of the presence vs absence of peritonectomy on PK has not been studied. Future studies in this line, including peritonectomy in rats, can help to confirm the presented results in this work. The results of our study concluded that LIHI affects the oxaliplatin elimination and its distribution from blood to peripheral tissues in Wistar rats, causing an increased systemic drug exposure, reflected through the significant increase in $AUC_{pla\ 0-\infty}$. Thus, comparison in clinical practice of oxaliplatin PK parameters obtained after a single iv administration with those obtained after HIPEC interventions must be done carefully. This would limit the use of iv PK parameters to simulate new scenarios for oxaliplatin in HIPEC.

6. ACKNOWLEDGEMENTS

The authors would like to acknowledge the Animal Experimentation Service of San Juan de Alicante, UMH, for all the assistance received.

7. FUNDING

This study was funded by the Fundación Navarro Tripodi and from Proyecto Bancaja-UMH. The funding sources had no involvement in study design, collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

8. COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical approval: All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Research involving animals: Development of experimental model was held at the Animal Experimentation Service of San Juan de Alicante, attached to Miguel Hernández University of Elche (UMH). At the end of the procedure, rats were sacrificed. Care of the animals and drug administration were performed under veterinary control according to European Union Directive 2010/63/EU for animal experiments and with approval from the Ethics Committee of the UMH.

9. REFERENCES

1. Sugarbaker PH (1999) Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol 43:S15–S25
2. Dedrick RL, Flessner MF (1997) Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst 89:480–487
3. Elias D, Gilly F, Boutitie F et al (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric french study. J Clin Oncol 28:63–68
4. Elias D, Bonnay M, Puizillou JM et al (2002) Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 13:267–272
5. Pérez-Ruixo C, Peris JE, Escudero-Ortiz V et al (2014) Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol 73:1009–1020. doi:10.1007/s00280-014-2436-6

6. Gesson-Paute A, Ferron G, Thomas F et al (2008) Pharmacokinetics of oxaliplatin during open versus laparoscopically assisted heated intraoperative intraperitoneal chemotherapy (HIPEC): anexperimental study. Ann Surg Oncol 15:339–344. doi:10.1245/ s10434-007-9571-9

7. Ferron G, Dattez S, Gladieff L et al (2008) Pharmacokinetics of heated intraperitoneal oxaliplatin. Cancer Chemother Pharmacol 62:679–683. doi:10.1007/s00280-007-0654x

8. Pestieau S, Belliveau JF, Griffin H et al (2001) Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies. J Surg Oncol 76:106–114

9. Pelz JOW, Doerfer J, Hohenberger W et al (2005) A new survival model for hyperthermic intraperitoneal chemotherapy (HIPEC) in tumor-bearing rats in the treatment of peritoneal carcinomatosis. BMC Cancer 5:56. doi:10.1186/1471-2407-556

10. Escudero-Ortiz V, Duart-Duart MJ, Pérez-Ruixo C et al (2014) Stability study of oxaliplatin and doxorubicin for intraperitoneal administration with hyperthermia. Farm Hosp 38:154–161. doi:10.7399/fh.2014.38.3.1170

11. Beal SL, Sheiner LB, Boeckmann AJ et al (eds). (1989–2013) NONMEM 7.3.0 users guides. ICON development solutions, Hanover, Maryland, USA

12. R Studio Team (2015) RStudio: Integrated Development for R. R Studio, Inc, Boston, MA. URL http://www.rstudio.com/.

13. R Core Team (2016) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/.

14. Karlsson MO, Savic RM (2007) Diagnosing model diagnostics. Clin Pharmacol Ther 82:17–20

15. Bergstrand M, Hooker AC, Wallin JE et al (2011) Predictioncorrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 13:143–151. doi:10.1208/s12248-011-9255-z

16. Gremonprez F, Willaert W, Ceelen W (2014) Intraperitoneal chemotherapy (IPC) for peritoneal carcinomatosis: review of animal models. J Surg Oncol 109:110–116. doi:10.1002/jso.23464

17. Jing L, Kraut EH, Balcerzak S et al (2001) Dosing sequencedependent pharmacokinetic interaction of oxaliplatin with paclitaxel in the rat. Cancer Chemother Pharmacol 50:445–453. doi:10.1007/s00280-002-0531-6

18. Van der Speeten K, Stuart OA, Mahteme H et al (2010) Pharmacology of perioperative 5-fluorouracil. J Surg Oncol 102:730– 735. doi:10.1002/jso.21702

19. Sladen RN (1987) Effect of anesthesia and surgery on renal function. Crit Car Clin 3:373–393

20. Mustafa S, Abdelhamid HE, Essam H et al (2007) Hyperthermia alters kidney function and renal scintigraphy. Am J Nephrol 27:315–321. doi:10.1159/000102597

21. de Lima Vazquez V, Stuart OA, Mohamed F et al (2003) Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics. Cancer Chemother Pharmacol 52:108–112. doi:10.1007/s00280-003-06268

Anexo III-1. Archivo control NM-TRAN y output abreviado de NONMEM correspondiente al modelo final.

Anexo III-2. Reprint publicación original.

UNIVERSITAS
Miguel
Hernández

CAPÍTULO IV

UNIVERSITAS
Miguel
Hernández

CAPÍTULO IV

(Submitted) Original Research Article

Population Pharmacokinetics of Oxaliplatin after Intraperitoneal Administration with Hyperthermia in Wistar Rats

María Isabel Mas Fuster[1*], Amelia Ramón López[1*], Javier Lacueva[2], Antonio Compañ[2], Patricio Más Serrano[1,3], Ricardo Nalda Molina[1]

1. Division of Pharmacy and Pharmaceutics, Department of Engineering, School of Pharmacy, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.
2. Department of Pathology and Surgery, School of Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.
3. Clinical Pharmacokinetics Unit, Pharmacy Department, Hospital General Universitario de Alicante, Alicante, Spain.

*M.I. Mas-Fuster and A. Ramon-Lopez contributed equally to the article as first authors.

Submitted to AAPS J

Impact Factor 2015	3,819
Pharmacology and Pharmacy (Q1)	Rank: 50/255

UNIVERSITAS
Miguel
Hernández

1. ABSTRACT

Introduction: The evaluation of the efficacy and toxicity of hyperthermic intraoperative peritoneal chemotherapy presents some difficulties, due in part to the lack of information about the pharmacokinetic behavior of the drugs administered in this procedure. The aim of this study was to characterize the population pharmacokinetics of hyperthermic intraoperative peritoneal oxaliplatin in Wistar rats and to evaluate the effect of treatment-related covariates dose, instillation time and temperature on the pharmacokinetic parameters. Methods: Oxaliplatin peritoneal and plasma concentrations from 37 rats treated by either intravenous or intraperitoneal oxaliplatin administrations under different instillation times, temperatures and doses were analyzed according to a population pharmacokinetic approach using the software NONMEM V7.3®. Results and Discussion: Intraperitoneal (n=115) and plasma (n=263) concentrations were successfully described according to a two-compartment model with first order absorption. No significant effect of dose, temperature and instillation time on pharmacokinetic parameters was found. However, an abrupt decrease in the elimination process was observed, reflected in the structural pharmacokinetic model through a modification in clearance. The typical parameters values and the interindividual variability (CV %) in clearance, central volume and peripheral volume were 3.25 mL/min (39.1%), 53.6 mL (37.8%) and 54.1 mL (77.3%), respectively. Clearance decreased to 0.151 mL/min (39.1%) when the instillation was still ongoing, at 31.4 minutes. Conclusion: This study described the deterioration of the drug elimination process due to the procedure, and estimated the time at which this deterioration is most likely to occur. In addition, dose, instillation time and temperature had no influence in the PK parameters.

Keywords

- Population pharmacokinetics
- Oxaliplatin
- Intraperitoneal chemotherapy
- Peritoneal metastasis
- Animal models

2. INTRODUCTION

Peritoneal metastasis (PM) is a frequent site of dissemination of colorectal and gastric cancer. The PM treatment based on systemic chemotherapy is considered palliative (1). However, a different treatment strategy including complete cytoreductive surgery (CRS) and hyperthermic intraoperative peritoneal chemotherapy (HIPEC), followed by systemic chemotherapy (2), has demonstrated to improve survival of selected patients with a limited peritoneal carcinomatosis index (3-5).

The aim of CRS is to remove all visible tumor nodules within the abdominal cavity, while HIPEC eliminates the residual tumor cells. The addition of hyperthermia in the instillation solution has proved to increase the drug transport across membranes, accelerate the cell damage and generate free oxygen radicals (6). Oxaliplatin is one of the drugs that fits the requirements to be used in HIPEC, with a high molecular weight that allows to maintain the concentration in the peritoneal cavity, heat synergy and good depth penetration profile, around 1-2 mm (7,8).

The evaluation of the potential superiority of HIPEC over other treatments is troublesome due to the heterogeneity of the administration protocols among the different surgical teams worldwide, concerning the drug selection, dose, level of hyperthermia, carrier solution and duration of the instillation (9-17). However, few of them have evaluated the impact of those variables in the systemic absorption and the toxicity derived from this absorption (13,16,17). Randomized clinical trials may adequately answer the questions related to the impact of components on different endpoints but, as pointed out by Sugarbaker, they are not likely to be completed in a timely manner, given the difficulties of being carried out (18,19). Instead, reviews establishing theoretical considerations for HIPEC as well as animal models are proposed as an alternative to the clinical studies (20).

Development of suitable animal models contributes to evaluate the impact of the multiple components in HIPEC separately and gives useful information for future clinical research. To date, models in rat and pig have studied pharmacokinetics (PK), tumor growth and survival with different drugs (20), given that PK models provide a better understanding of the involved mechanisms (21). However, any of the studies with oxaliplatin considers the population PK approach in the data analysis.

Therefore, the aim of this study was to characterize the population PK model of hyperthermic intraoperative peritoneal oxaliplatin (HIPEO) in Wistar rats, by jointly analyzing the time course of oxaliplatin concentrations in peritoneum and plasma after intraperitoneal (ip) and intravenous (iv) administrations. The effect of treatment-related covariates dose, instillation time and temperature was also evaluated.

3. MATERIAL AND METHODS

Animals

The PK of oxaliplatin was characterized in healthy male Wistar rats weighing on average 267 ± 22 g (mean ± standard deviation, SD), kept in the standard housing conditions with free access to water and a fasting day before surgery. The development of the experimental model, previously validated in rat (22), was held at the Animal Experimentation Service of San Juan de Alicante, associated with Miguel Hernández University of Elche (UMH). At the end of the procedure, rats were sacrificed. Care of the animals and drug administration was performed under veterinary control according to European Union Directive 2010/63/EU for animal experiments and with approval from the Ethics Committee of the UMH.

Study Design

For the design of the experiment, the sample size was estimated to be 42 rats. Rats were randomly allocated in six groups (G1-G6) and submitted to different experimental conditions of temperature, instillation time or dose (Table I). As a common procedure, all of rats underwent an intraperitoneal hyperthermic instillation (LIHI) with 100 mL of 5% dextrose solution under anesthetic conditions. Out of them, 36 were assigned to receive HIPEO administration, carried by the heated 5% dextrose solution, as used in HIPEC procedure.

In addition, to allow determination of the fraction of dose absorbed (F), six rats of one additional group (G7) were administered with one dose of iv oxaliplatin undergoing LIHI procedures, without adding oxaliplatin in the instillation solution. This procedure ensured that iv administrations were done at similar surgical conditions to the HIPEC groups (23).

The iv dose of oxaliplatin was 1.5 mg, based on previous experimental studies (24). Two different ip concentrations of 100 mg/L and 200 mg/L were evaluated. These concentrations are within the range of the concentrations used in clinical settings. No addition of carrier solution was done during the procedure in order to maintain original concentrations.

To evaluate the influence of temperature on oxaliplatin PK, three different instillation ranges of temperatures were selected: 38-40 ºC, 40-42 ºC and 42-43 ºC. To evaluate the influence of instillation time on oxaliplatin PK, three different instillation times were selected: 30, 45 and 60 minutes.

Considering that the standard schedule applied in the clinical settings is the administration of oxaliplatin under 42 ºC for 30 minutes (25), this schedule was selected as the standard conditions for G3, G4, G6 and G7.

Table I. Experimental groups according to doses, instillation time and temperatures. n: number of subjects.

Oxaliplatin route of administration	Temperature (ºC)	Instillation time (minutes)	Dose (mg)		
			10	20	1.5
Intraperitoneal	38 - 40	30	G1 (n=6)		
	40 - 42	30	G2 (n=6)	G6 (n=6)	
		45	G3 (n=6)		
		60	G4 (n=6)		
	42 - 43	30	G5 (n=6)		
Intravenous	40 - 42	30			G7 (n=6)

Surgical Procedure

All rats were operated under general anesthesia, induced by isoflurane (Isovet®) with oxygen vaporization. Intensity was regulated during the induction and maintenance phases (Fluovac®, Surgivet®). To avoid hypothermia induced by the anesthesia and by the laparotomy, rats were placed in the surgical area on a thermal blanket. Buprenorphine (Buprex® 0.3 mg/mL) was administered as analgesic at a subcutaneous dose of 0.05 mg/kg.

A permanent jugular vein catheterization was performed to all rats, as previously described (26), to allow blood sampling and also to administer iv oxaliplatin in G7. To balance the blood loss and to prevent the catheter obstruction, the catheter was rinsed with 0.2 mL of saline and filled with a 60% polyvinylpyrrolidone solution with heparinized saline (500 IU/mL) after each extraction.

In all the groups, a laparotomy from the pubic symphysis to the xiphoid cartilage was made to simulate the open Coliseum technique proposed by Sugarbaker, meaning open abdomen and closed circuit (22,27). The skin of the abdomen was attached to a retractor structure and covered with saline solution coated dressings to avoid drying. Before the beginning of HIPEC, a choledochus ligature was done in all the rats in order to interrupt enterohepatic recirculation (28,29,30).

To perform recirculation of the solution, inlet and outlet drains were placed in the abdominal cavity, creating a closed circuit with the reservoir. The volume of the instillation solution was 100 mL of 5% dextrose. The instillation solution was heated by using a thermostatic bath (JpSelecta®). Once the reservoir volume reached the target temperature,

recirculation of the solution started for the corresponding instillation times at 50 mL/min using an infusion pump (Masterflex® L / S EasyLoad 77202-50) (Fig 1).

Temperature of the instillation solution in the abdominal cavity was monitored during the procedure. Once the HIPEC finalized, volume remaining in the peritoneal cavity was drained and the abdominal cavity was closed.

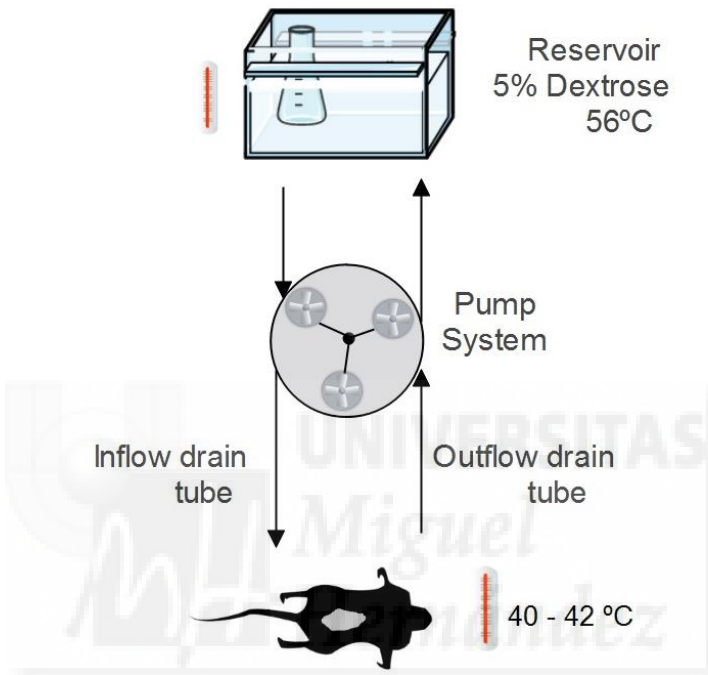


Fig 1. Diagram of the experimental setup. One inflow and one outflow drain tubes were placed in the abdomen and connected to the pump system.

Collection of samples and bioanalytical procedure

Blood samples were taken after the administration of oxaliplatin at times 1, 10, 20, 30, 45, 60, 90, 150, 270 and 510 minutes and the total volume of these samples was kept to 0.2 mL with volume replacement during each sample extraction. Three peritoneal fluid samples per rat were taken, one at the beginning of the instillation, in order to know the actual initial peritoneal concentration of oxaliplatin, one in the middle of the procedure and one at the end of the HIPEC, depending on instillation time scheduled. Samples were collected in heparin tubes and immediately centrifuged for 10 minutes at room temperature. Samples were

collected in heparin tubes, centrifuged at room temperature and stored at -20°C until their analysis.

Total platinum was measured by a validated graphite furnace atomic absorption spectrophotometry method (31). The analytical technique employed has a limit of quantification of 0.06 mg/L of oxaliplatin. All the results were expressed as oxaliplatin concentrations in mg/L.

Pharmacokinetic model development

Software. A population PK modeling approach was applied to the data using the first order conditional (FOCE) method implemented in NONMEM version 7.3 (32), with the ADVAN 6 routine. Post-processing of the model results and diagnostic plots were performed with R 3.3.2 (33), implemented in R-studio (34).

Structural model building. Based on a preliminary graphical analysis, HIPEO was assumed to be absorbed into the plasma according to a linear process, characterized by the first order absorption rate constant (k_a). ka was calculated as a secondary parameter of the peritoneum to plasma clearance (Q_1) and the volume of distribution in the peritoneum, considered as V_1, fixed to 100 mL.

An open, two-compartment model with linear elimination and linear distribution from the central to peripheral compartment (compartments 2 and 3, respectively) was selected to describe the oxaliplatin plasma concentrations after ip and iv administrations. This model was parameterized in terms of clearance (CL), central volume of distribution (V_2), intercompartmental clearance (Q_2) and volume of distribution of the peripheral compartment (V_3).

Preliminary graphical analysis showed a sharp inflection point in the course of the oxaliplatin plasma concentrations before the end of instillation and thus, before the achievement of the maximum drug plasma concentration (C_{max}). Initial hypothesis for this phenomenon were based on the change in disposition processes at a certain time or the increase of the permeability of the peritoneum, causing the corresponding increase in the oxaliplatin plasma concentrations. These hypothesis were translated into a step function in time, consisting on a sigmoid function with high sigmoidicity factor (35) (Eq 1). The step function was used to explore, in a continuous way, a quick change in distribution and/or elimination processes or the enhanced absorption process, reflected through a change in CL, V_2, V_3 or k_a:

$$STEP = \frac{TIME^{SIG}}{T_{50}{}^{SIG} + TIME^{SIG}} \quad (1)$$

where *TIME* is the dependent variable, T_{50} is the population estimate for the inflection time point, and *SIG* is the sigmoidicity factor, fixed to the value of 20. An example of the use of the step function is showed in Eq 2- 4 for CL, modelled through the elimination rate constant (k_{el}).

$$CL_1 = THETA\ (1) * EXP(ETA(1)) \quad (2)$$

$$CL_2 = THETA\ (2) * EXP(ETA(1)) \quad (3)$$

$$k_{el} = \frac{CL1}{V_2} + \left(\frac{CL2}{V_2} - \frac{CL1}{V_2}\right) * STEP \quad (4)$$

Stochastic model building. Taking into account the population model, variability of PK parameters between rats (interindividual variability, IIV) was assumed to follow a log-normal distribution in all population parameters, therefore, an exponential error model was used:

$$P_i = THETA * \exp(n_i) \quad (5)$$

Being $THETA$ the population estimate for parameter P, P_i is the individual estimate and n_i is the normally distributed between-subject random variable with mean zero and variance Ω^2.

Residual variability was evaluated using an additive error model after natural logarithmic transformation of the measured concentrations and model predictions, according to Eq 6. Magnitude of the residual and interindividual variability was expressed as coefficient of variation (CV%):

$$Y_{ij} = IPRED + W1 * EPS(1) * (1 - TYPE) + W2 * EPS(2) * TYPE \quad (6)$$

where Y is the *jth* observed concentration in the *ith* individual, $IPRED$ is the predicted concentration and $W1$ and $W2$ are the SD of the normally distributed residual random variable for peritoneal and plasma concentrations, respectively, with mean zero and variance, Σ^2.

Model selection criteria. Model selection was based on the likelihood ratio test, using the improvement of the fit obtained for each model by NONMEM-generated minimum value of the objective function (MVOF); MVOF equal to minus twice the log likelihood of the data. The significance level was set to p-value=0.01, one degree of freedom (df), which corresponds to a decrease in MVOF of ≥6.64 points after the inclusion of one parameter, assuming that the difference in minimum value of the MVOF between two nested models is χ^2 distributed.

In addition, improvement of the fit was assessed by the reduction in the IIV and residual variability, parameter relative standard errors (RSE%) <50%, normalized prediction distribution errors (NPDE), correlation in parameter estimates and the examination of shrinkage. Based on the FOCE approximation, any individual observation with an absolute conditional weighted residual (CWRES) >6 was identified as statistical outlier, as the CWRES has a mean zero and

unit variance (36). The visual inspection of the classic goodness-of-fit plots was employed to detect bias in model fits: individual and population estimates vs observed concentrations as well as CWRES and NPDE vs time or population predicted values. Once the population PK model that best described the data was established, it was followed by covariate analysis and model validation.

Covariate analysis. In explaining part of the IIV, a covariate analysis was performed. In the absence of significant shrinkage, meaning lower than 30% (37), empirical Bayes estimates (EBE) of the interindividual random effects were used to identify potential relationships between individual PK estimates and the experimental covariates, instillation time, temperature and dose. Dose was indirectly evaluated by the initial concentration in the peritoneal fluid. These covariates were first examined using scatterplots and then added to and removed from the population model in a stepwise manner (38). Again, a change of at least 6.64 points in the MVOF was required to consider the parameter significantly dependent of the covariate. Once the structural model was identified, EBE were computed.

To analyze the statistical power of the study design for detecting clinically relevant effects of these covariates on the PK parameters, 1000 stochastic simulations of the final model were performed, including an effect of 30% of change in the parameters for every 10 minutes of instillation time, 1ºC in the temperature or 10 mg/L in the dose. Then, the 1000 datasets simulated were fitted to the same model used in the simulation and also to the model without the covariate effect. Finally, the improvement in the MVOF was calculate to each simulation, and considered “positive” if greater than 6.64 or “negative” if not. The percentage of positives in the 1000 simulation for every covariate was considered to be the statistical power for each covariate.

Model validation. A nonparametric bootstrap analysis (NPBS) (39) and a prediction-corrected visual predictive check (pcVPC) (40) were used as internal evaluation methods to qualify the robustness and the predictive performance.

The NPBS was made after the generation of 1000 databases by random sampling with replacement by using the software WINGS for NONMEM (N. Holford, Version 616, Auckland, New Zealand). The mean and the 95% CI of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset. pcVPC was based on 1000 simulations of the oxaliplatin plasma concentrations from PK parameters obtained. Thus, observed and simulated oxaliplatin plasma concentrations were graphically compared.

4. RESULTS

Exploratory analysis

The experiment was well tolerated in all groups except G5. Rats of G5 showed a rapid deterioration after the procedure and died at early post-instillation times. Thus, for ethical reasons, and following the recommendations of the members of the ethical committee, experiments in these group were stopped, being the final sample size of G5 n=3. One of the rats from G6 and one from G7 died during the surgical procedure for unknown etiology. Concentration-time profiles for all the scenarios are depicted in Fig 2.

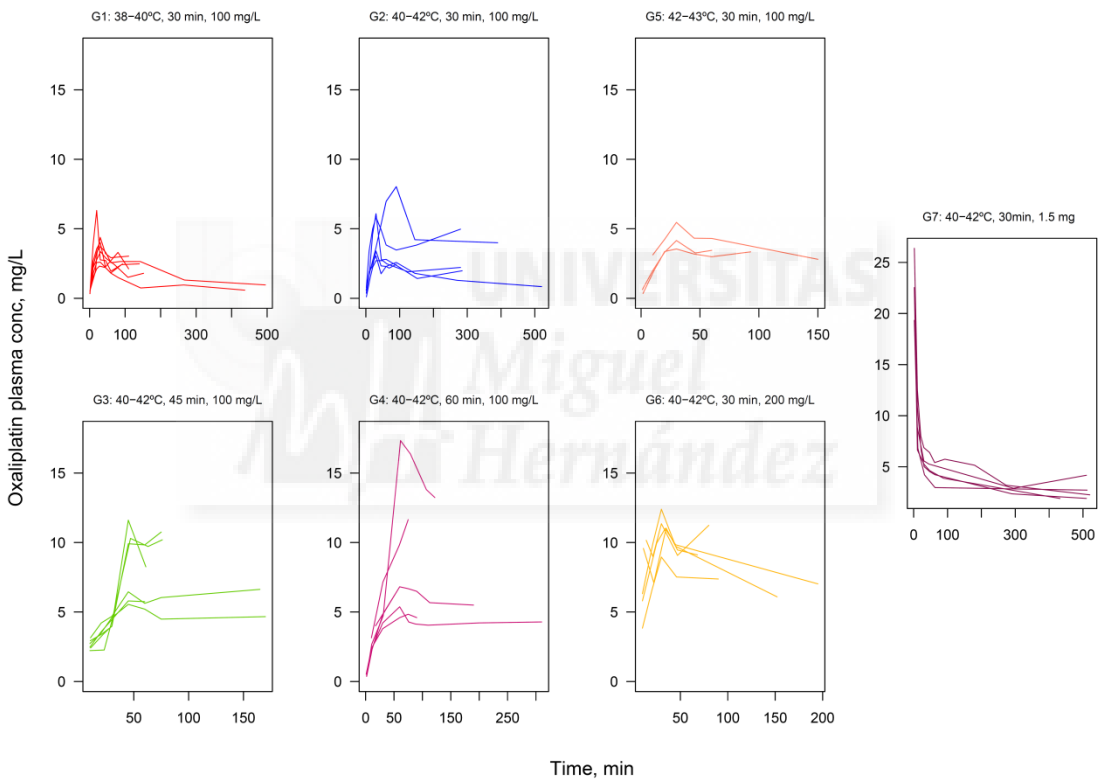


Fig 2. Oxaliplatin concentration-time profiles for different scenarios of the study.

A total of 115 and 263 oxaliplatin concentrations from peritoneum and plasma, respectively, were available to describe oxaliplatin PK. Mean of the oxaliplatin C_{max} (±SD) and

mean area under the plasma concentration-time curve from zero to infinite ($AUC_{0-\infty}$) (±SD) for each group are summarized in Table II.

Table II. Mean plasma C_{max} (±SD) and mean plasma $AUC_{0-\infty}$ (±SD) for each group of rats

Group	C_{max} (±SD) mg/L	$AUC_{0-\infty}$ (±SD) mg*min/L
G1 (n=6)	3.81 (1.33)	2210 (1050)
G2 (n=6)	4.85 (2.13)	3500 (1540)
G3 (n=6)	8.03 (2.91)	4370 (1370)
G4 (n=6)	8.71 (4.88)	7830 (1090)
G5 (n=3)	4.39 (0.98)	2620 (643)
G6 (n=5)	11.0 (1.3)	6240 (480)
G7 (n=5)	22.5 (2.5)	3730 (1360)

The peritoneal oxaliplatin concentrations observed during the instillation were in a range of 66.8-142 mg/L and 124-256 mg/L for 100 and 200 mg/L administrations, respectively. The evaporation of the carrier solution was not significant, since the residual volume after each procedure was measured and considered close to 100% of the initial volume in all the rats.

Population pharmacokinetic analysis

Oxaliplatin plasma concentrations after ip and iv administrations were jointly analyzed to allow an integrated modelling. The population PK analysis of oxaliplatin was best described by an open two-compartment disposition model with non-specific distribution to a peripheral compartment, linear elimination from the central compartment and first-order absorption from peritoneum to plasma, which is in agreement with other studies regarding HIPEO (13,16).

However, the plasma concentration profile showed an inflection point between 30 and 45 minutes, while the instillation was still ongoing, increasing the slope (e.g. ID18, ID21, ID22 or ID28 in Fig 3). A statistically significant decrease in the MVOF of -50.4 points (*df*=3; *p*-value<0.001) was observed when the final structural model included a decrease of the CL during the instillation, modelled through a step function on k_{el}. Including additional step functions in microconstants k_{23}, k_{32} or in k_a did not significantly improve the fit. This PK model

successfully fitted the time course of oxaliplatin plasma concentrations after iv and ip administrations for different instillation times (Fig 3).

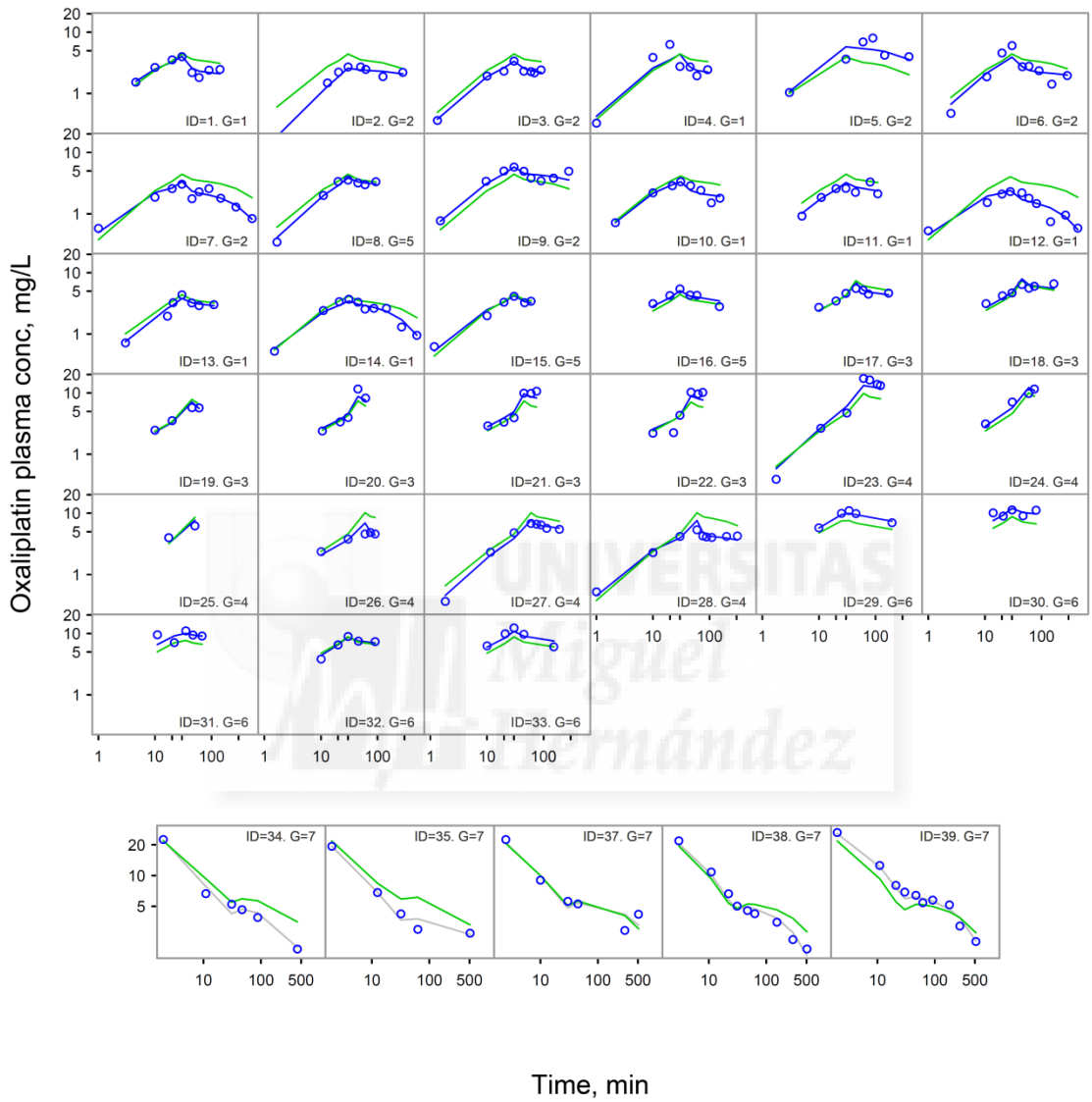


Fig 3. Individual oxaliplatin plasma concentration-time profiles. Upper and lower panels represent the ip and iv oxaliplatin administrations, respectively. Circles represent the observed plasma concentrations while the blue and green lines represent the individual and the population predictions, respectively.

In addition, other absorption models were tested, such as lag time or transit compartments models (35,41). However, the fit of these models did not result in a significant decrease in the MVOF, and the change in the slope was not visually well captured. The change in the slope could have also been explained by the late entrance of part of the HIPEO dose, accumulated as

a depot. This hypothesis was also tested by using models with a depot compartment. Although this model improved the MVOF and the goodness of fit plots, compared with a basic two-compartment structural model, it resulted over-parameterized, as well as the MVOF (ΔMVOF=32.19 points, *df*=2*, p*-value<*0.01*) was worse than the final model proposed in this manuscript. Enterohepatic recirculation (28) was not tested as a structural part of the model because a choledochus ligature was performed in all the rats.

The final estimates of the PK model parameters and the results of the NPBS are presented in Table III. IIV was estimated for CL, V_2 and V_3. The shrinkage values were lower than 30% in all the IIV. Values of CL_1 and CL_2 were 3.25 mL/min and 0.15 mL/min, respectively. T_{50} is defined as the time at which CL_1 changed into CL_2, and it was estimated to be 31.4 minutes. This result agrees with the visual detection of this change in rats undergoing 45 or 60 minutes of instillation. Volumes of distribution, V_2 and V_3, were estimated in 53.6 mL and 54.1 mL, respectively while k_a was estimated to be of 0.00864 min^{-1} (peritoneal $t_{1/2}$ = 80.2 min). Estimation of F after ip administrations was not significantly different from 100%.

Table III. Parameter estimates and bootstrap analysis of the oxaliplatin population pharmacokinetic model.

Model parameters	Original dataset Estimate[a] (RSE)	Nonparametric Bootstrap	
		Mean (RSE)[a]	95% CI
Fixed effect parameters			
CL_1 (mL/min)	3.25 (16.3)	3.18 (17.2)	2.00 - 4.14
CL_2 (mL/min)	0.151 (19.1)	0.154 (21.9)	0.0950 - 0.237
V_1 (mL)	100 FIX	100 FIX	-
Q_1 (mL/min)	0.864 (11.3)	0.866 (12.3)	0.660 - 1.09
V_2 (mL)	53.6 (13.4)	54.0 (14.3)	39.9 - 69.4
Q_2 (mL/min)	3.66 (28.4)	3.76 (34.0)	1.67 - 6.38
V_3 (mL)	54.1 (35.3)	54.5 (35.9)	22.1 - 98.8
T_{50} (min)	31.4 (2.70)	32.3 (8.80)	30.3 - 43.1
Between subject variability (η)[b]			
η_{CL}	39.1 (21.8)	36.9 (29.5)	15.2 - 59.3
η_{V2}	37.8 (24.5)	34.9 (29.7)	14.2 - 53.2
η_{V3}	77.3 (21.8)	78.9 (25.2)	46.9 – 125
Residual variability[b]			
Peritoneal	13.3 (9.64)	13.3 (9.64)	10.9 - 16.0
Plasma	20.0 (7.92)	19.7 (8.36)	16.7 - 23.0

Shrinkage values (%) of IIV in CL, V_2 and V_3 were estimated at 27.3, 18.1, and 17.6.

[a] Results expressed as parameter (RSE: relative standard error of the parameter estimate, %).

[b] Results expressed as coefficient of variation, CV %.

Covariate analysis. Within the range of covariate values analyzed, the graphical and statistical analyses evidenced no effect of dose, temperature and instillation time on the PK model parameters. The statistical power calculated for the study design to detect clinically relevant changes in the PK parameters due to the studied covariates was greater than 80% in all the scenarios.

Model evaluation. There was good association between the observed and predicted concentrations, indicating the absence of significant bias or model misfit. Similarly, no obvious trends in the CWRES or in the NPDE, indicating model inadequacy, were detected for the plasma concentrations (Fig 4) or for the peritoneal concentrations (Fig 5). In fact, the mean (±SD) and its confidence interval (CI) of the NPDE of peritoneal concentrations was 0.04 (95% CI -0.16:0.21) and 0.99 (95% CI 0.86:1.17), respectively. Likewise, for plasma concentrations these results were -0.0006 (95% CI -0.12:0.11) and 0.96 (95% CI 0.88:1.06), respectively. These results confirmed that observations were accurately predicted by the model without bias.

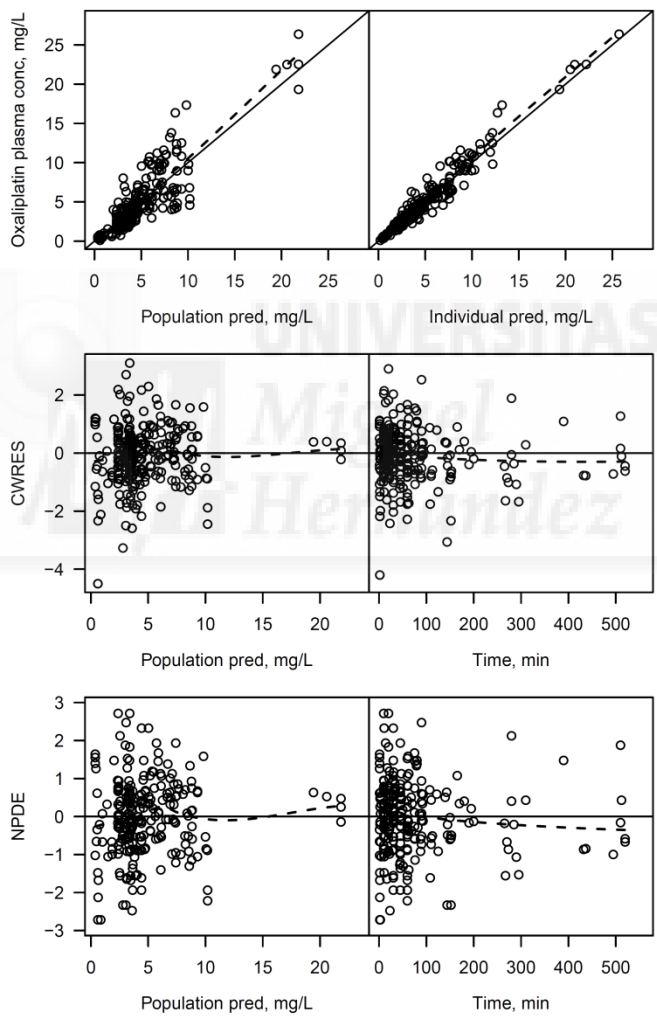


Fig 4. Final model diagnostic plots of the PK model for oxaliplatin plasma concentrations. Upper panels, association between observed and predicted concentrations; middle and lower panels, CWRES and NPDE, respectively, vs time and population predicted values.

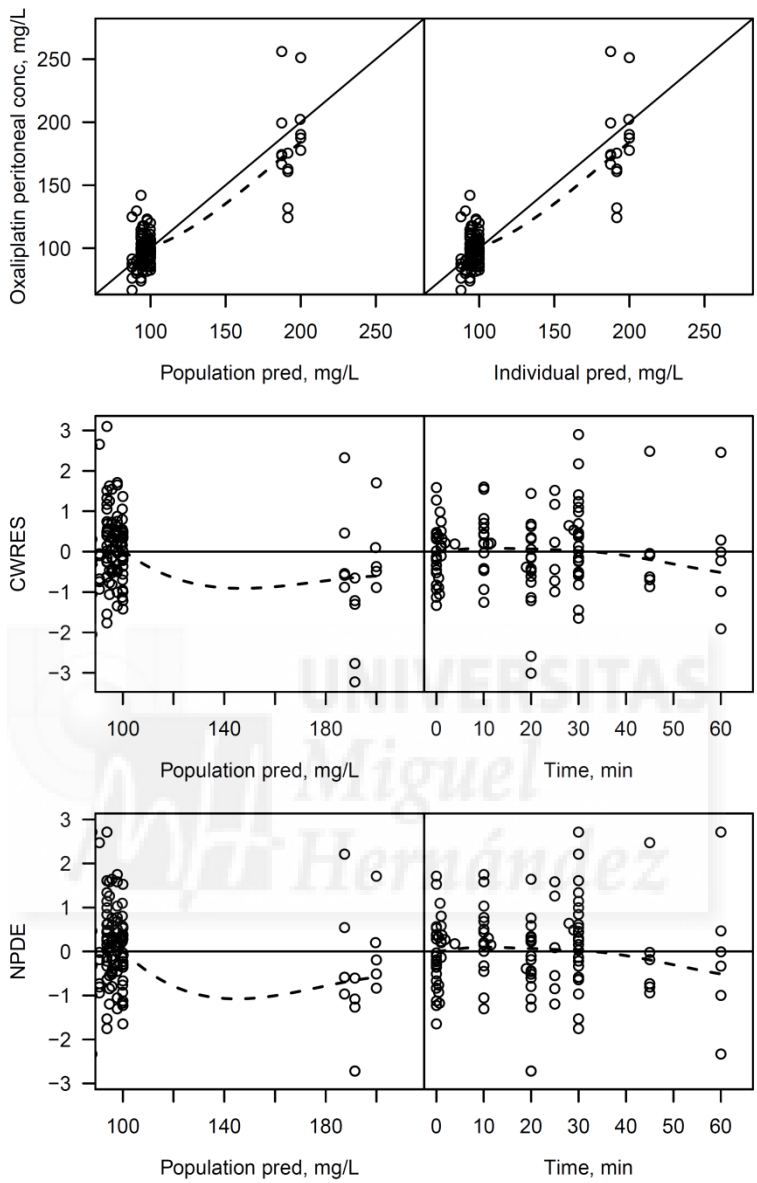


Fig 5. Final model diagnostic plots of the PK model for oxaliplatin peritoneal concentrations. Upper panels, association between observed and predicted concentrations; middle and lower panels, CWRES and NPDE, respectively, vs time and population predicted values.

From 1000 replicates analyzed during the NPBS analysis, 2.2% failed to minimize successfully and were excluded from the analysis. The population estimates for the final model were similar to the mean of the NPBS replicates that minimized successfully and were contained within the 95% CI. The precision of the parameter estimates, based on the RSE%

calculated from the bootstrap analysis, were lower than 36% for fixed effects and lower than 30% for random effects.

In addition, the results of the pcVPC depicted in Fig 6 evidenced that the model developed was appropriate to describe the time course of oxaliplatin plasma concentrations and their associated variability.

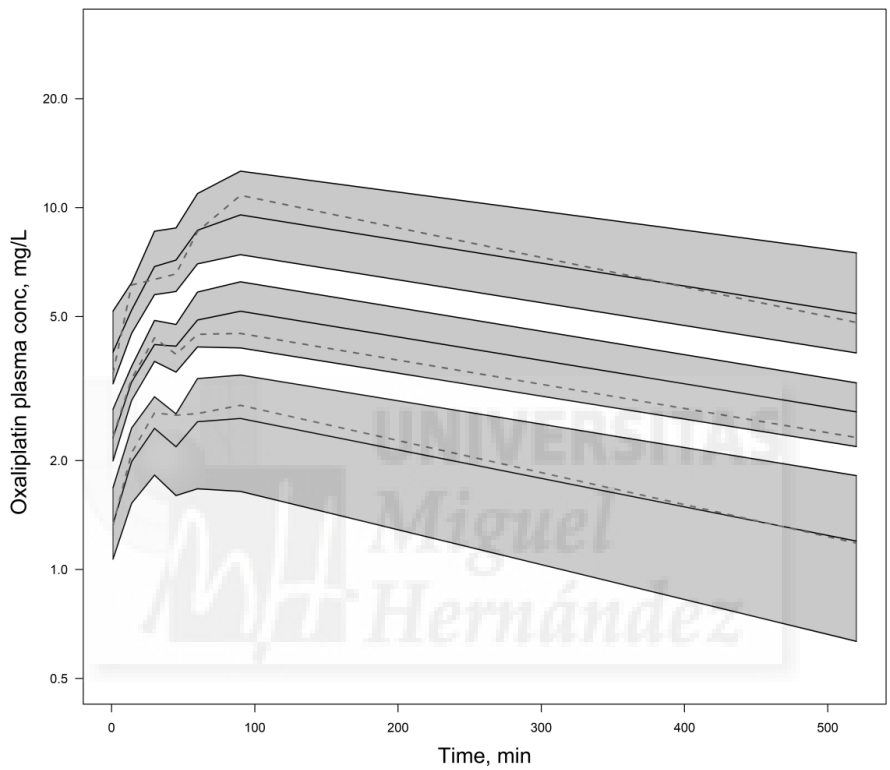


Fig 6. Model validation. pcVPC, showing the 5th, 50th, and 95th percentiles of the observed values (dashed lines), and the 95% CI for the corresponding model-based predicted percentiles (solid lines).

5. DISCUSSION

This is the first time that a population PK model for oxaliplatin after ip hyperthermic instillation has been studied in experimental models. The population PK of oxaliplatin was well described by a two-compartment model with non-specific distribution to a peripheral compartment, linear elimination from the central compartment and first-order absorption from peritoneum to plasma. Dose, instillation time and temperature had neither significant impact on PK parameters, according to the MVOF, nor impact in decreasing the IIV of the parameters, these results being in line with other studies (16,42-46).

However, the profile of HIPEO plasma concentrations was unusual in some rats, with an increase in the slope while the instillation was still ongoing. Thus, the structural model was updated to describe, for the first time, a deterioration of drug elimination mechanisms, reflected through a change in the parameter CL. These findings are in line with the alteration of renal function attributed to surgery and/or hyperthermia observed in other studies (47-49). A previous study showed that rats undergoing a similar surgical procedure had significant lower CL and V_2 than those that were not submitted to surgery (23). Moreover, there is no literature regarding the identification of the time at which this deterioration begins, neither at preclinical experiments nor in clinical settings, except for one study that evaluated the impact of the duration of the whole surgical procedure (50) including cytoreduction steps on the PK parameters. The CL_1 and CL_2 values obtained in our study are different from the value obtained in other experimental study in rats receiving oxaliplatin in similar surgical conditions (23). However, it must be pointed out that the mean CL in our study was estimated to be 0.49 mL/min when no step function was added to the model, which agrees with the results obtained in that study.

Most of the surgical teams establish the instillation times of the drugs employed in HIPEC from an empirical basis. Some studies justified somehow the duration of the instillation, attending to its peritoneal $t_{1/2}$ (16,19). But any study has considered the impact of the surgical procedure and the instillation on the PK parameters, and therefore, on the exposure of the drug and its toxicity. The knowledge of the time when the impact on the renal function becomes clinically relevant could be helpful and should be considered when choosing the duration of the instillation. However, clinical studies must be done to evaluate if this phenomenon also occurs in patients.

One of the limitations of our study is related to the high mortality observed in G5, that can be attributed to the high level of hyperthermia applied to this group (51,52). Thus, the results of the covariate analysis regarding temperature obtained in this study should be restricted to the range of 38ºC to 42ºC. In addition, this study has been conducted in healthy rats, with no peritonectomy performed, and therefore, actual conditions of cytoreduction were not

completely recreated. The impact of the peritonectomy vs non-peritonectomy performance on PK parameters has not been studied previously, even though no changes in the PK have been reported related to the extent of peritonectomy (53).

In conclusion, this study shows the deterioration of the drug elimination process due to the HIPEC procedure, and estimates the time at which this deterioration is most likely to occur. On the other hand, our results confirm that covariates dose, instillation time and temperature had no influence in the PK parameters, in the studied range. This model may help in the understanding of how HIPEC procedure affects PK parameters and may contribute in the construction of solid hypothesis for future clinical trials.

6. ACKNOWLEDGEMENTS

The authors would like to acknowledge the Animal Experimentation Service of San Juan de Alicante, UMH, for all the assistance received.

7. REFERENCES

1. Coccolini F, Gheza F, Lotti M, Virzi S, Iusco D, Ghermandi C, et al. Peritoneal carcinomatosis. World J Gastroenterol. 2013;19(41):6979-6994.

2. Sugarbaker PH. Strategies for the prevention and treatment of peritoneal carcinomatosis from gastrointestinal cancer. Cancer Invest. 2005; 23:155-172

3. Elias D. Goere D, Dumont F, Honore C, Dartigues P, Stoclin A, et al. Role of hyperthermic intraoperative peritoneal chemotherapy in the management of peritoneal metastases. Eur J Cancer. 2014;50:332-340.

4. Verwaal V, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737-3743.

5. Glehen O, Gilly F, Arvieux C, Cotte E, Boutitie F, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17:2370-2377

6. Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, et al. The cellular and molecular basis of hyperthermia. Crit Rev Onc Hematol. 2002;43(1):33–56.

7. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, et al. Heated Intra-Operative Intraperitoneal Oxaliplatin after Complete Resection of Peritoneal Carcinomatosis: Pharmacokinetics and Tissue Distribution. Ann Oncol. 2002;13:267–72.

8. Rietbroek RC, van der Vaart PJ, Haveman J, Blommaert FA, Geerdink A, Bakker PJ, et al. Hyperthermia Enhances the Cytotoxicity and Platinum-DNA Adduct Formation of Lobaplatin and Oxaliplatin in Cultured SW 1573 Cells. J Cancer Res Clin Oncol. 1997;123:6–12.

9. Hompes D, D'Hoore A, Wolthuis A, Fieuws S, Mirck B, Bruin S, et al. The use of Oxaliplatin or Mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. J Surg Oncol. 2014;109(6):527–32.

10. Glockzin G, Gerken M, Lang SA, Klinkhammer-Schalke M, Piso P, Schlitt HJ. Oxaliplatin-based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastasis from appendiceal and colorectal cancer: a retrospective analysis. BMC Cancer. 2014;14:807.

11. Muller M, Chérel M, Dupré PF, Gouard S, Collet M. Cytotoxic effect of hyperthermia and chemotherapy with platinum salt on ovarian cancer cells: results of an in vitro study. Eur Surg Res. 2011;46:139–47.

12. Sticca RP, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. Surg Oncol Clin N Am. 2003;12(3):689–701.

13. Pérez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farré-Alegre J, et al. Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery. Cancer Chemother Pharmacol. 2013;71(3):693–704.

14. Dubé P, Sideris L, Law C, Mack L, Haase E, Giacomantonio C, et al. Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms. Curr Oncol. 2015;22(2):e100.

15. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol. 2016;29:14:128.

16. Ferron G, Dattez S, Gladieff L, Delord J-P, Pierre S, Lafont T, et al. Pharmacokinetics of heated intraperitoneal oxaliplatin. Cancer Chemother Pharmacol. 2008;62(4):679–83.

17. Pérez-Ruixo C, Peris JE, Escudero-Ortiz V, Bretcha-Boix P, Farré-Alegre J, Pérez-Ruixo JJ, et al. Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol. 2014;73(5):1009-20. doi: 10.1007/s00280-014-2436-6.

18. Elias D, Delperro J-R, Sideris L, Benhamou E, Pocard M, Baton O, et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. Ann Surg Oncol. 2004;11(5):518–21.

19. Sugarbaker PH, Van der Speeten K. Surgical technology and pharmacology of hyperthermic perioperative chemotherapy. J Gastrointest Oncol. 2016; 7(1):29–44. doi: 10.3978/j.issn.2078-6891.2015.105

20. Gremonprez F, Willaert W, Ceelen W. Intraperitoneal chemotherapy (IPC) for peritoneal carcinomatosis: review of animal models. J Surg Oncol. 2014;109(2):110–6.

21. Elishmereni M, Kheifetz Y, Søndergaard H, Overgaard RV, Agur Z. An Integrated Disease/Pharmacokinetic/Pharmacodynamic Model Suggests Improved Interleukin-21 Regimens Validated Prospectively for Mouse Solid Cancers. PLoS Comput Biol. 2011;7(9):e1002206. doi: 10.1371/journal.pcbi.1002206.

22. Pelz JO, Doerfer J, Hohenberger W, Meyer T. A new survival model for hyperthermic intraperitoneal chemotherapy (HIPEC) in tumor-bearing rats in the treatment of peritoneal carcinomatosis. BMC Cancer. 2005;5:56.

23. Mas-Fuster MI, Ramon-Lopez A, Lacueva J, Compañ A, Más-Serrano P, Nalda-Molina R. Impact of Laparotomy and Intraperitoneal Hyperthermic Instillation (LIHI) on the oxaliplatin pharmacokinetics after intravenous administration in Wistar rats. Cancer Chemother Pharmacol. 2017;1–7. doi: 10.1007/s00280-017-3244-6.

24. Pestieau SR, Belliveau JF, Griffin H, Stuart OA, Sugarbaker PH. Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies. J Surg Oncol 2001;76(2):106–14.

25. Elias D, Raynard B, Bonnay M, Pocard M. Heated intra-operative intraperitoneal oxaliplatin alone and in combination with intraperitoneal irinotecan: Pharmacologic studies. Eur J Surg Oncol. 2006;32(6):607–13.

26. Liu J, Kraut EH, Balcerzak S, Grever M, D'Ambrosio S, Chan KK. Dosing Sequence-Dependent Pharmacokinetic Interaction of Oxaliplatin with Paclitaxel in the Rat. Cancer Chemother Pharmacol.2001;50:445–53. doi:10.1007/s00280-002-0531-6.

27. Sugarbaker PH, Averbach AM, Jacquet P, Stephens AD, Stuart OA. A Simplified Approach to Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIIC) Using a Self Retaining Retractor. Cancer Treat Res. 1996;82:415–21.

28. Huntjens DRH, Strougo A, Chain A, Metcalf A, Summerfield S, Spalding DJM, et al. Population pharmacokinetic modelling of the enterohepatic recirculation of diclofenac and rofecoxib in rats. Br J Pharmacol. 2008;153(5):1072–84.

29. Roberts MS, Magnusson BM, Burczynski FJ, Weiss M. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. Clin Pharmacokinet. 2002;41:751–790.

30. Bastian G, Barrail A, Urien S. Population pharmacokinetics of oxaliplatin in patients with metastatic cancer. Anticancer Drugs. 2003;14(10):817–24.

31. Escudero-Ortiz V, Duart-Duart MJ, Pérez-Ruixo C, Pérez-Ruixo JJ, Valenzuela B. Stability study of oxaliplatin and doxorubicin for intraperitoneal administration with hyperthermia. Farm Hosp. 2014;38:154–61. doi:10.7399/fh.2014.38.3.1170.

32. Beal S, Sheiner LB, Boeckmann A, & Bauer RJ, NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

33. R Core Team 2016. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/.

34. RStudio Team 2015. RStudio: Integrated Development for R. RStudio, Inc., Boston, MA. URL

35. Hénin E, Bergstrand M, Standing JF, Karlsson MO. A mechanism-Based Approach for Absorption Modeling: The Gastro-Intestinal Transit Time (GITT) Model. AAPS J. 2012;14(2):155–63.

36. Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007;82(1):17–20.

37. Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009;11(3):558–69.

38. Wahlby U, Jonsson EN, Karlsson MO. Comparison of stepwise covariate model building strategies in population pharmacokinetic-pharmacodynamic analysis. AAPS PharmSci. 2002;4:E27.

39. Efron B, Tibshirani R. An introduction to the bootstrap. New York: Chapman & Hall/CRC; 1993.

40. Bergstrand M, Hooker AC. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J. 2011;13:143–51.

41. Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34(5): 711–26.

42. Sladen RN. Effect of Anesthesia and Surgery on Renal Function. Crit Car Clin. 1987;3:373–93.

43. Mustafa S, Elgazzar AH, Essam H, Gopinath S, Mathew M. Hyperthermia alters kidney function and renal scintigraphy. Am J Nephrol. 2007;27(3):315–21.

44. Ceresoli M, Coccolini F, Ansaloni L. HIPEC and nephrotoxicity: A cisplatin induced effect? Eur J Surg Oncol. 2016 Jun;42(6):909-10. doi: 10.1016/j.ejso.2015.08.174.

45. van Ruth S, Mathôt RAA, Sparidans RW, Beijnen JH, Verwaal VJ, Zoetmulder FAN. Population pharmacokinetics and pharmacodynamics of mitomycin during intraoperative hyperthermic intraperitoneal chemotherapy. Clin Pharmacokinet 2004;43(2):131–43.

46. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. Cancer Chemother Pharmacol. 1998;41(2):147–54.

47. Bendavid Y, Leblond FA, Dubé P. A study of the effect of temperature on the pharmacokinetic profile of raltitrexed administered by intraperitoneal route in the rat. Med Sci Monit. 2005;11(1):BR1–5.

48. Sørensen O, Andersen AM, Kristian A, Giercksky K-E, Flatmark K. Impact of hyperthermia on pharmacokinetics of intraperitoneal mitomycin C in rats investigated by microdialysis. J Surg Oncol. 2014;109(6):521–6.

49. Pestieau SR, Stuart OA, Chang D, Jacquet P, Sugarbaker PH. Pharmacokinetics of intraperitoneal gemcitabine in a rat model. Tumori. 1998;84(6):706–11.

50. Zakris EL, Dewhirst MW, Riviere JE, Hoopes PJ, Page RL, Oleson JR. Pharmacokinetics and toxicity of intraperitoneal cisplatin combined with regional hyperthermia. J Clin Oncol. 1987;5(10):1613–20.

51. Yonemura Y, Fujimura T, Nishimura G, FallaR null, Sawa T, Katayama K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery. 1996;119(4):437–44

52. Elias D, Gilly F, Boutitie F, Quenet F, Bereder J-M, Mansvelt B, et al. Peritoneal Colorectal Carcinomatosis Treated With Surgery and Perioperative Intraperitoneal Chemotherapy: Retrospective Analysis of 523 Patients From a Multicentric French Study. JCO. 2010;28(1):63–8.

53. de Lima Vazquez V, Stuart OA, Mohamed F, Sugarbaker PH. Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics. Cancer Chemother Pharmacol. 2003;52(2):108–12.

Anexo IV-1. Archivo control NM-TRAN y output abreviado de NONMEM correspondiente al modelo final.

CAPÍTULO V

UNIVERSITAS
Miguel
Hernández

CAPÍTULO V

(Submitted) Original Research Article

Suitability of the AUC ratio as an indicator of the Pharmacokinetic Advantage in HIPEC

María Isabel Mas Fuster[1*], Amelia Ramón López[1*], Javier Lacueva[2], Patricio Más Serrano[1,3], Ricardo Nalda Molina[1]

1. Division of Pharmacy and Pharmaceutics, Department of Engineering, School of Pharmacy, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.
2. Department of Pathology and Surgery, School of Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain.
3. Clinical Pharmacokinetics Unit, Pharmacy Department, Hospital General Universitario de Alicante, Alicante, Spain.

Submitted to Cancer Chemother Pharmacol

Impact Factor 2015	2,824
Oncology (Q3)	Rank: 111/213
Pharmacology and Pharmacy (Q2)	Rank: 89/255

UNIVERSITAS
Miguel
Hernández

1. ABSTRACT

Purpose: The purpose of this study was to evaluate the area under the concentration time curve (AUC) ratio as an optimal indicator of the pharmacokinetic advantage for drugs employed during hyperthermic intraperitoneal perioperative chemotherapy (HIPEC).

Methods: The impact on the AUC ratio of the variables related to the calculation of systemic drug exposure, instillation time and peripheral drug distribution was evaluated through simulations as well as through a retrospective analysis of studies published in literature reporting a pharmacokinetic analysis of HIPEC with oxaliplatin.

Results: Both model simulations and the retrospective analysis showed that the three variables evaluated had an impact on the AUC ratio value if the complete systemic exposure was not fully considered. However, when that complete systemic exposure was considered, none of these variables affected the AUC ratio value.

Conclusions: AUC ratio is not a characteristic parameter of a drug if the calculated systemic drug exposure is not complete. Thus, AUC ratio is not valid for comparing the pharmacokinetic advantage of two drugs and it should not be employed to prove whether a drug can be used in HIPEC safely with regard to toxicity. As an alternative to the AUC ratio, the study of the absorption rate constant and the bioavailability are proposed as the true and independent parameters that reflect the amount of drug absorbed.

Keywords: HIPEC, peritoneal, oxaliplatin, pharmacokinetics, AUC ratio, hyperthermia.

2. INTRODUCTION

During the last two decades, there has been an increased interest in the use of hyperthermic intraoperative peritoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis. In this context, platinum drugs are among the preferred options [1], including oxaliplatin when the primary cancer is the colorectal cancer [2]. Oxaliplatin is one of the drugs that fits the requirements to be used in HIPEC, with a high molecular weight that allows to maintain the concentration in the peritoneal cavity, heat synergy and good depth penetration profile, around 1-2 mm [3,4].

The administration of heated chemotherapy in the abdominal cavity immediately after a cytoreductive surgery allows the treatment of both micrometastases and nodules up to 2 mm. This multimodal treatment suggested for the locoregional approach of peritoneal carcinomatosis was mainly driven by Sugarbaker [5] as an alternative to the standard treatment with intravenous (iv) systemic chemotherapy, with palliative intent. The local

administration of the drug allows dose intensification in the biophase (peritoneal cavity) while the systemic exposure is diminished, leading to an increased efficacy and a possible reduction of systemic toxicity. The difference in drug concentration or drug exposure between the biophase and systemic circulation has been named *pharmacokinetic advantage* (PKA) and it is attributed to the peritoneum-plasma barrier [6]. Since the first time that PKA was defined in the literature, there have been several authors that have considered it as an attribute of the goodness of a given drug to be used in HIPEC procedures [7-10]. Therefore, the maximum PKA would be achieved in a drug that keeps the drug in the peritoneal cavity during the HIPEC procedure, with no absorption to the systemic circulation. However, there are discrepancies in the scientific literature for the choice and calculation of the reference pharmacokinetic parameter to evaluate the PKA.

Theoretically, the magnitude of the PKA should be a function of the absorption of the drug through the peritoneal-plasma barrier to the systemic circulation in terms of rate (absorption rate constant, k_a) and magnitude (bioavailability, F) of the drug. For the sake of simplicity, apparent k_a (k_{a_app}) will be considered as the combined parameter $k_a \cdot F$, that fully affects the PKA. The k_{a_app} depends only on the intrinsic properties of the drug, such as the hydrophilic properties or the molecular weight and the physiologic properties related to the drug, as the first-pass effect or binding to abdominal cavity tissues. Thus, the "true" parameter that reflects the rate and the extension of the absorption from peritoneum cavity to blood is the k_{a_app}.

However, instead of k_{a_app}, most groups use the area under the drug concentration time curve (AUC) ratio as main reference for PKA, calculated as the ratio of the peritoneal AUC (AUC_{per}) and plasma AUC (AUC_{pla}) [1-14]. Intuitively and following the aim of the PKA definition, this approach would seem reasonable, as a simple way for comparing the absorbed drug amount in the systemic circulation with the remaining amount in the peritoneal cavity. Nevertheless, to be a valid surrogate of k_{a_app}, the AUC ratio needs to be a function exclusively of the k_a or/and F, and therefore, independent of any other variables not related to the absorption.

The hypothesis in this work is that there are variables, unrelated to the extent of absorption or the absorption rate, which can modify the AUC ratio. In this case, the AUC ratio would become a weak parameter to evaluate the PKA of a given drug. In this context, the variables that will be considered are the last time considered for the calculation of the AUC_{pla} (T_{last_pla}), the instillation time and the systemic drug distribution, represented by the intercompartmental clearance, (Q_2).

Thus, the main objective of this study was to evaluate the use of the AUC ratio as a parameter for determining the PKA of hyperthermic intraperitoneal oxaliplatin (HIPEO).

3. MATERIALS AND METHODS

To evaluate the impact of the T_{last_pla}, the instillation time and Q_2 on the AUC ratio, deterministic simulations of plasma and peritoneal concentration profiles of HIPEO were performed. The structural pharmacokinetic model and the parameter values used in the simulations were taken from an HIPEO population pharmacokinetic model previously described [15]. The initial oxaliplatin peritoneal concentration in all the simulated scenarios was 230 mg/L. Briefly, the pharmacokinetic model was parameterized in terms of systemic clearance (CL_{el}) =1.03 L/h, clearance from peritoneum to plasma (Q_1) = 3.27 L/h, central volume of distribution (V_2) = 10.8 L, intercompartmental clearance (Q_2) = 24.6 L/h, peripheral volume of distribution (V_3) = 33.9 L and F= 0.376.

The AUC ratio was calculated as indicated in Eq. 1:

$$\frac{(AUC_{T0}^{Tlast})_{per}}{(AUC_{T0}^{Tlast})_{pla}} \quad (1)$$

being T_0 the start of the instillation and T_{last} the last time used for the calculation of the AUC, either in peritoneum cavity or in plasma.

Evaluation of the impact of T_{last_pla} on the AUC ratio

Six different simulated scenarios were studied by selecting different values of T_{last_pla}. T_{last_pla} equal to infinite was also considered to obtain the asymptotic value of the AUC ratio. Those scenarios were performed for instillation times of 30 minutes (min) and 120 min, which are the minimum and maximum instillation times for HIPEC with oxaliplatin used in clinical practice. AUC_{per} was calculated from time 0 to the end of instillation in all cases. AUC_{pla} was calculated from time 0 to the T_{last_pla} selected in each condition. Then, the AUC ratio was calculated for each scenario, and plotted against the T_{last_pla}. None of the rest of the parameters were modified, neither the pharmacokinetic parameters, nor the dose.

In addition, to verify that the impact of the T_{last_pla} on the AUC ratio described in the simulations truly reflects the clinical behaviour of HIPEO, AUC ratio values reported from the literature were evaluated and compared with the simulations. Articles published in English through PubMed-MEDLINE database until March 2017 were reviewed. The search was focused on studies that developed a pharmacokinetic analysis of HIPEO, including peritoneal and plasma concentration time profiles from which AUC data can be obtained. The literature search was conducted using combinations of the search terms “oxaliplatin”, “pharmacokinetics”, “HIPEC”, “peritoneal”, “hyperthermia” and “pharmacologic”. Then, the plasma and peritoneal concentrations were extracted by digitalization of the graphics. Finally, for each study, different AUC ratios were calculated by truncating the T_{last_pla} to times 30, 60,

90,120, 240, 480, 720 and 1440 min when possible, depending of the last blood sampling time of each study.

Evaluation of the impact of the instillation time on the AUC ratio

Five different simulated scenarios were studied by selecting the instillation times 30, 45, 60, 90 and 120 min. The T_{last_per} comprised the instillation time of each scenario and the T_{last_pla} was fixed to 120 min for all of them. Then, the AUC ratio was calculated for each scenario, and plotted against the instillation time. None of the rest of the parameters were modified in these group of simulations, neither the pharmacokinetic parameters, nor the dose.

Evaluation of the impact of disposition parameters on the AUC ratio

Taking into account that Q_2 reflects the systemic drug distribution in this model, three different simulated scenarios were studied by selecting values of Q_2 different from the Q_2 described in the pharmacokinetic model [15], i.e. twice the original value of Q_2 and half the original value of Q_2. Different T_{last_pla}, i.e 30, 120, 480 min and infinite, were also tested. The instillation time was assumed to be 30 min in all the scenarios.

Software

Deterministic simulations were obtained using NONMEM® version 7.3 software package [16]. The graphs and statistical calculations were performed using the R software v3.3.3 [17], implemented in R-studio [18]. The plasma concentration profiles were digitalized, when necessary, from the graphs included in the articles for data collection. The digitalization was performed with the software PlotDigitizer v2.6.8 [19].

4. RESULTS

Impact of T_{last_pla} on the AUC ratio

The simulated AUC ratio values for HIPEO, obtained from the six scenarios evaluated under different T_{last_pla}, are summarised in Table 1, split by two different instillation times of 30 and 120 min. The pattern observed agreed in both conditions, consisting on a decrease of the AUC ratio as T_{last_pla} increased, reaching the same value at time equal infinite. These simulations indicated that AUC ratios calculated are dependent on the T_{last_pla} selected.

Table 1. AUC ratios for instillation times of 30 and 120 min obtained at different Tlast_pla

T_{last_pla} (min)	AUC_{per} (mg/L*min)		AUC_{pla} (mg/L*min)		AUC ratio (mg/L*min)	
	30 min	120 min	30 min	120 min	30 min	120 min
120	5467	12177	408	737	13.4	16.5
240			680	1376	8.04	8.85
480			1189	2522	4.60	4.83
720			1655	3570	3.30	3.41
1440			2827	6208	1.93	1.96
∞			6650	14813	0.822	0.822

Regarding the evaluation of this variable in the literature, data from three Phase I studies [4,20,21] and five retrospective studies [15,22,23,27,28] were suitable for the AUC ratio evaluation (Table 2).

Table 2. Data of the oxaliplatin studies suitable for the AUC ratio evaluation

Study	Article	Patients	Dosing schedule (mg/m^2)	Instillation Volume	Instillation Time (min)	Last blood sampling time (min)	T_{last_pla} (min)
1	Elias D, et al. [4]	20	460	2 L/m^2	30	1500	NA*
2	Ferron G, et al [22]	24	460 (n=17) 306 (n=7)	2 L/m^2	30	480	480
3a	JH Stewart, et al.[20]	12	200	3L	120	150	60 and 120
3b		3	250				
4	Mahteme, et al. [27]	8	427	2 L/m^2	30	150	30
5a	Pérez Ruixo, et al. [15]	21	410	3.7 L	30	480	NA*
5b					120		
6	Valenzuela, et al. [28]	30	360	2.5-6 L	30	1680	NA*
7	Shimizu, et al.[21]	9	130	5L	30	2880	NA*
8	Elias D, et al. [23]	16	460	2 L/m^2	30	1440	30

* NA Data not available

Fig. 1 represents the simulated AUC ratios (dashed lines) and the AUC ratios obtained from literature. The simulated results followed the same pattern that those obtained from the literature, where the AUC ratio decreased as T_{last_pla} lengthened.

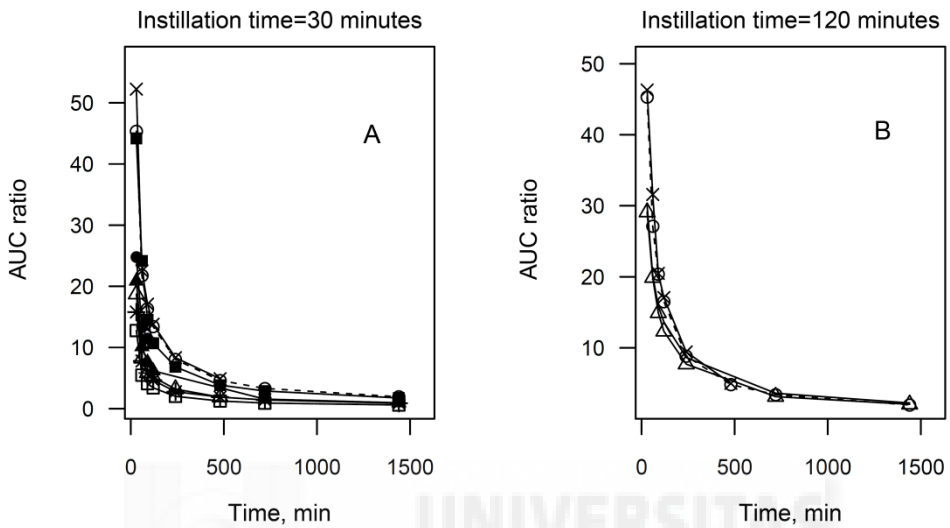


Fig 1. Panel A: AUC ratios obtained after 30 min instillation time simulation (dashed lines) and from the literature: Pérez-Ruixo [15] (crosses), Valenzuela [28] (black squares), Mahteme [27] (black circles); Shimizu [21] (black triangles), Ferron [22] (empty triangles), Elias [4] (empty squares) and Elias [23] (asterisks). Panel B: AUC ratios obtained after 120 min instillation time simulation (dashed lines) and from literature: Stewart [20] 200 mg/m2 (empty squares) and 250 mg/m2 (empty triangles) and Pérez-Ruixo [15] (crosses).

Impact of the instillation time on the AUC ratio

The simulated AUC ratio values for HIPEO, obtained from the five scenarios evaluated under different instillation times, are summarised in Table 3 and Fig. 2**.** The simulated AUC ratio values presented a linear increase as instillation time increased, registering a range of values from 13.4 to 16.5.

Table 3. AUC ratio for the five scenarios evaluated at different instillation times

Instillation time (min)	AUC_{per}* (mg/L*min)	AUC_{pla}** (mg/L*min)	AUC ratio
30	5467	408	13.4
45	7352	529	13.9
60	8832	614	14.4
90	10903	709	15.4
120	12177	737	16.5

* T_{last_per} considered at the time at which the instillation finishes.

** T_{last_pla} fixed to 120 min.

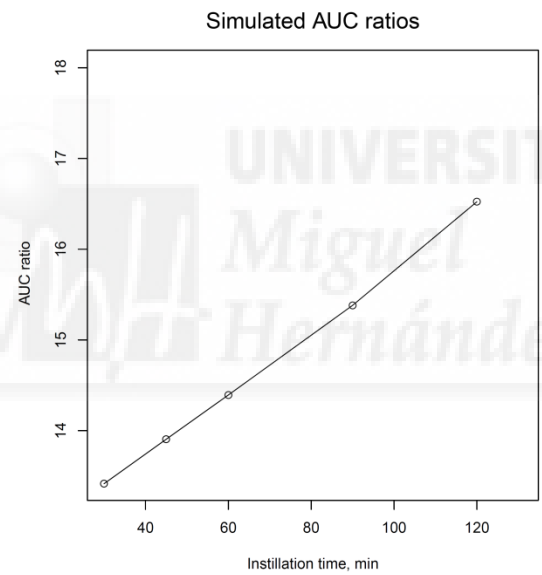


Fig 2. AUC ratio for the five scenarios evaluated at different instillation times.

Impact of disposition parameters on the AUC ratio

The simulated AUC ratio values for HIPEO, obtained from the three scenarios evaluated under different Q_2, are summarised in Table 4 and Fig. 2. The AUC ratio values were 56.6, 45.2 and 39.1 when Q_2 was twice, the original and half its reported value, respectively. The change in Q_2 had an impact on the AUC_{pla} value, so the greatest Q_2, the lowest AUC_{pla}. The same pattern was observed in the rest of scenarios at different T_{last_pla} (Table 4 and Fig. 3).

Table 4. AUC ratios for original Q2 value, Q2·2 and Q2/2, attending to Clast for calculating AUCpla.

T_{last_pla} (min)	AUC ratio		
	Q_2	$Q_2 \cdot 2$	$Q_2/2$
30	45.2	56.6	39.1
120	13.4	16.3	10.3
480	4.60	4.82	4.21
∞	0.822	0.822	0.822

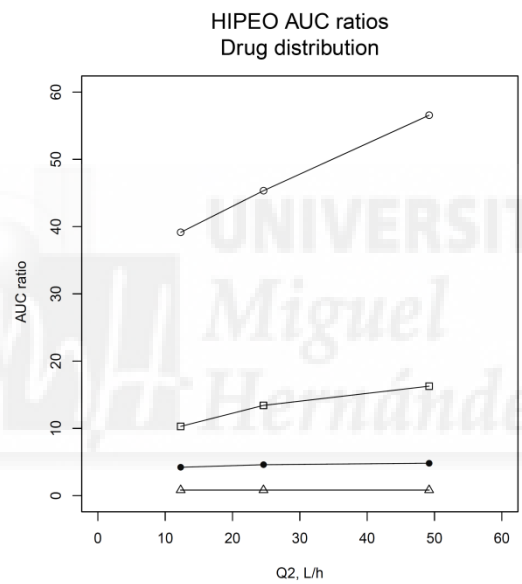


Fig 3. AUC ratios obtained when Tlast_pla was 30 (empty circles), 120 (empty squares) or 480 min (black circles) and ∞ (empty triangles) for $Q_2/2$, Q_2, and $Q_2 \cdot 2$.

5. DISCUSSION

The PKA mechanism has been discussed in several studies [4,25]. Currently, the AUC ratio is the most commonly used parameter [4,11,26], considering that the higher its value, the greater the PKA of the drug. Therefore, a drug with a higher PKA would be preferred over other drugs with lower PKA, if any other considerations are similar (as efficacy, toxicity, etc.). Elias et al. have considered oxaliplatin in HIPEC as a drug with a low AUC ratio of 16,

considering it to be compensated by the rapid absorption of the drug into the tumour nodules [4]. However, the literature review highlights that its determination is not homogeneous among the studies [7,27-30].

Our results show that the use of the AUC ratio as the sole indicator of the PKA or as a reference to compare two drugs has one main limitation, which is that AUC ratio depends on variables not related to the systemic absorption. Thus, as T_{last_pla} lengthened, the AUC ratio of HIPEO systematically decreased. An opposite trend was observed in the AUC ratio when the second variable evaluated, instillation time, was prolonged. The third variable evaluated, the systemic drug distribution to a peripheral compartment, also had an impact on the AUC ratio, where the greater Q_2 value, the smaller AUC_{pla}, increasing the AUC ratio value. It is worth noting that there was no variability in the simulations, so statistical analysis was not required.

Therefore, when two drugs, "A" and "B", are compared, and also considering that "A" and "B" could have different instillation times, different $T_{last\ pla}$ or different systemic drug distribution, taking the AUC ratio as a measure of the PKA may mistakenly result in the selection of drug "A" over drug "B", when in fact drug "B" would have presented a lower absorption to the systemic circulation. Moreover, different authors could report different AUC ratio values for the same drug if the instillation time or the T_{last} are different, when the PKA should be a characteristic parameter of the drug.

However, these variables did not have an impact on the AUC ratio when T_{last_pla} was equal to infinite, and therefore, the AUC_{pla} was calculated as $AUC_{T0_{pla}}^{\infty}$. In this line, following the definition of the $AUC_{C0}^{\infty} = D/CL$ and assuming that at a given time part of the dose (D) amount is absorbed (A_{abs}) into the systemic circulation, it fulfils

$$AUC_{C0}^{Clast} = AUC_{C0}^{\infty} - AUC_{Clast}^{\infty} \quad (2)$$

$$AUC\ ratio = \frac{A_{abs}/CL_{abs}}{F*A_{abs}/CL_{el}} = \frac{CL_{el}}{F \cdot CL_{abs}} \quad (3)$$

Thus, AUC ratio tends toward the ratio between CL_{el} and CL_{abs} when T_{last_pla} approaches to infinite, i.e the total systemic drug exposure is taken into account. In this scenario, AUC ratio only depends on the intrinsic drug parameters CL_{el}, CL_{abs} and F, without the influence of other variables as instillation time or the systemic distribution. Following this equation and taking the PK parameters from the model, AUC ratio for HIPEO is 0.822, the same value obtained among all the simulations in this work at time considered infinite. This value is consistent for any value of the instillation time or the Q_2, confirming Eq. 3.

Remarkably, the data obtained from the literature followed the same trend that the obtained in our simulations. To our knowledge, there is only one mention highlighted in the

literature about the modification of the AUC ratio calculated at different times of the instillation [20]. However, the authors did neither further discussed this finding, nor gave any mathematical explanation.

6. CONCLUSIONS

The results of the simulations performed, supported by the data analysis of the reviewed studies, indicate that AUC ratio is not a correct parameter to estimate the absorption from the peritoneal cavity to the systemic circulation of a drug. The AUC ratio is not unique and characteristic for each drug if AUC_{pla} is calculated at any time different from infinite.

The AUC ratio is not valid for comparing the PKA of two drugs and it should not be employed to prove whether a drug can be used in HIPEC safely with regard to toxicity, given that it is highly dependent on the instillation time, the T_{last_pla} and the grade of drug distribution in the body. As an alternative to the AUC ratio, the study of k_a and F is proposed as the true and independent parameters that reflect the rate and the amount of drug absorbed. Our results warrant prospective clinical or pre-clinical studies designed specifically to prove these conclusions.

7. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

8. REFERENCES

[1] Kusamura S, Elias D, Baratti D, Younan R, Deraco M (2008) Drugs, Carrier Solutions and Temperature in Hyperthermic Intraperitoneal Chemotherapy. J Surg Oncol 98: 247–252. doi:10.1002/jso.21051

[2] Pinto A, Eveno C, Pocard M (2017) Update on clinical trials in colorectal cancer peritoneal metastasis. Int J Hyperthermia 31; 1–16

[3] Rietbroek RC, van der Vaart PJ, Haveman J, Blommaert FA, Geerdink A et al (1997) Hyperthermia Enhances the Cytotoxicity and Platinum-DNA Adduct Formation of Lobaplatin and Oxaliplatin in Cultured SW 1573 Cells. J Cancer Res Clin Oncol 123: 6–12

[4] Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA et al (2002) Heated Intra-Operative Intraperitoneal Oxaliplatin after Complete Resection of Peritoneal Carcinomatosis: Pharmacokinetics and Tissue Distribution. Ann Oncol 2002; 13: 267–72

[5] Sugarbaker PH (1999) Successful Management of Microscopic Residual Disease in Large Bowel Cancer. Cancer Chemother Pharmacol 43: S15–25

[6] Van der Speeten K, Stuart OA, Sugarbaker PH (2009) Pharmacokinetics and Pharmacodynamics of Perioperative Cancer Chemotherapy in Peritoneal Surface Malignancy. Cancer J 15: 216–224. doi:10.1097/PPO.0b013e3181a58d95

[7] Goodman MD, McPartland S, Detelich D, Saif MW (2016) Chemotherapy for intraperitoneal use: a review of hyperthermic intraperitoneal chemotherapy and early post-operative intraperitoneal chemotherapy. J Gastrointest Oncol 7:45–57. doi: 10.3978/j.issn.2078-6891.2015.111

[8] Yan TD, Stuart OA, Yoo D, Sugarbaker PH (2006) Perioperative intraperitoneal chemotherapy for peritoneal surface malignancy. J Transl Med 4:17

[9] De Smet L, Ceelen W, Remon JP, Vervaet C (2013) Optimization of Drug Delivery Systems for Intraperitoneal Therapy to Extend the Residence Time of the Chemotherapeutic Agent. Scientific WorldJournal 2013: 720858. doi: 10.1155/2013/720858

[10] González-Moreno S, González-Bayón LA, Ortega-Pérez G (2010) Hyperthermic intraperitoneal chemotherapy: Rationale and technique. World J Gastrointest Oncol 2:68–75. doi: 10.4251/wjgo.v2.i2.68

[11] Rossi C, Foletto M, Mocellin S, Pilati P, De SM, Deraco M et al (2002) Hyperthermic Intraoperative Intraperitoneal Chemotherapy with Cisplatin and Doxorubicin in Patients Who Undergo Cytoreductive Surgery for Peritoneal Carcinomatosis and Sarcomatosis: Phase I Study. Cancer 94: 492–99. doi:10.1002/cncr.10176

[12] Jacquet P, Averbach A, Stephens AD, Stuart OA, Chang D, Sugarbaker PH (1998) Heated Intraoperative Intraperitoneal Mitomycin C and Early Postoperative Intraperitoneal 5-Fluorouracil: Pharmacokinetic Studies. Oncology 55: 130–38

[13] De Lima Vazquez V, Stuart OA, Mohamed F, Sugarbaker PH (2003) Extent of Parietal Peritonectomy Does Not Change Intraperitoneal Chemotherapy Pharmacokinetics. Cancer Chemother Pharmacol 52: 108–12. doi: 10.1007/s00280-003-0626-8

[14] https://clinicaltrials.gov/ct2/show/NCT03028155

[15] Pérez-Ruixo C, Peris JE, Escudero-Ortiz V, Bretcha-Boix P, Farré-Alegre J, Pérez-Ruixo JJ et al (2014) Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol 73:1009-20. doi: 10.1007/s00280-014-2436-6

[16] Beal S, Sheiner LB, Boeckmann A, & Bauer RJ, NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

[17] R Core Team 2016. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/.

[18] RStudio Team 2015. RStudio: Integrated Development for R. RStudio, Inc., Boston, MA.

[19] Plotdigitizer, V2.6.8. http://plotdigitizer.sourceforge.net/

[20] Stewart IV JH, Shen P, Russell G , Fenstermaker J, McWilliams L, Coldrun FM et al (2008) A Phase I Trial of Oxaliplatin for Intraperitoneal Hyperthermic Chemoperfusion for the Treatment of Peritoneal Surface Dissemination from Colorectal and Appendiceal Cancers. Ann Surg Oncol 15: 2137–45. doi: 10.1245/s10434-008-9967-1

[21] Shimizu T, Sonoda H, Murata S, Takebayashi K, Ohta H, Miyake T et al (2014) Hyperthermic intraperitoneal chemotherapy using a combination of mitomycin C,5-fluorouracil, and oxaliplatin in patients at high risk of colorectal peritoneal metastasis: A Phase I clinical study. Eur J Surg Oncol 40: 521-8. doi: 10.1016/j.ejso.2013.12.005

[22] Ferron G, Dattez S, Gladieff L, Delord J-P, Pierre S, Lafont T et al (2008) Pharmacokinetics of heated intraperitoneal oxaliplatin. Cancer Chemother Pharmacol 62: 679–83. doi: 10.1007/s00280-007-0654-x

[23] Elias D, El Otmany A, Bonnay M, Paci A, Ducreux M, Antoun S et al (2002) Human pharmacokinetic study of heated intraperitoneal oxaliplatin in increasingly hypotonic solutions after complete resection of peritoneal carcinomatosis. Oncology 63: 346–52.

[24] Flessner MF, Fenstermacher JD, Dedrick RL, Blasberg RG (1985) A Distributed Model of Peritoneal-Plasma Transport: Tissue Concentration Gradients. Am J Physiol 248: F425–435

[25] Cueto-Manzano AM (2009) Rapid Solute Transport in the Peritoneum: Physiologic and Clinical Consequences. Perit Dial Int 29 Suppl 2: S90–5

[26] Stephens AD, Belliveau JF, Sugarbaker PH (1996) Intraoperative Hyperthermic Lavage with Cisplatin for Peritoneal Carcinomatosis and Sarcomatosis. Cancer Treat Res 81: 15–30

[27] Mahteme H, Wallin I, Glimelius B, Påhlman L, Ehrsson H (2008) Systemic exposure of the parent drug oxaliplatin during hyperthermic intraperitoneal perfusion. Eur J Clin Pharmacol 64: 907–11. doi: 10.1007/s00228-008-0511-9

[28] Valenzuela B, Nalda-Molina R, Bretcha-Boix P, Escudero-Ortíz V, Duart MJ, Carbonell V et al (2011) Pharmacokinetic and pharmacodynamic analysis of hyperthermic intraperitoneal oxaliplatin-induced neutropenia in subjects with peritoneal carcinomatosis. The AAPS journal 13: 72–82. doi: 10.1208/s12248-010-9249-2

[29] Sugarbaker PH, Mora JT, Carmignani P, Stuart OA, Yoo D (2005) Update on chemotherapeutic agents utilized for perioperative intraperitoneal chemotherapy. Oncologist 10:112–22. doi: 10.1634/theoncologist.10-2-112

[30] Chalret du Rieu Q, White-Koning M, Picaud L, Lochon I, Marsili S, Gladieff L et al (2014) Population pharmacokinetics of peritoneal, plasma ultrafiltrated and protein-bound oxaliplatin concentrations in patients with disseminated peritoneal cancer after intraperitoneal hyperthermic chemoperfusion of

oxaliplatin following cytoreductive surgery: correlation between oxaliplatin exposure and thrombocytopenia. Cancer Chemother Pharmacol 74: 571–82. doi: 10.1007/s00280-014-2525-6

UNIVERSITAS
Miguel
Hernández

CAPÍTULO VI. RESULTADOS Y DISCUSIÓN

UNIVERSITAS
Miguel
Hernández

1. ESTANDARIZACIÓN DE LA DOSIFICACIÓN EN HIPEC

La administración intraperitoneal (ip) de un fármaco determinado mediante HIPEC requiere de la determinación tanto de la dosis como del volumen de solución transportadora en la que se va a disolver el citotóxico. Tomando como base la premisa farmacológica de que una misma concentración produce un efecto y toxicidad similares, las concentraciones en la biofase deben ser homogéneas. En el caso del HIPEC, dado que se trata de un tratamiento locorregional, la biofase comprende la totalidad de la cavidad peritoneal, por lo que las concentraciones de fármaco en la misma deben ser homogéneas durante todo el procedimiento. Sin embargo, actualmente en la práctica clínica esta dosificación no es homogénea entre grupos de trabajo. Por tanto, el primer objetivo de esta Memoria de Tesis Doctoral, presentado en el Capítulo II, fue revisar y exponer las formas de dosificación en HIPEC empleadas actualmente en la clínica y establecer la fundamentación teórica para una adecuada dosificación, teniendo en cuenta el objetivo de esta administración locorregional.

La revisión de la literatura evidenció que la dosificación en HIPEC, tanto para la dosis de fármaco como para el volumen de la solución transportadora, se realiza en función a la superficie corporal de cada paciente, de acuerdo a los protocolos establecidos tanto por Sugarbaker como como por Elias (1-3). En este caso las concentraciones se mantendrían constantes, y la exposición de la biofase al fármaco sería homogénea en todos los pacientes. Sin embargo, en determinadas ocasiones este volumen calculado puede resultar inapropiado para el volumen real de la cavidad peritoneal, como por ejemplo en caso de existir ascitis. Como resultado, este volumen basado en características antropométricas podría presentar una relación pobre respecto a la capacidad de la cavidad abdominal y en el caso en que resultase insuficiente, las compensaciones de volumen durante la instilación alterarían la concentración del fármaco en la biofase. Este procedimiento incrementaría la variabilidad en la exposición tumoral y sistémica, como se ha demostrado en otros estudios (2).

2. IMPACTO DE LA INSTILACIÓN INTRAPERITONEAL HIPERTÉRMICA (LIHI) TRAS LAPAROTOMÍA EN LA FARMACOCINÉTICA DEL OXALIPLATINO TRAS SU ADMINISTRACIÓN INTRAVENOSA

En la actualidad el uso de HIPEC en la clínica está incrementado, respaldado por los resultados ventajosos mostrados frente a esquemas de tratamiento más clásicos basados en la quimioterapia sistémica. A nivel preclínico, se ha evaluado el impacto de ciertas covariables en los parámetros farmacocinéticos de algunos fármacos citotóxicos. Sin embargo, la influencia de la técnica quirúrgica en la modalidad abierta de HIPEC, comprendida como la realización de una laparotomía seguida de una instilación ip hipertérmica (LIHI) de solución transportadora,

no ha sido evaluada como una covariable que pueda tener un impacto en dichos parámetros farmacocinéticos, a pesar de ser un proceso común en todos los experimentos.

Por tanto, el segundo objetivo de esta Memoria de Tesis Doctoral, presentado en el Capítulo III, fue desarrollar un modelo farmacocinético poblacional de oxaliplatino en rata Wistar que permitiese evaluar el impacto aislado del procedimiento LIHI, inherente a la técnica abierta, en los parámetros farmacocinéticos de oxaliplatino. Para delimitar la influencia aislada de este procedimiento, el fármaco fue administrado por vía intravenosa (iv) en dos grupos de ratas, de forma que fuesen estrictamente iguales exceptuando el procedimiento LIHI. El estudio permitió, por tanto, determinar la cinética de oxaliplatino tras una administración iv única de 1,5 mg en presencia y ausencia de las condiciones descritas anteriormente y evaluar el impacto LIHI en la distribución sistémica del fármaco y en su eliminación.

La técnica, desarrollada sobre un total de 12 ratas Wistar, fue en general bien tolerada, exceptuando la muerte por etiología desconocida durante la cirugía de una de las ratas en el grupo sometido a las condiciones LIHI. El análisis farmacocinético se desarrolló, por tanto, sobre los datos de un total de 11 ratas, todas ellas recibiendo 1,5 mg de oxaliplatino mediante un bolus iv. En 6 de las 11 ratas, el fármaco iv se administró sin aplicar ningún otro procedimiento adicional en los animales (grupo control), mientras que en las otras 5 se administró en condiciones LIHI (grupo experimental) mediante una solución hipertérmica de dextrosa al 5% durante un tiempo de instilación de 30 minutos y a una temperatura objetivo en la cavidad peritoneal de 42ºC, simulando las condiciones HIPEC. Para el análisis de las concentraciones plasmáticas de oxaliplatino total se analizaron un total de 91 muestras plasmáticas, 49 de ellas correspondientes al grupo control y 42 al grupo LIHI. Dichas concentraciones fueron caracterizadas, en consonancia con los modelos obtenidos en anteriores trabajos publicados [4], mediante un modelo farmacocinético bicompartimental.

La media de la concentración máxima en plasma (C_{max}) y su desviación estándar (SD) fue de 23,7 (6,9) mg/L en el grupo control y 22,5 (2,5) mg/L en el grupo LIHI, alcanzadas inmediatamente después de la administración iv del bolus de oxaliplatino. La media (SD) de la exposición sistémica de oxaliplatino, evaluada mediante análisis no parámetrico del área bajo la curva de concentraciones plasmáticas ($AUC_{pla\ 0-\infty}$), fue 1375 (645) mg·min/L y 2766 (440) mg·min/L para los grupos control y LIHI, respectivamente, mostrando diferencias significativas en ambos grupos ($p < 0,01$).

Al realizar el análisis farmacocinético poblacional de las concentraciones de las 11 ratas incluidas en el estudio, asumiendo un modelo bicompartimental, la covariable LIHI, considerada como una covariable dicotómica, mejoró de forma significativa el valor de la función objetivo (MVOF) del modelo cuando ésta se incluyó en los parámetros aclaramiento

(CL) y volumen de distribución periférico (V_2), con una disminución en su valor de 18,3 puntos (*p<0,001*). Por tanto, LIHI se incluyó como covariable de ambos parámetros y este modelo se consideró el modelo final.

El valor de CL en el grupo control fue de 0,94 (28,3) mL/min, acorde a otros estudios en literatura que cuantifican oxaliplatino total tras administraciones iv (5), mientras que en el grupo LIHI fue de 0,42 (14,0) mL/min, suponiendo una disminución del 55,3%. Dado que una cavidad abdominal abierta y llena de la solución transportadora podría actuar como compartimento "sink" (6), causando la distribución de oxaliplatino desde sangre hasta la cavidad peritoneal, se podría haber esperado un CL aparente mayor en el grupo experimental. Sin embargo, éste no fue el resultado del estudio. Una posible hipótesis explicativa de la disminución del valor de CL en condiciones LIHI consiste en el cambio de la función renal que puede ocurrir a causa del estrés quirúrgico (7,8), dado que los compuestos de platino se excretan principalmente a través del riñón. Este deterioro de la función renal podría haber compensado el efecto "sink", siendo incluso más determinante y resultando, finalmente, en un valor de CL menor en condiciones LIHI.

En línea con los resultados de CL en este estudio podrían encontrarse aquellos estudios clínicos previos que evidenciaron una exposición sistémica similar de oxaliplatino tras una administración HIPEC comparada con una administración iv (4), a pesar de que se esperase que la primera fuera menor, debido al paso limitado desde peritoneo a plasma de los fármacos que ofrece la barrera peritoneo-plasma. Los resultados del estudio correspondiente al Capítulo III sugieren que este hecho podría atribuirse a la disminución del CL causada por el estrés quirúrgico que sufrirían los pacientes sometidos a HIPEC.

Los valores de V_2 en el grupo control y grupo LIHI fueron de 430 (12,3) mL y 221 (11,8) mL, respectivamente. De nuevo, cuando la administración del bolus iv ocurrió en condiciones LIHI, el valor del parámetro supuso una disminución respecto al del grupo control, en concreto del 48.6 %. El volumen de distribución central (V_1) en ambos grupos fue de 53,2 (7,80) mL y el aclaramiento intercompartimental (Q) fue de 6.01 (9,58) mL/min.

Las estimaciones de los parámetros farmacocinéticos del modelo poblacional bicompartimental que caracteriza la farmacocinética de oxaliplatino en plasma tras una administración iv predicen con exactitud las observaciones de oxaliplatino, como confirman los gráficos de bondad de ajuste del modelo, junto con los resultados de los errores de distribución normalizados por la predicción (NPDE) (Figura 2, Capítulo III), indicando, además, la ausencia de sesgos en el modelo. Dichas estimaciones, junto con los resultados del bootstrap no parámetrico (Tabla 1, Capítulo III) y del pcVPC (Figura 3, Capítulo III), evidencian que el modelo desarrollado es apropiado para describir la evolución temporal de las

concentraciones de oxaliplatino en plasma y su variabilidad asociada en rata Wistar, tanto en condiciones LIHI o tras una administración iv sola.

El modelo farmacocinético describió los datos con una adecuada variabilidad inter-individual (IIV) menor del 35% en todos los parámetros farmacocinéticos y una variabilidad residual menor del 12%. Los valores de shrinkage de la IIV se estimaron en menos de un 14%.

Una limitación con la que cuenta este estudio es la realización del experimento en ratas Wistar sanas, sin realizar ninguna de las técnicas de peritonectomía que se realizan en la clínica previa a la instilación de HIPEC. Por tanto, las condiciones reales de citorreducción no se recrearon en su totalidad. En la literatura no se han observado cambios en la farmacocinética en función de la extensión de las peritonectomías (9), sin embargo, el impacto de la presencia frente a la ausencia de esta técnica en los parámetros farmacocinéticos no ha sido evaluada. Por tanto, futuros estudios en esta línea, incluyendo peritonectomías en ratas, podrían ayudar a confirmar los resultados de este trabajo.

3. FARMACOCINÉTICA POBLACIONAL DE OXALIPLATINO INTRAPERITONEAL HIPERTÉRMICO EN RATA WISTAR

Hasta la fecha, diferentes autores han estudiado aspectos como el crecimiento tumoral, la supervivencia o la farmacocinética de distintos fármacos indicados para HIPEC en modelos animales experimentales como la rata y el cerdo. Estos modelos animales han contribuido a valorar el impacto de múltiples componentes de HIPEC de forma aislada y han proporcionado información útil para la futura investigación clínica. Sin embargo, ninguno de los estudios que se han realizado en modelos animales con oxaliplatino ip hipertérmico (HIPEO) ha considerado el enfoque poblacional en el análisis farmacocinético de sus datos. Por tanto, el tercer objetivo de esta Memoria de Tesis Doctoral, presentado en el Capítulo IV, fue caracterizar el HIPEO a través de un modelo farmacocinético poblacional en rata Wistar, mediante el análisis conjunto de concentraciones peritoneales y plasmáticas tras administraciones ip e iv de oxaliplatino. El efecto de las covariables asociadas al tratamiento dosis, tiempo de instilación y temperatura también fueron evaluadas.

En total, 36 ratas fueron agrupadas de forma aleatoria en seis grupos (G1-G6, n=6) y sometidas a distintas condiciones experimentales de dosis, tiempo de instilación o temperatura. Un grupo adicional de ratas (G7, n=6) fue sometido a una administración iv de oxaliplatino en lugar de ip, en condiciones LIHI (Tabla 3, Capítulo IV). El experimento fue bien tolerado en general en todos los grupos, excepto en el G5, correspondiente a la administración del HIPEO en el rango de temperaturas más elevado (42ºC-43ºC). Estas ratas mostraron un rápido deterioro tras el procedimiento y murieron a tiempos tempranos tras finalizar la

instilación. Por tanto, por razones éticas y siguiendo las recomendaciones de la Oficina Evaluadora de Proyectos de la Universidad Miguel Hernández, los experimentos en este grupo se suspendieron, siendo el tamaño final del G5 n=3. La elevada mortalidad en este grupo se consideró una limitación del estudio, siendo posiblemente atribuida a la elevada hipertermia, en consonancia con hallazgos previos en literatura (10,11). Por tanto, la evaluación de la covariable temperatura en el actual estudio quedó restringida al rango de temperaturas de 38ºC a 42ºC. Por otro lado, una de las ratas del G6, correspondiente a la administración ip de 200 mg/L de oxaliplatino, y una de G7 murieron durante el procedimiento quirúrgico por etiología desconocida.

Un total de 115 y 263 muestras de peritoneo y plasma, respectivamente, fueron analizadas para determinar la concentración de oxaliplatino total y caracterizar su farmacocinética. La C_{max} (SD) y el $AUC_{pla\ 0-\infty}$ se determinaron para cada grupo de ratas (Tabla 1, Capítulo IV). Las concentraciones peritoneales de oxaliplatino durante la instilación se encontraron en el rango de 66,8-142 mg/L y 124-256 mg/L para las administraciones de 100 y 200 mg/L de HIPEO, respectivamente. La evaporación de la solución transportadora no se consideró significativa, considerándose el volumen final de solución cercano al 100% del inicial en todas las ratas.

La farmacocinética de oxaliplatino tras las administraciones iv e ip fue descrita mediante un modelo bicompartimental con distribución inespecífica a compartimentos periféricos, eliminación lineal desde el compartimento central y absorción de primer orden desde peritoneo a plasma, cinética en línea con otros estudios relativos a HIPEO (12,13). Sin embargo, el perfil de concentración plasmática de oxaliplatino fue inusual en algunas ratas, mostrando un punto de inflexión entre los 30 y los 45 minutos de instilación, dando lugar a un incremento de la pendiente (Figura 2, Capítulo IV). Por tanto, el modelo fue adaptado para describir un deterioro en los mecanismos de eliminación del fármaco, reflejado a través de una disminución en el valor del parámetro CL durante la instilación. Este cambio en su valor (CL_1 a CL_2) se modeló mediante una función escalón sobre la constante de eliminación (k_{el}), mejorando de forma significativa la FVO. Este resultado estaría en línea con la alteración de la función renal atribuida a la cirugía y/o hipertermia observada en otros estudios (7,14) así como con los resultados del Artículo II, en los que el grupo experimental de ratas sometido a las condiciones LIHI registró unos valores de CL significativamente menores a las del grupo no sometido a cirugía. La inclusión de esta función escalón en el modelo estructural de forma adicional a las microconstantes k_{23} o k_{32} o a la constante de absorción (k_a) no mejoró el ajustado del modelo de forma significativa.

Además del modelo estructural propuesto, se evaluaron otros modelos de absorción, incluyendo un periodo de latencia en la absorción (*lag time)* o modelos de compartimentos de tránsito. Sin embargo, el ajustado de estos modelos no supuso una disminución significativa de

la MOFV, además de que el cambio en la pendiente de concentraciones plasmáticas no se observó claramente de forma visual. Por otro lado, el mencionado cambio en la pendiente podría haber sido explicado también por la entrada tardía de parte de la dosis de HIPEO, quedando acumulada como depósito. Esta hipótesis también fue evaluada mediante la inclusión de un compartimento depósito. A pesar de que este modelo sí mejoró significativamente la MOFV y los gráficos de bondad de ajuste en comparación al modelo bicompartimental estructural básico, resultó un modelo sobreparametrizado y con un valor de MOFV superior al resultante del modelo final propuesto en este estudio. La circulación enterohepática (15) no se evaluó como parte estructural del modelo debido a que todas las ratas del estudio fueron sometidas a una ligadura del colédoco previamente a la instilación del fármaco. El modelo farmacocinético planteado describió correctamente el curso de las concentraciones de oxaliplatino en plasma y peritoneo tras las administraciones iv e ip durante distintos tiempos de instilación (Figura 2, Capítulo IV).

Actualmente no hay estudios publicados a nivel preclínico o clínico respecto a la identificación del tiempo al que comienza el deterioro de la función renal. La ausencia de estudios farmacocinéticos clínicos que incluyan en su modelo estructural un cambio en el valor de CL puede deberse a la elevada variabilidad asociada a los datos farmacocinéticos de los pacientes sometidos a este tratamiento. En este sentido el modelo farmacocinético poblacional presentado en el Capítulo IV fue capaz de estimar el tiempo al que el valor de CL cambia con una precisión aceptable.

Por otro lado, la mayoría de los equipos quirúrgicos establecen la duración de las instilaciones de HIPEC bajo una aproximación empírica. Algunos estudios justifican esta duración en función de la semivida peritoneal del oxaliplatino (13,16). Sin embargo, ningún estudio ha considerado el impacto del procedimiento quirúrgico y de HIPEC en los parámetros farmacocinéticos y, por tanto, en la exposición del fármaco y su toxicidad. Conocer el tiempo en el cual se produce un deterioro clínicamente relevante en la función renal podría ser útil y considerarse como factor a considerar cuando se establezca la duración de la instilación. Sin embargo, se requiere la realización de estudios en la clínica que evalúen si este fenómeno ocurre también en humanos .

En el rango de valores analizados, el análisis gráfico y estadístico evidenció que ninguna de las covariables evaluadas, dosis, temperatura y tiempo de instilación tuvieron efecto en los parámetros farmacocinéticos del modelo, de acuerdo al valor de la FVO, ni en la disminución de la correspondiente VII, resultados en línea con otros estudios evaluando covariables asociadas al tratamiento (13,17-21).

La IIV se pudo estimar para los parámetros CL, volumen de distribución central (V2) y volumen de distribución a compartimentos periféricos (V_3) (Tabla 2, Capítulo IV), con valores de shrinkage menores del 30%. Los valores de CL_1 y CL_2 fueron de 3,25 mL/min y de 0,15 mL/min, respectivamente. Estos valores difieren del valor de CL obtenido en el grupo experimental de ratas sometidas a condiciones experimentales similares en el Capítulo III. Sin embargo, cuando la función escalón no fue considerada en este modelo, es decir, cuando no se contempló a través del modelo estructural el cambio en el valor de CL, la media de este parámetro fue de 0,49 mL/min, resultado que sí se encuentra en concordancia con el obtenido en el Capítulo III. El valor T_{50}, definido como el tiempo al que CL_1 toma el valor de CL_2, fue estimado en 31,4 minutos. Este cambio puede observarse en las gráficas que representan la evolución temporal de las concentraciones plasmáticas de oxaliplatino en las ratas sometidas a tiempos de instilación de 45 o 60 minutos. V_2 y V_3 se estimaron en 53,6 mL y 54,1 mL, respectivamente, mientras que ka fue estimada en 0,00864 min^{-1} (semivida peritoneal = 80,2 minutos). La estimación de la fracción de dosis absorbida (F) tras las administraciones ip no fue significativamente diferente del 100%.

Las estimaciones de los parámetros farmacocinéticos del modelo poblacional bicompartimental final que caracteriza la farmacocinética de oxaliplatino en plasma y peritoneo tras una administración iv e ip predicen con exactitud las observaciones de oxaliplatino, como confirman los gráficos de bondad de ajuste del modelo, indicando, además, la ausencia de sesgos (Figuras 3 y 4, Capítulo IV). De forma similar, tampoco se observaron tendencias que indicaran la no idoneidad del modelo en el valor de las residuales condicionales ponderadas (CWRES) o en los NPDE para las concentraciones peritoneales y plasmáticas (Figuras 3 y 4, Capítulo IV). De hecho, la media (SD) y su intervalo de confianza (CI) de los NPDE para las concentraciones peritoneales fue de 0,04 (IC 95% -0,16:0,21) y 0,99 (IC 95% 0,86:1,17), respectivamente. De la misma manera, estos resultados para las concentraciones plasmáticas fueron de -0,0006 (CI 95% -0,12:0,11) y 0,96 (IC 95% 0,88:1,06), respectivamente, confirmando que las observaciones se predijeron por el modelo con exactitud y sin sesgo.

Dichas estimaciones, junto con los resultados del bootstrap no parámetrico (Tabla 2, Capítulo IV) y del pcVPC (Figura 5, Capítulo IV), evidencian que el modelo desarrollado es apropiado para describir la evolución temporal de las concentraciones de oxaliplatino en plasma y peritoneo y su variabilidad asociada en rata Wistar, tanto tras una administración iv sola o mediante LIHI.

Una de las limitaciones del estudio realizado en el Capítulo IV y comentada anteriormente, hace referencia al limitado tamaño muestral para el G5, causado por la elevada mortalidad registrada en este grupo de ratas, posiblemente atribuida a la elevada hipertermia. Por tanto, la ausencia de impacto de la covariable temperatura en los parámetros farmacocinéticos del

modelo como resultado de su evaluación, quedaría restringida al rango de temperaturas de 38ºC a 42ºC. Por otro lado, y en línea con la técnica experimental realizada en las ratas del Artículo II, este estudio fue realizado en ratas Wistar sanas, sin la realización de peritonectomías, por lo que las condiciones reales de citorreducción y HIPEC que se presentan en la clínica no fueron recreadas en su totalidad.

4. IDONEIDAD DEL AUC RATIO COMO INDICADOR DE LA VENTAJA FARMACOCINÉTICA EN HIPEC

Una de las características de la administración HIPEC que la hacen preferible frente a la administración iv es la mayor concentración de fármaco en la cavidad peritoneal, con una baja absorción sistémica, debido a la necesidad del paso del fármaco a través de la barrera peritoneal. Esta característica se ha denominado ventaja farmacocinética (PKA) y permitiría comparar distintos fármacos en función de la cantidad del mismo que pasa a sangre. Inicialmente, se empleaba el ratio de concentraciones máximas peritoneales y plasmáticas (22), sin embargo, en la actualidad, el AUC ratio es el parámetro utilizado con más frecuencia para determinar esta PKA, de forma que cuanto más elevado es su valor, mayor es su PKA. Por tanto, fármacos con PKA elevados prevalecerían sobre otros que presentaran menores valores, cuando otras consideraciones, como la eficacia y la toxicidad, fueran similares. Sin embargo, la revisión inicial de la literatura puso en evidencia que tanto la determinación de este ratio como los valores resultantes del mismo para un mismo fármaco no era homogéneos entre estudios.

Por tanto, el cuarto objetivo de esta Memoria de Tesis Doctoral, presentado en el Capítulo V, fue evaluar el uso del AUC ratio como parámetro para determinar la PKA de HIPEO mediante la realización de simulaciones determinísticas en base a un reciente modelo farmacocinético poblacional presentado en la literatura (4) y la validación de las conclusiones de dichas simulaciones con valores de AUC ratio de estudios publicados en la literatura para HIPEO. Para ello, se consideraron tres variables que podrían modificar el AUC ratio sin afectar al paso de fármaco a través de la barrera peritoneal, y se incluyeron en los escenarios simulados. Dichas variables fueron, en primer lugar, el tiempo al que se obtiene la última concentración plasmática para la determinación del AUC_{pla} (T_{last_pla}), en segundo lugar, la duración de la instilación y, en tercer lugar, el grado de distribución del fármaco en el organismo, evaluado mediante el parámetro farmacocinético aclaramiento intercompartimental (Q_2).

En cuanto a la evaluación de la primera variable, impacto en el valor del AUC ratio del T_{last_pla}, los valores de AUC ratio obtenidos tras las simulaciones de seis escenarios para los tiempos de instilación de 30 y 120 minutos, mostraron que el AUC ratio era dependiente de la

variable T_{last_pla} (Tabla 1, Capítulo V). Este valor decrecía a medida que T_{last_pla} se prolongaba en el tiempo, alcanzando el mismo valor para ambos tiempos de instilación cuando T_{last_pla} se calculaba para un tiempo equivalente a infinito.

Esta variable se evaluó en la literatura a partir de tres estudios Fase 1 y cinco estudios retrospectivos (Tabla 2, Capítulo V), a partir de los que se evidenció que el último tiempo de muestreo para determinar las concentraciones plasmáticas no era homogéneo. La obtención de los valores de AUC ratio a partir de la digitalización de los perfiles de concentración-tiempo de estos estudios confirmó el patrón de las simulaciones anteriormente realizadas: el valor de AUC-ratio disminuía a medida que T_{last_pla} se prolongaba (Figura 1, Capítulo V).

La segunda variable evaluada, tiempo de instilación, demostró alterar linealmente el valor del AUC ratio obtenido tras la simulación de cinco escenarios, que abarcaron tiempos de instilación desde los 30 hasta los 120 minutos. De esta de manera, un aumento de la duración de la instilación resultó en un incremento del valor del AUC ratio, obteniendo un rango de valores desde 13,4 hasta 16,5 para 30 y 120 minutos, respectivamente (Tabla 3 y Figura 2, Capítulo V).

En cuanto a la evaluación de la tercera variable, Q_2, los valores de AUC ratio fueron 56,6, 45,2 y 39,1 cuando el valor de Q_2 fue el doble de su valor original, su valor original y la mitad de dicho valor, respectivamente. (Figura 3 y Tabla 4, Capítulo V). La modificación del valor de Q_2 tuvo un impacto en el valor de AUC_{pla}, de manera que cuanto mayor era Q_2, menor resultó la exposición sistémica. El mismo patrón se observo en el resto de escenarios para distintos T_{last_pla}.

En consecuencia y siguiendo los resultados de este estudio, emplear el AUC ratio como el único indicador de la PKA o como referencia para comparar dos fármacos presenta una limitación principal, que consiste en la dependencia del AUC ratio de variables no relacionadas con la absorción sistémica. Así, a medida que T_{last_pla} aumentaba, el valor del AUC ratio de HIPEO decrecía sistemáticamente. La tendencia opuesta se observó en el valor de AUC ratio cuando la segunda variable evaluada, el tiempo de instilación, se prolongó. La tercera variables estudiada, la distribución sistémica del fármaco a un compartimento periférico, también tuvo un impacto en su valor, de manera que cuanto vayo era Q_2, menor el AUC_{pla}, aumentando el valor del AUC ratio.

Por tanto, cuando dos fármacos, “A” y “B”, son comparados y teniendo en cuenta que ambos podrían tener distintos tiempos de instilación, distinto T_{last_pla} y distinto Q_2, tomar el valor de AUC ratio como una medida de la PKA podría resultar erroneamente en la elección “A” sobre “B”, aun cuando “B” podría presentar una menor absorción a circulación sistémica. Además, podría ocurrir que se registrasen distintos valores de AUC ratio en la literatura para el

mismo fármaco si no se considera la exposición sistémica completa, cuando, por el contrario, la PKA debería ser un parámetro característico de cada fármaco.

Sin embargo, estas variables no tuvieron un impacto en el valor del AUC ratio cuando T_{last_pla} se consideró equivalente a infinito y, por tanto, el AUC_{pla} fue calculado como $AUC_{T0_{pla}}^{\infty}$. Siguiendo las ecuaciones 2 y 3 planteadas en el Capítulo V, el AUC ratio en este escenario tendería al ratio entre CL_{el} y CL_{abs} , es decir, cuando se tiene en cuenta la exposición sistémica del fármaco de forma completa. En este escenario, el AUC ratio solo dependería de los parámetros intrínsecos del fármaco CL_{el}, CL_{abs} y F, sin la influencia de otras variables como las evaluadas en este capítulo. Para el caso de HIPEO, y siguiendo estas ecuaciones, su AUC ratio resultó en un valor de 0,822, el mismo valor obtenido a lo largo de todas las simulaciones presentadas en este Capítulo a un tiempo considerado infinito. Este valor es consistente para cualquier tiempo de instilación o cualquier valorde Q2, confirmando la ecuación 3 del Capítulo V. De forma notable, los datos obtenidos de la literatura siguieron la misma tendencia que la obtenida durante las simulaciones.

Por tanto, los resultados de las simulaciones, apoyados por el análisis de la literatura revisada, indicarían que el AUC ratio no es un parámetro correcto para estimar la absorción desde la cavidad peritoneal a la circulación sistémica. El valor del AUC ratio no es único y característico de cada fármaco cuando AUC_{pla} se calcula para cualquier tiempo distinto de infinito. Además, este ratio tampoco sería válido para comparar la PKA de dos fármacos y no debería emplearse para demostrar si un fármaco puede usarse en HIPEC de forma segura respecto a su toxicidad, dado que este valor es altamente dependiente de T_{last_pla} , el tiempo de instilación y el grado de distribución del fármaco en el organismo. Como alternativa al AUC ratio, se propone el estudio de k_a y F como los parámetros verdaderos e independientes que reflejan el grado de distribución absorbido. Las conclusiones aquí obtenidas podrían evaluarse mediante estudios preclínicos o clínicos prospectivos correctamente diseñados.

5. REFERENCIAS

1. Sugarbaker PH, Van der Speeten K, Stuart OA. Pharmacologic rationale for treatments of peritoneal surface malignancy from colorectal cancer. World J Gastrointest Oncol. 2010; 2:19–30.

2. Sugarbaker PH, Stuart OA, Carmignani CP. Pharmacokinetic changes induced by the volume of chemotherapy solution in patients treated with hyperthermic intraperitoneal mitomycin C. Cancer Chemother Pharmacol. 2006; 57:703–708

3. Elias D, Goéré D, Dumont F, Honoré C, Dartigues P, Stoclin A, et al. Role of hyperthermic intraoperative peritoneal chemotherapy in the management of peritoneal metastases. Eur J Cancer. 2014; 50:332–40.

4. Pérez-Ruixo C, Peris JE, Escudero-Ortiz V, Bretcha-Boix P, Farré-Alegre J, Pérez-Ruixo JJ, et al. Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol. 2014; 73:1009-20. doi: 10.1007/s00280-014-2436-6.

5. Jing L, Kraut EH, Balcerzak S et al. Dosing sequencedependent pharmacokinetic interaction of oxaliplatin with paclitaxel in the rat. Cancer Chemother Pharmacol. 2001; 50:445–453. doi:10.1007/s00280-002-0531-6

6. Van der Speeten K, Stuart OA, Mahteme H, Sugarbaker PH. Pharmacology of perioperative 5-fluorouracil. J Surg Oncol. 2010; 102:730–5.

7. Sladen RN. Effect of anesthesia and surgery on renal function. Crit Care Clin. 1987; 3:373–93.

8. Mustafa S, Elgazzar AH, Essam H, Gopinath S, Mathew M. Hyperthermia alters kidney function and renal scintigraphy. Am J Nephrol. 2007; 27:315–21.

9. De Lima Vazquez V, Stuart OA, Mohamed F, Sugarbaker PH. Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics. Cancer Chemother Pharmacol. 2003; 52:108–12.

10. Yonemura Y, Fujimura T, Nishimura G, FallaR null, Sawa T, Katayama K, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. Surgery. 1996; 119:437–44.

11. Elias D, Gilly F, Boutitie F, Quenet F, Bereder J-M, Mansvelt B, et al. Peritoneal Colorectal Carcinomatosis Treated With Surgery and Perioperative Intraperitoneal Chemotherapy: Retrospective Analysis of 523 Patients From a Multicentric French Study. JCO. 2010; 28:63–8.

12. Pérez-Ruixo C, Valenzuela B, Peris JE, Bretcha-Boix P, Escudero-Ortiz V, Farré-Alegre J, et al. Population pharmacokinetics of hyperthermic intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis after cytoreductive surgery. Cancer Chemother Pharmacol. 2013; 71:693–704.

13. Ferron G, Dattez S, Gladieff L, Delord J-P, Pierre S, Lafont T, et al. Pharmacokinetics of heated intraperitoneal oxaliplatin. Cancer Chemother Pharmacol. 2008; 62:679–83.

14. Mustafa S, Elgazzar AH, Essam H, Gopinath S, Mathew M. Hyperthermia alters kidney function and renal scintigraphy. Am J Nephrol. 2007; 27:315–21.

15. Huntjens DRH, Strougo A, Chain A, Metcalf A, Summerfield S, Spalding DJM, et al. Population pharmacokinetic modelling of the enterohepatic recirculation of diclofenac and rofecoxib in rats. Br J Pharmacol. 2008; 153:1072–84.

16. Sugarbaker PH, Van der Speeten K. Surgical technology and pharmacology of hyperthermic perioperative chemotherapy. J Gastrointest Oncol. 2016; 7:29–44.

17. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. Cancer Chemother Pharmacol. 1998; 41:147–54.

18. Bendavid Y, Leblond FA, Dubé P. A study of the effect of temperature on the pharmacokinetic profile of raltitrexed administered by intraperitoneal route in the rat. Med Sci Monit. 2005; 11:BR1–5

19. Sørensen O, Andersen AM, Kristian A, Giercksky K-E, Flatmark K. Impact of hyperthermia on pharmacokinetics of intraperitoneal mitomycin C in rats investigated by microdialysis. J Surg Oncol. 2014; 109:521–6.

20. Pestieau SR, Stuart OA, Chang D, Jacquet P, Sugarbaker PH. Pharmacokinetics of intraperitoneal gemcitabine in a rat model. Tumori. 1998; 84:706–11.

21. Zakris EL, Dewhirst MW, Riviere JE, Hoopes PJ, Page RL, Oleson JR. Pharmacokinetics and toxicity of intraperitoneal cisplatin combined with regional hyperthermia. J Clin Oncol. 1987; 5:1613–20.

22. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Rationale for Peritoneal Drug Administration in the Treatment of Ovarian Cancer. Cancer Treat Rep. 1978; 62: 1–11.

CAPÍTULO VII. CONCLUSIONES

UNIVERSITAS
Miguel
Hernández

1. CONCLUSIONES

1. Considerando la técnica HIPEC como una administración local, sin intención a nivel sistémico, se recomienda el uso de concentraciones de fármaco fijas en lugar de su dosificación en función de la superficie corporal de cada paciente. Aunque muchos grupos de trabajo emplean concentraciones homogéneas, debido a que tanto dosis como volumen se normalizan en función de la superficie corporal, sería más práctico definir previamente una concentración fija e independiente de las características antropométricas.

2. Las condiciones quirúrgicas asociadas a HIPEC, entendidas como la realización de una laparotomía seguida de una instilación de solución hipertérmica a la cavidad peritoneal (LIHI), afectan a los procesos de eliminación y distribución desde sangre a tejidos periféricos del fármaco en rata Wistar, causando un incremento en la exposición sistémica del mismo. Por tanto, la comparación a nivel clínico de los parámetros farmacocinéticos de oxaliplatino obtenidos tras administraciones iv con aquéllos obtenidos tras intervenciones HIPEC debe ser realizada con cautela. Los resultados de este estudio evidenciarían un uso limitado de los parámetros farmacocinéticos obtenidos tras administraciones iv para simular nuevos escenarios en HIPEC para oxaliplatino.

3. El perfil de las concentraciones peritoneales y plasmáticas de oxaliplatino tras administraciones iv e ip en rata Wistar se caracteriza correctamente mediante un modelo bicompartimental con absorción de primer orden desde peritoneo a plasma. Durante la administración de oxaliplatino mediante la técnica HIPEC a ratas Wistar el proceso de eliminación del fármaco sufrió un deterioro, asociado a la propia técnica. El modelo farmacocinético poblacional final propuesto fue capaz de estimar el tiempo al que este deterioro ocurre, estimándose en 31,4 minutos.

4. Las covariables asociadas al tratamiento HIPEC: dosis, tiempo de instilación y temperatura no tienen un impacto significativo sobre los parámetros farmacocinéticos del modelo desarrollado. El análisis de la potencia del estudio para detectar efectos clínicamente significativos de estas covariables sobre los parámetros farmacocinéticos demostró una potencia superior al 80% para todas las covariables.

5. Los resultados de las simulaciones realizadas para administraciones de oxaliplatino intraperitoneal hipertérmico (HIPEO), reforzados por los resultados del análisis de los estudios revisados en la bibliografía, demuestran que emplear el AUC ratio como indicador de la ventaja farmacocinética de los fármacos empleados en HIPEC presenta importantes limitaciones, ya que depende de variables que no tienen relación con el grado de absorción del fármaco. Como

alternativa al AUC ratio, se propone el estudio de ka como el parámetro característico e independiente que refleja la cantidad de fármaco absorbido desde la cavidad peritoneal.

CAPÍTULO VIII. ANEXOS

UNIVERSITAS
Miguel
Hernández

1. ANEXO II-1. PUBLICACIÓN ORIGINAL "IMPORTANCE OF STANDARDIZING THE DOSE IN HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC): A PHARMACODYNAMIC POINT OF VIEW"

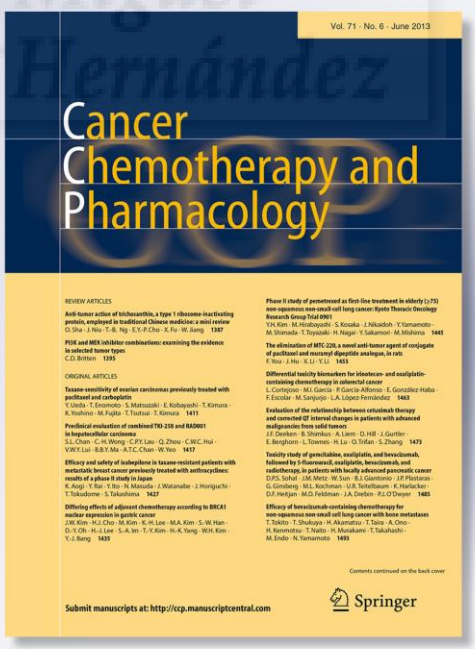
Importance of standardizing the dose in hyperthermic intraperitoneal chemotherapy (HIPEC): a pharmacodynamic point of view

Maria Isabel Mas-Fuster, Amelia Ramon-Lopez & Ricardo Nalda-Molina

Cancer Chemotherapy and Pharmacology

ISSN 0344-5704

Cancer Chemother Pharmacol
DOI 10.1007/s00280-013-2204-z



Springer

UNIVERSITAS
Miguel
Hernández

Cancer Chemother Pharmacol
DOI 10.1007/s00280-013-2204-z

LETTER TO THE EDITOR

Importance of standardizing the dose in hyperthermic intraperitoneal chemotherapy (HIPEC): a pharmacodynamic point of view

Maria Isabel Mas-Fuster · Amelia Ramon-Lopez · Ricardo Nalda-Molina

Received: 20 March 2013 / Accepted: 22 May 2013

Peritoneal carcinomatosis is a severe disease progression in patients with intra-abdominal cancer, and it remains one of the most common causes of incurability in these cases. An aggressive strategy with cytoreductive surgery (CCR) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a therapeutic schedule focused on the local handling of this progression, with many studies showing a significant increase in the median overall survival compared to the systemic chemotherapy treatment. Examples of drugs used in this type of administration are oxaliplatin, carboplatin, cisplatin, mitomycin C, irinotecan, paclitaxel, docetaxel, doxorubicin and melphalan.

Given that this protocol is a local treatment, with no systemic effect intention, and based on the premise that the same concentration produces a similar effect and toxicity, doses should be considered in terms of concentration instead of being defined by the body surface area (BSA). It should be kept in mind that, in HIPEC, the drug does not need to be distributed in order to reach the biophase (peritoneal cavity) and, therefore, homogenous concentrations should be achieved in the instillation solution.

M. I. Mas-Fuster · A. Ramon-Lopez · R. Nalda-Molina (✉)
Division of Pharmacy and Pharmaceutics, Department of Engineering, School of Pharmacy, Miguel Hernandez University, Ctra. Alicante-Valencia Km 87, PC 03550, San Juan de Alicante, Alicante, Spain
e-mail: jnalda@umh.es

However, in the reviewed literature, the doses in HIPEC were defined by the BSA. In some of the studies, the method for calculating the volume of instillation was not specified. Therefore, the volume may vary depending on the capacity of the abdominal cavity to hold liquid or may be fixed for all patients [1]. Consequently, the initial drug concentration is no longer constant, and it depends on the volume of the instilled solution.

Other authors calculate both volume and dose from each patient's BSA [2, 3]. In these cases, the initial concentration was constant for all of them. Even though BSA may be helpful to calculate the volume of instillation needed to maintain a desired flow rate in the closed-technique HIPEC, in some cases this volume may be inappropriate. For instance, the abdominal capacity can be altered by individual pathophysiological characteristics or by the relatively frequent complications in these patients (as ascites). As a result, volumes based on the anthropometric characteristics could present a poor relationship with the abdominal cavity [4]. Thus, patients with small BSA and large abdominal cavities may have an insufficient volume to cover the entire peritoneum, and subsequent increases in volume to resolve it would change the concentration at baseline. This procedure takes us away from the initial homogenous drug concentration desired, increasing the variability in the systemic and tumor exposure to the drug. In fact, a previous study showed that the plasma drug concentrations were higher, the lower the volume was [5].

In conclusion, considering the HIPEC as a local administration, with no systemic intention, we recommend using fixed concentrations instead of dosing by BSA. Although many authors actually use homogeneous concentrations when normalizing both dose and volume by BSA, it would be more practical to define a fixed concentration independent of anthropometric characteristics.

Published online: 05 June 2013

Thus, the variability of the abdominal capacity would not influence the systemic and tumor exposure to the drug.

Conflict of interest None.

References

1. Glockzin G, von Breitenbuch P, Schlitt HJ, Piso P (2012) Treatment-related morbidity and toxicity of CRS and oxaliplatin-based HIPEC compared to a mitomycin and doxorubicin-based HIPEC protocol in patients with peritoneal carcinomatosis: a matched-pair analysis. J Surg Oncol 107:574–578
2. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S et al (2002) Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 13:267–272
3. Sugarbaker PH (1999) Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol 43(suppl):S15–S25
4. Duez A, Cotte E, Glehen O, Cotton F, Bakrin N (2009) Appraisal of peritoneal cavity's capacity in order to assess the pharmacology of liquid chemotherapy solution in hyperthermic intraperitoneal chemotherapy. Surg Radiol Anat 31:573–578
5. Sugarbaker PH, Stuart OA, Carmignani CP (2006) Pharmacokinetic changes induced by the volume of chemotherapy solution in patients treated with hyperthermic intraperitoneal mitomycin C. Cancer Chemother Pharmacol 57:703–708

2. ANEXO III-1. ARCHIVO CONTROL NM-TRAN Y OUTPUT ABREVIADO DE NONMEM CORRESPONDIENTE AL MODELO FINAL

Archivo Control NONMEM

```
$PROB  IV PARAMETERS MODEL
$INPUT  ID TIME AMT CONC LNC=DV EVID PESO FLAG
$DATA  DatosIV3.csv IGNORE=#
$SUBROUTINE ADVAN3 TRANS4

$PK

;----PK  PARAMETERS----
CL      = THETA (1) * THETA (2)**FLAG * EXP(ETA(1))
V1      = THETA (3) * EXP(ETA(2))
Q       = THETA (4) * EXP(ETA(3))
V2      = THETA (5) * THETA (6)**FLAG * EXP(ETA(4))

;----REPARAMETERIZATION----
S1      = V1/1000
S2      = V2/1000
K       = CL/V1
K12     = Q/V1
K21     = Q/V2


$ERROR
  W = THETA(7)
  IPRED = LOG(F+0.0001)
  Y =  IPRED + W*EPS(1)
  IRES = DV- IPRED
  IWRES = IRES/W

$THETA
(0.01 0.42)   ;CL if Flag eq 0
(0.01 2.19)   ;CL if Flag eq 1
(0.01 55)     ;V1
(0.01 6)      ;Q
(0.01 220)    ;V2 if Flag eq 0
(0.01 2)      ;V2 if Flag eq 0
 (0.01 0.13) ;W
```

```
$OMEGA
0.05
0.05
0.05
0.05

$SIGMA   1 FIX

$COV

$EST MAXEVAL=9990 PRINT=10 POSTHOC NOABORT
METHOD=1 MSFO=Mod02.msf

$TABLE  ID TIME AMT ETA1 ETA2 ETA3 ETA4 IPRED IWRES NOPRINT ONEHEADER FILE=TAB_MOD60.TXT

$TABLE  ID TIME AMT CL V1 Q V2 PESO ETA1 ETA2 ETA3 ETA4 IWRES
NOPRINT FIRSTONLY ONEHEADER FILE=PAR_MOD60.TXT
```

NONMEM Output

```
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0 ORIGINALLY DEVELOPED BY
STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
PROBLEM NO.:        1
IV PARAMETERS MODEL
NO. OF DATA RECS IN DATA SET:      96
 NO. OF DATA ITEMS IN DATA SET:   9
TOT. NO. OF OBS RECS:      85
 TOT. NO. OF INDIVIDUALS:     11
MONITORING OF SEARCH:

0ITERATION NO.:    0    OBJECTIVE VALUE:  -192.062669037113        NO. OF FUNC. EVALS.:   9
 CUMULATIVE NO. OF FUNC. EVALS.:        9
 NPARAMETR:  4.2000E-01  2.1900E+00  5.5000E+01  6.0000E+00  2.2000E+02  2.0000E+00  1.3000E-01
5.0000E-02  5.0000E-02  5.0000E-02 5.0000E-02
 PARAMETER:  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01
1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01
 GRADIENT:  -1.0452E+01 -6.8059E+00  9.3713E+00 -2.1998E-01  3.4819E+00  3.0958E+00  8.3648E+00 -
8.8614E+00  3.6153E+00 -7.7314E+00 -7.2669E+00

0ITERATION NO.:   10    OBJECTIVE VALUE:  -196.519310080899        NO. OF FUNC. EVALS.:  10
 CUMULATIVE NO. OF FUNC. EVALS.:      116
```

NPARAMETR: 4.2182E-01 2.2640E+00 5.3237E+01 6.0209E+00 2.2169E+02 1.9521E+00 1.1397E-01 1.1568E-01 4.3483E-02 8.5173E-02 7.3891E-02
PARAMETER: 1.0444E-01 1.3337E-01 6.7407E-02 1.0349E-01 1.0765E-01 7.5630E-02 -4.3357E-02 5.1940E-01 3.0179E-02 3.6633E-01 2.9528E-01
GRADIENT: 2.6970E+00 1.6832E+00 2.8765E-01 2.4931E-01 1.3944E+00 1.1613E+00 -1.3233E+00 5.6977E-01 7.3999E-02 3.0989E-01 5.8032E-01

0ITERATION NO.: 19 OBJECTIVE VALUE: -196.563438353567 NO. OF FUNC. EVALS.: 14
CUMULATIVE NO. OF FUNC. EVALS.: 226
NPARAMETR: 4.1687E-01 2.2561E+00 5.3212E+01 6.0149E+00 2.2143E+02 1.9419E+00 1.1525E-01 1.1060E-01 4.2420E-02 8.3142E-02 7.1387E-02
PARAMETER: 9.2328E-02 1.2988E-01 6.6941E-02 1.0249E-01 1.0648E-01 7.0366E-02 -3.1191E-02 4.9693E-01 1.7794E-02 3.5426E-01 2.7805E-01
GRADIENT: 8.8656E-03 2.0189E-03 -1.0516E-02 4.5402E-03 -5.5213E-04 3.1053E-03 2.9604E-03 1.1220E-03 1.4896E-03 -2.5761E-04 2.5884E-03

0MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 226
NO. OF SIG. DIGITS IN FINAL EST.: 3.1
ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.
ETABAR: 1.2432E-02 -8.9295E-03 -1.9772E-03 -5.1004E-03
P VAL.: 8.9052E-01 8.6207E-01 9.8037E-01 9.4581E-01
MINIMUM VALUE OF OBJECTIVE FUNCTION: - 196.563

FINAL PARAMETER ESTIMATE
THETA - VECTOR OF FIXED EFFECTS PARAMETERS

TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 7
4.17E-01	2.26E+00	5.32E+01	6.01E+00	2.21E+02	1.94E+00	1.15E-01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS

	ETA1	ETA2	ETA3	ETA4
ETA1	1.11E-01			
ETA2	0.00E+00	4.24E-02		
ETA3	0.00E+00	0.00E+00	8.31E-02	
ETA4	0.00E+00	0.00E+00	0.00E+00	7.14E-02

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

	EPS1
EPS1	1.00E+00

STANDARD ERROR OF ESTIMATE

THETA - VECTOR OF FIXED EFFECTS PARAMETERS

TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 7
8.20E-02	5.35E-01	4.15E+00	5.82E-01	2.77E+01	3.47E-01	1.78E-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS

	ETA1	ETA2	ETA3	ETA4
ETA1	5.49E-02			
ETA2	.....	2.45E-02		
ETA3	.....	.....	3.03E-02	
ETA4	.....	.....	.....	2.69E-02

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

	EPS1
EPS1	.....

3. ANEXO III-2. PUBLICACIÓN ORIGINAL "IMPACT OF LAPAROTOMY AND INTRAPERITONEAL HYPERTHERMIC INSTILLATION (LIHI) ON THE OXALIPLATIN PHARMACOKINETICS AFTER INTRAVENOUS ADMINISTRATION IN WISTAR RATS"

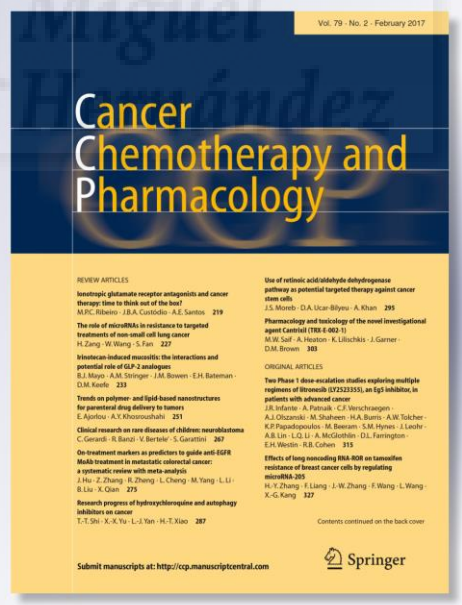
Impact of Laparotomy and Intraperitoneal Hyperthermic Instillation (LIHI) on the oxaliplatin pharmacokinetics after intravenous administration in Wistar rats

María Isabel Mas-Fuster, Amelia Ramon-Lopez, Javier Lacueva, Antonio Compañ, Patricio Más-Serrano & Ricardo Nalda-Molina

Cancer Chemotherapy and Pharmacology

ISSN 0344-5704

Cancer Chemother Pharmacol
DOI 10.1007/s00280-017-3244-6



Springer

UNIVERSITAS
Miguel
Hernández

Cancer Chemother Pharmacol
DOI 10.1007/s00280-017-3244-6

SHORT COMMUNICATION

Impact of Laparotomy and Intraperitoneal Hyperthermic Instillation (LIHI) on the oxaliplatin pharmacokinetics after intravenous administration in Wistar rats

María Isabel Mas-Fuster[1] · Amelia Ramon-Lopez[1] · Javier Lacueva[2] · Antonio Compañ[2] · Patricio Más-Serrano[1,3] · Ricardo Nalda-Molina[1]

Received: 13 November 2016 / Accepted: 12 January 2017

Abstract
Purpose In peritoneal metastasis condition, the fact that most of the disease is limited to the peritoneal cavity laid the foundations for a surgical treatment, including intraperitoneal hyperthermic chemotherapy (HIPEC). The aim of this study was to evaluate the impact of the surgical procedures implied in open HIPEC technique, referred to laparotomy procedures followed by an intraperitoneal hyperthermic instillation (LIHI) on oxaliplatin tissue distribution and elimination. To delimit the influence of this procedure alone, oxaliplatin was administered as an intravenous (iv) bolus in both groups.
Methods An experimental model in Wistar rats was employed, and LIHI was evaluated as a dichotomous covariate by using a population pharmacokinetic (PK) approach. Rats were randomized in two groups receiving 1.5 mg iv oxaliplatin alone or 1.5 mg iv oxaliplatin under LIHI conditions, carrying out a hyperthermic 5% dextrose instillation. The oxaliplatin plasma concentrations were characterized by an open two-compartment PK model.
Results Results concluded that surgical conditions affect the oxaliplatin elimination and distribution from blood to peripheral tissues, increasing the systemic drug exposure. Concretely, oxaliplatin peripheral volume of distribution, and clearance decreased by 48.6% and 55.3%, respectively, compared to the control group that resulted in a two-fold increase of the area under the concentration time curve.
Conclusions Comparison in clinical practice of oxaliplatin PK parameters obtained after iv administrations with those obtained after HIPEC interventions must be done carefully. This would limit the use of iv PK parameters to simulate new scenarios for oxaliplatin in HIPEC.

Keywords Population pharmacokinetics · Oxaliplatin · Hyperthermia · Intraperitoneal chemotherapy · Peritoneal metastasis

Abbreviations

HIPEC	Hyperthermic intraperitoneal chemotherapy
PM	Peritoneal metastasis
PK	Pharmacokinetic
LIHI	Laparotomy + intraperitoneal hyperthermic instillation
iv	Intravenous
$AUC_{pla\ 0-\infty}$	Area under the plasma concentration time curve from time zero to infinite
CL	Clearance
V_1	Central volume of distribution
Q	Intercompartmental clearance

✉ Amelia Ramon-Lopez
aramon@umh.es

María Isabel Mas-Fuster
maria.mas.fuster@gmail.com

Javier Lacueva
fj.lacueva@umh.es

Antonio Compañ
af.company@umh.es

Patricio Más-Serrano
patricio.mas.serrano@gmail.com

Ricardo Nalda-Molina
jnalda@umh.es

[1] Division of Pharmacy and Pharmaceutics, Department of Engineering, School of Pharmacy, Miguel Hernández University, San Juan de Alicante, Alicante, Spain

[2] Department of Pathology and Surgery, School of Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain

[3] Clinical Pharmacokinetics Unit, Pharmacy Department, Hospital General Universitario de Alicante, Alicante, Spain

Published online: 06 February 2017

V_2	Peripheral volume of distribution
IIV	Interindividual variability
CV	Coefficient of variation
GOF	Goodness of fit plots
NPDE	Normalized prediction distribution errors
OFV	Objective function value
NPBS	Nonparametric bootstrap
pcVPC	Prediction-corrected visual predictive check
CI	Confidence intervals
SD	Standard deviation
RSE	Relative standard errors

Introduction

Multimodal therapy consisting of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) has shown a potential benefit in selected patients with peritoneal metastasis (PM) [1]. This procedure increases the efficacy of chemotherapy by exposing remaining microscopic tumor cells in peritoneal cavity directly to a high drug concentration while minimizing systemic drug exposure due to the peritoneum-plasma barrier [2].

To this purpose, drugs used in HIPEC must have specific characteristics, such as a high capacity of tumor penetration, a low capacity to diffuse into the subperitoneal tissues and capillaries, and a synergetic profile with hyperthermia. Oxaliplatin is one of the most used drugs in HIPEC for the PM treatment from colorectal origin [3], given that it fulfills the aforementioned characteristics as well as its cytotoxicity is not cell cycle specific [4]. Several pharmacokinetic (PK) studies have evaluated the impact of different variables involved in HIPEC on the oxaliplatin plasma concentration profile, such as the type of carrier solution, the oxaliplatin administration procedure, and the type of technique [5–7]. However, the impact of the surgical procedures implied in open HIPEC technique, referred to laparotomy procedures followed by an intraperitoneal hyperthermic instillation (LIHI), on the systemic oxaliplatin PK parameters has not been previously studied. It is worth mentioning that this factor is common during this treatment, regardless of other variables, and a significant impact on parameters, such as systemic clearance and volume of distribution, could affect drug plasma concentrations and thus toxicity of drug therapy.

Ideally, one would expect that the PK parameters obtained after systemic administration were useful for simulation purposes (e.g., evaluation of new doses for HIPEC treatments). However, this assumption would require that these parameters were not affected by the surgical conditions that occur in HIPEC. Thus, this work has considered LIHI as an independent covariate and has evaluated its impact on the oxaliplatin tissue distribution and elimination through an experimental model in Wistar rats using a population PK approach.

Materials and methods

Experimental procedure

Animals

The technique was developed in 12 healthy male Wistar rats, weighing 250–300 grams, kept in the standard housing conditions with free access to water and a fasting day before surgery. Sample size was selected, after statistical evaluation, as minimally required while still being able to assess experimental variability. The development of the experimental model, previously validated in rat (unpublished work), was held at the Animal Experimentation Service of San Juan de Alicante, associated with Miguel Hernández University of Elche (UMH). At the end of the procedure, rats were sacrificed. Care of the animals and drug administration was performed under veterinary control according to European Union Directive 2010/63/EU for animal experiments and with approval from the Ethics Committee of the UMH.

Experimental design

Anesthesia was induced by isoflurane (Isovet®) with oxygen vaporization. Intensity was regulated during the induction and maintenance phases (Fluovac®, Surgivet®). To avoid hypothermia induced by the anesthesia and by the opening of the abdominal cavity, rats were placed in the surgical area on a thermal blanket.

To evaluate the impact of LIHI on the oxaliplatin PK parameters, rats were randomized into two groups. An oxaliplatin dose of 1.5 mg, calculated from previous experimental studies [8], was administered as an intravenous (iv) bolus to the rats of both groups through a permanent jugular vein catheterization.

In the control group (group 1, $n=6$), no surgery was performed. In the LIHI group (group 2, $n=6$), a laparotomy followed by hyperthermic intraperitoneal 5% dextrose instillation was performed, simulating the conditions of the open HIPEC procedure [9], without adding any intraperitoneal drug. To perform recirculation of dextrose, an inlet and outlet drains were placed in the abdominal cavity. A total volume of 100 mL of dextrose solution was recirculated for 30 min at 50 mL/min using an infusion pump (Masterflex® L/S EasyLoad 77202-50). In this group, oxaliplatin was administered 5 min after the start of the hyperthermic intraperitoneal instillation. Temperature of the solution in the abdominal cavity was maintained to 40–42 °C using a

thermostatic bath (JpSelecta®). Once the instillation finalized, the volume remaining in the peritoneal cavity was drained and the abdominal cavity was closed.

Buprenorphine (Buprex® 0.3 mg/mL) was administered as analgesic at a subcutaneous dose of 0.05 mg/kg after surgery.

According to previous simulation studies, blood samples were taken after the iv bolus administration of oxaliplatin at times 1, 10, 20, 30, 45, 60, 90, 150, 270, and 510 min. To balance blood loss by the sampling schedule and to prevent the catheter obstruction, the catheter was rinsed with saline and filled with a 60% polyvinylpyrrolidone solution with heparinized saline (500 IU/mL) after each extraction. Samples were collected in heparin tubes and centrifuged at room temperature.

Plasma was stored at −20 °C until their analysis. Total oxaliplatin was measured by a validated graphite furnace atomic absorption spectrophotometry method [10]. The analytical technique employed has a limit of quantification of 0.06 mg/L of oxaliplatin.

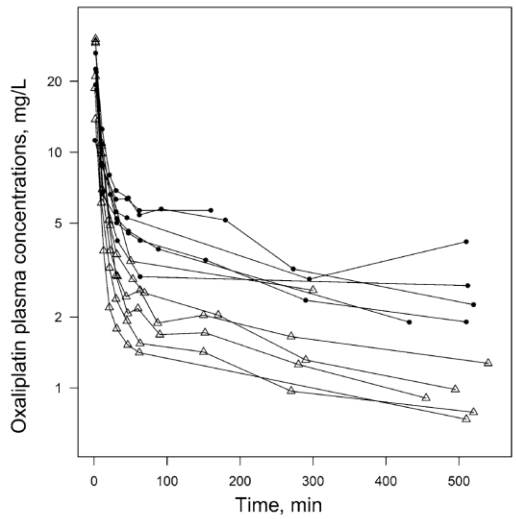


Fig. 1 Oxaliplatin plasma concentration profile for control group (*empty triangles*) and LIHI group (*black circles*)

Pharmacokinetic model development

Nonparametric area under the plasma concentration time curve from time zero to infinite ($AUC_{pla\,0-\infty}$) was calculated in both groups.

To characterize the time course of oxaliplatin plasma concentrations, a population PK modeling was applied to the data. Data fitting was performed using the FOCE algorithm in the NONMEM 7.3 software package [11]. Post-processing of results and diagnostic plots was performed using R Studio 0.99.486 [12] implemented with R 3.2.5 [13].

Structural model

Time course of iv oxaliplatin plasma concentrations decayed in a bi-exponential fashion (Fig. 1), indicating that the iv oxaliplatin PK is characterized by a two-compartment model, with linear elimination and nonspecific distribution to peripheral tissues, consistent with previous studies [5]. Thus, this model was parameterized in terms of clearance (CL), central volume of distribution (V_1), intercompartmental clearance (Q) and peripheral volume of distribution (V_2).

Statistical model

Taking into account the population model, variability of PK parameters between rats (interindividual variability, IIV) was assumed to follow a log-normal distribution. The unexplained or residual variability was assessed using an additive model after log-normal transformation of observed and model predicted oxaliplatin plasma concentrations. Magnitude of the residual and interindividual variability was expressed as coefficient of variation (CV). The shrinkage of the empirical Bayes estimate of the IIV was calculated as previously suggested [14]. Once the population PK model that best described the data was established, it was followed by covariate analysis and model validation.

Model selection criteria

The improvement of the fit obtained for each model was assessed by the likelihood ratio test for nested models (significance level, $p=0.01$), the reduction in the IIV and residual variability, the precision and correlation in parameter estimates, and the examination of shrinkage, the goodness of fit plots (GOF) and the normalized prediction distribution errors (NPDE) [14].

Covariate analysis

Once the model was validated, the impact of LIHI on its parameters was evaluated as a dichotomous covariate. The NONMEM-generated objective function value (OFV) was used to perform the likelihood ratio test for nested models. The significance level was set to $p=0.01$, which corresponds to a decrease in OFV of ≥6.635 points, after the inclusion of one parameter, assuming that the difference in minimum value of the OFV between two nested models is χ^2 distributed.

Model validation

A nonparametric bootstrap (NPBS) and a prediction-corrected visual predictive check (pcVPC) [15] were used as internal evaluation methods to qualify the estimates of the PK model parameters.

The NPBS was made after the generation of 1000 databases with resampling and replacement by using the software WINGS for NONMEM (N. Holford, Version 616, Auckland, New Zealand). The mean and the 95% confidence intervals (CI) of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset.

To perform the pcVPC, the 5th, 50th and 95th percentiles of the observed values, and the 95% CI for the corresponding model-based predicted percentiles computed from 1000 replicates, obtained by simulating the design of the underlying dataset with the final model parameters, were calculated.

Results

The technique was well tolerated in general, although death of one of the rats from LIHI group was recorded during surgery for unknown etiology.

Oxaliplatin plasma profiles

A total of 91 plasma samples were available for PK analysis, 49 of them corresponding to the control group and 42 to LIHI group. Differences between both groups were visually detected (Fig. 1), with the highest drug plasma concentrations corresponding to the group that suffered LIHI. The oxaliplatin average maximum plasma concentration and standard deviation (±SD) were 23.7 (6.9) mg/L in control group and 22.5 (2.5) mg/L in LIHI group, reached immediately after iv oxaliplatin bolus administration. The mean (±SD) $AUC_{pla\ 0-\infty}$ was 1375 (645) mg*min/L and 2766 (440) mg*min/L for control and LIHI groups, respectively, showing significant differences in the $AUC_{pla\ 0-\infty}$ in both groups ($p < 0.01$).

Pharmacokinetics

LIHI, considered as a dichotomous covariate, significantly improved the objective function value of the model when it was included in CL and V_2, with a decrease of 18.3 points ($p < 0.001$). Therefore, LIHI was included as a covariate of both parameters and this model was considered as the final model. Values of CL in control group and LIHI group were 0.94 (28.3) mL/min and 0.42 (14.0) mL/min, respectively. Values of V_2 in control group and LIHI group were 430 (12.3) mL and 221 (11.8) mL, respectively (Table 1).

Table 1 Parameter estimates (relative standard errors) and nonparametric bootstrap analysis of the oxaliplatin population pharmacokinetic model

Model parameters	Original dataset Estimate (RSE %[a])	Nonparametric Bootstrap	
		Mean (RSE %)	95% CI
Fixed effect parameters			
$CL_{control\ group}$ (mL/min)	0.94 (28.3)	0.94 (15.2)	0.67–1.20
$CL_{LIHI\ group}$ (mL/min)	0.42 (14.0)	0.42 (19.4)	0.29–0.59
V_1 (mL)	53.2 (7.80)	53.4 (8.16)	46.7–62.4
Q (mL/min)	6.01 (9.58)	6.05 (9.92)	5.15–7.38
$V_{2\ control\ group}$ (mL)	430 (12.3)	436 (12.8)	350–557
$V_{2\ LIHI\ group}$ (mL)	221 (11.8)	223 (13.4)	181–287
Interindividual variability (η)[b]			
η_{CL}	33.3 (24.7)	29.7 (31.9)	15.0–49.0
η_{V1}	20.6 (28.8)	17.7 (42.5)	0.20–29.0
η_{Q}	28.8 (18.1)	26.7 (22.9)	16.6–37.7
η_{V2}	26.7 (18.3)	22.7 (27.2)	11.7–32.6
Residual variability[b]	11.5 (15.0)	11.4 (14.5)	8.90–14.9

Shrinkage values (%) of BSV in CL, V_1, Q and V_2 were estimated at 5.70, 13.2, 3.02 and 2.32

[a]Relative standard error

[b]Expressed as CV (%)

Upper panels in Fig. 2 show GOF for the population (panel A) and individual (panel B) oxaliplatin plasma predicted *vs* observed concentrations, indicating the absence of bias in the model. Panels C and D show the results of NPDE check, confirming a normal distribution around each individual observation within the predictions of the model. In fact, the mean (±SD) of the NPDE for plasma concentrations was 0.02 (95% CI −0.14:0.22) and 0.90 (95% CI 0.78:−1.06), respectively. These results confirmed that observations were accurately predicted by the model without bias. Panels of Fig. 3 show the pcVPC, evidencing that the model developed was appropriate to describe the time course of oxaliplatin and its variability in both groups. Final model estimates were similar to the average of the NPBS replications and were included within the 95% CI (Table 1).

The PK model described the data accurately, with an adequate IIV of less than 35% in all the PK parameters and a residual variability of less than 12%. Shrinkage values of IIV were estimated in less than 14%.

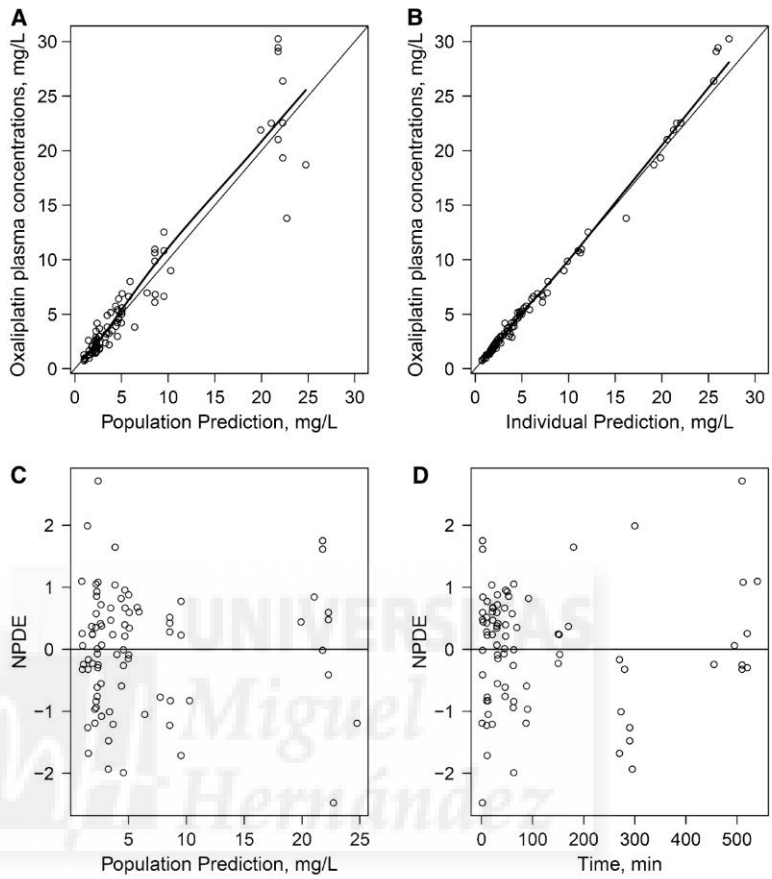


Fig. 2 *Diagnostic plots* for the PK analysis. The *upper panels* represent the observed vs population (**a**) and individual (**b**) predicted concentrations. The *lower panels* represent the NPDE vs population predicted concentrations (**c**) and time (**d**). The mean (±SD) of the NPDE for plasma concentrations was 0.02 (95% CI −0.14:0.22) and 0.90 (95% CI 0.78:1.06), respectively

Discussion

The use of HIPEC in the clinical practice is increasing, supported by the advantageous results against more classic treatments based on systemic chemotherapy. There have been preclinical studies in HIPEC that considered the impact of different variables on the PK parameters of cytotoxic drugs [16]. However, influence of LIHI, despite being a process common to all experiments, has not been evaluated as a covariate that can modify the PK parameters of oxaliplatin.

This experimental study evaluated the impact of the LIHI procedure, inherent in the open HIPEC technique, in Wistar rat. To delimit the influence of this procedure alone, it was decided to administer oxaliplatin as an iv bolus in both groups, resulting in two strictly equal groups, except from LIHI procedure. Therefore, this study evaluated only the impact of LIHI on the systemic drug distribution and elimination. Kinetics of oxaliplatin distribution and elimination after a single iv administration of 1.5 mg were determined, in the presence and absence of the conditions described above.

A nonparametric analysis of the results revealed that the systemic exposure of the drug, $AUC_{pla\ 0-\infty}$in the control group was significantly lower than the $AUC_{pla\ 0-\infty}$obtained for LIHI group (1375 mg*min/L vs 2766 mg*min/L, respectively). In agreement with the literature [5], a structural two-compartment model described successfully the oxaliplatin plasma concentration profile. CL and V_2 decreased by 55.3% and 48.6%, respectively, when iv administration of oxaliplatin occurred in LIHI conditions, compared to the values achieved in the control group. CL value in control group is consistent with other studies found in literature quantifying total oxaliplatin after iv administration [17]. One might have expected CL in LIHI group being higher than CL in control group, given that an open

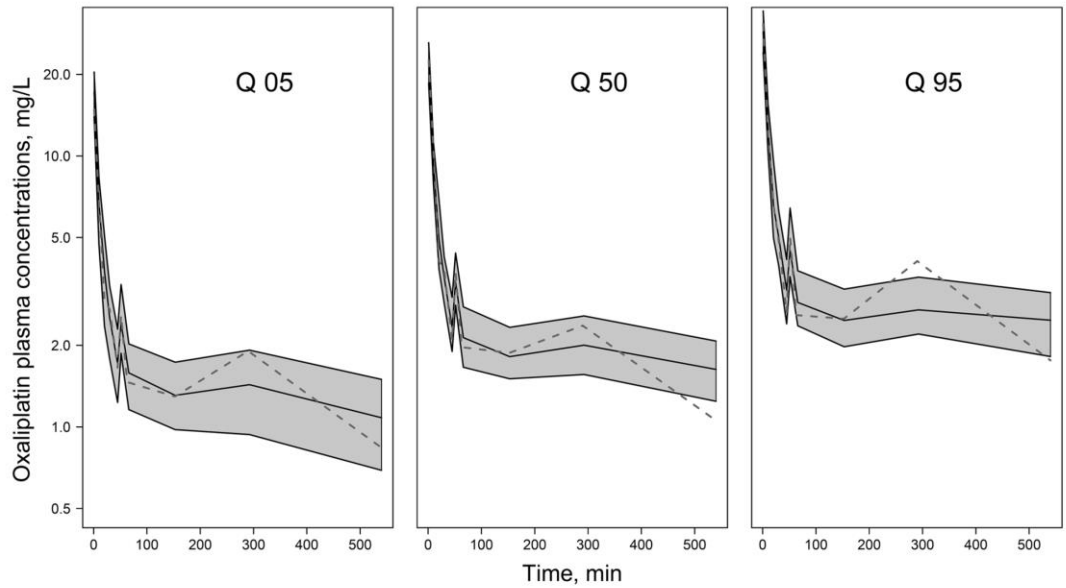


Fig. 3 pcVPC, showing the 5th (Q05), 50th (Q50), and 95th (Q95) percentiles of the observed values (*dashed lines*), and the 95% confidence interval for the corresponding model-based predicted percentiles (*solid lines*)

abdominal cavity filled with 5% dextrose solution could act as a sink [18], causing the distribution of oxaliplatin from blood to the peritoneal cavity, and therefore, increasing the apparent CL obtained. However, it has not been the result of this study. Given that platinum compounds are mainly excreted by the kidney, one possible hypothesis would be that the decrease in CL observed in LIHI group could have been caused by a change in renal function due to the surgical stress [19, 20]. This deterioration in renal function could have balanced out the "sink" effect, being even more determinant and thus, resulting in a final decrease of CL when rats are submitted to these conditions. This hypothesis would have been confirmed with greater robustness by taking peritoneal samples or by placing a bladder catheter. This would have allowed to determine oxaliplatin concentrations in the peritoneum or urine and the volume of urine excreted, respectively, and therefore to better explore the origin of the modification in CL value.

Previous clinical studies showed that, although the peritoneum-plasma barrier limits the oxaliplatin access from peritoneum into the blood, the systemic exposure of oxaliplatin after HIPEC administration was similar to the systemic exposure after iv administration [5], even though the former would be expected to be lower than the latter. The results of our study suggested that this fact could be due to the decrease in CL due to the surgical stress in patients administered by HIPEC technique.

A limitation of this study is that it has been conducted in healthy rats, with no peritonectomy performed. Therefore, actual conditions of cytoreduction were not completely recreated. Even though no changes in the PK have been reported based on the extent of peritonectomy [21], the impact of the presence vs absence of peritonectomy on PK has not been studied. Future studies in this line, including peritonectomy in rats, can help to confirm the presented results in this work.

The results of our study concluded that LIHI affects the oxaliplatin elimination and its distribution from blood to peripheral tissues in Wistar rats, causing an increased systemic drug exposure, reflected through the significant increase in $AUC_{pla\ 0-\infty}$. Thus, comparison in clinical practice of oxaliplatin PK parameters obtained after a single iv administration with those obtained after HIPEC interventions must be done carefully. This would limit the use of iv PK parameters to simulate new scenarios for oxaliplatin in HIPEC.

Acknowledgements The authors would like to acknowledge the Animal Experimentation Service of San Juan de Alicante, UMH, for all the assistance received.

Funding This study was funded by the Fundación Navarro Tripodi and from Proyecto Bancaja-UMH. The funding sources had no involvement in study design, collection, analysis and interpretation of

data, in the writing of the report or in the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Research involving animals Development of experimental model was held at the Animal Experimentation Service of San Juan de Alicante, attached to Miguel Hernández University of Elche (UMH). At the end of the procedure, rats were sacrificed. Care of the animals and drug administration were performed under veterinary control according to European Union Directive 2010/63/EU for animal experiments and with approval from the Ethics Committee of the UMH.

References

1. Sugarbaker PH (1999) Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol 43:S15–S25
2. Dedrick RL, Flessner MF (1997) Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst 89:480–487
3. Elias D, Gilly F, Boutitie F et al (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric french study. J Clin Oncol 28:63–68
4. Elias D, Bonnay M, Puizillou JM et al (2002) Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 13:267–272
5. Pérez-Ruixo C, Peris JE, Escudero-Ortiz V et al (2014) Rate and extent of oxaliplatin absorption after hyperthermic intraperitoneal administration in peritoneal carcinomatosis patients. Cancer Chemother Pharmacol 73:1009–1020. doi:10.1007/s00280-014-2436-6
6. Gesson-Paute A, Ferron G, Thomas F et al (2008) Pharmacokinetics of oxaliplatin during open versus laparoscopically assisted heated intraoperative intraperitoneal chemotherapy (HIPEC): an experimental study. Ann Surg Oncol 15:339–344. doi:10.1245/s10434-007-9571-9
7. Ferron G, Dattez S, Gladieff L et al (2008) Pharmacokinetics of heated intraperitoneal oxaliplatin. Cancer Chemother Pharmacol 62:679–683. doi:10.1007/s00280-007-0654-x
8. Pestieau S, Belliveau JF, Griffin H et al (2001) Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies. J Surg Oncol 76:106–114
9. Pelz JOW, Doerfer J, Hohenberger W et al (2005) A new survival model for hyperthermic intraperitoneal chemotherapy (HIPEC) in tumor-bearing rats in the treatment of peritoneal carcinomatosis. BMC Cancer 5:56. doi:10.1186/1471-2407-5-56
10. Escudero-Ortiz V, Duart-Duart MJ, Pérez-Ruixo C et al (2014) Stability study of oxaliplatin and doxorubicin for intraperitoneal administration with hyperthermia. Farm Hosp 38:154–161. doi:10.7399/fh.2014.38.3.1170
11. Beal SL, Sheiner LB, Boeckmann AJ et al (eds). (1989–2013) NONMEM 7.3.0 users guides. ICON development solutions, Hanover, Maryland, USA
12. R Studio Team (2015) RStudio: Integrated Development for R. R Studio, Inc, Boston, MA. URL http://www.rstudio.com/.
13. R Core Team (2016) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/.
14. Karlsson MO, Savic RM (2007) Diagnosing model diagnostics. Clin Pharmacol Ther 82:17–20
15. Bergstrand M, Hooker AC, Wallin JE et al (2011) Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 13:143–151. doi:10.1208/s12248-011-9255-z
16. Gremonprez F, Willaert W, Ceelen W (2014) Intraperitoneal chemotherapy (IPC) for peritoneal carcinomatosis: review of animal models. J Surg Oncol 109:110–116. doi:10.1002/jso.23464
17. Jing L, Kraut EH, Balcerzak S et al (2001) Dosing sequence-dependent pharmacokinetic interaction of oxaliplatin with paclitaxel in the rat. Cancer Chemother Pharmacol 50:445–453. doi:10.1007/s00280-002-0531-6
18. Van der Speeten K, Stuart OA, Mahteme H et al (2010) Pharmacology of perioperative 5-fluorouracil. J Surg Oncol 102:730–735. doi:10.1002/jso.21702
19. Sladen RN (1987) Effect of anesthesia and surgery on renal function. Crit Car Clin 3:373–393
20. Mustafa S, Abdelhamid HE, Essam H et al (2007) Hyperthermia alters kidney function and renal scintigraphy. Am J Nephrol 27:315–321. doi:10.1159/000102597
21. de Lima Vazquez V, Stuart OA, Mohamed F et al (2003) Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics. Cancer Chemother Pharmacol 52:108–112. doi:10.1007/s00280-003-0626-8

UNIVERSITAS
Miguel
Hernández

4. ANEXO IV-1. ARCHIVO CONTROL NM-TRAN Y OUTPUT ABREVIADO DE NONMEM CORRESPONDIENTE AL MODELO FINAL

Archivo Control NONMEM

```
$PROB  POPULATION PK OF HIPEO IN WISTAR RATS. STEP FUNCTION MODEL

$INPUT  ID NID TIME AMT CMT CONC LNC=DV EVID PESO TP TPF TIF TIF2 CINF CIRE VR COLF TFLAG

$DATA  DataBase.csv IGNORE=#

$SUBROUTINE ADVAN6 TOL5

$MODEL COMP = (PER1) COMP = (CENTRAL) COMP = (PER2)

$PK
VTOT     = 100
VPER     = 25
CL       = THETA (1) * EXP(ETA(1))
CL1      = THETA (2) * EXP(ETA(1))
V1       = VTOT * EXP(ETA(2))
Q        = THETA (3) * EXP(ETA(3))
V2       = THETA (4) * EXP(ETA(4))
Q2       = THETA (5)  * EXP(ETA(5))
V3       = THETA (6)  * EXP(ETA(6))
SIG      = THETA (7)  * EXP(ETA(7))
T50      = THETA (8)  * EXP(ETA(8))

;----REPARAMETERIZATION----
S1       = V1/1000
S2       = V2/1000
;K20     = CL/V2
KA1      = Q/V1
K23      = Q2/V2
K32      = Q2/V3

$DES
STEP = TIME**SIG/(T50**SIG + TIME**SIG)
K20 = CL/V2 + (CL1/V2 - CL/V2)*STEP
DADT(1) = -KA1*A(1)*VPER/V1
DADT(2) = KA1*A(1)*VPER/V1  +  K32*A(3)-K23*A(2) -K20*A(2)
DADT(3) = K23*A(2)-K32*A(3)
```

```
$ERROR  CALLFL = 0
W1 = THETA (9)
W2 = THETA (10)
IPRED  = LOG(F+0.000001)
 TYPE = 0
 IF(CMT.EQ.2) TYPE = 1
 Y     = IPRED + W1*EPS(1)*(1-TYPE) + W2*EPS(2)*TYPE
 IRES  = DV -IPRED
 IWRES = IRES/(W1*EPS(1)*(1-TYPE) + W2*EPS(2)*TYPE)

$THETA
(0 4)          ;TH1. CL
(0 0.5)        ;TH2. CL1
(0 1)          ;TH3. Q
(0 50)         ;TH4. V2 CENTRAL
(0 8)          ;TH5. Q2
(0 30)         ;TH6. V3 PERIPHERAL
20 FIX         ;TH7. SIG
(0 35)         ;TH8. T50
(0 0.12)       ;TH9.w1
(0 0.18)       ;TH10.w2

$OMEGA
0.1            ;CL AND CL1
0 FIX          ;V1
0 FIX          ;Q
0.1            ;V2
0 FIX          ;Q2
0.1            ;V3
0 FIX          ;SIG
0 FIX          ;T50

$SIGMA
1 FIX
1 FIX

$COV

$EST MAXEVAL=9990 PRINT=10 POSTHOC NOABORT METHOD=1

$TABLE  ID NID TIME AMT CMT CONC IPRED IRES DV CWRES NPDE IPRED CL CL1 V3 K20 K23 K32 PRED
TPF TIF TIF2 CINF NOAPPEND NOPRINT ONEHEADER FILE=TAB_MOD058at.TXT

$TABLE  ID NID TIME AMT CMT CONC CL CL1 V1 Q V2 Q2 V3 SIG T50 PESO TP TPF TIF CINF CIRE VR COLF
ETA1 ETA2 ETA3 ETA4 ETA6
```

NOPRINT FIRSTONLY ONEHEADER FILE=PAR_MOD058at.TXT

NONMEM Output

1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0
ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN

PROBLEM NO.: 1
POPULATION PK OF HIPEO IN WISTAR RATS. STEP FUNCTION MODEL
NO. OF DATA RECS IN DATA SET: 443
NO. OF DATA ITEMS IN DATA SET: 19
TOT. NO. OF OBS RECS: 372
TOT. NO. OF INDIVIDUALS: 38
MONITORING OF SEARCH:

0ITERATION NO.: 0 OBJECTIVE VALUE: -507.022365955432 NO. OF FUNC. EVALS.: 11
CUMULATIVE NO. OF FUNC. EVALS.: 11
PARAMETER: 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01
GRADIENT: -1.2130E+02 2.2995E+02 2.1002E+02 -1.4276E+02 3.1596E+01 -2.2713E+02 -5.1663E+01 -6.0421E+01 -3.6402E+02 -3.9349E+01 -4.7367E+01 -1.9520E+02

0ITERATION NO.: 10 OBJECTIVE VALUE: -739.917633799156 NO. OF FUNC. EVALS.: 12
CUMULATIVE NO. OF FUNC. EVALS.: 133
PARAMETER: -2.9398E-01 -1.0758E+00 -8.2047E-02 8.0883E-02 -5.8183E-01 5.5341E-01 8.6642E-03 1.7683E-01 9.3741E-02 4.2533E-01 2.5026E-01 7.8879E-01
GRADIENT: -3.1895E+01 1.4909E+01 5.2818E+01 -2.3641E+01 1.8853E+00 -3.0377E+01 -7.3555E+00 -1.6272E+01 -9.1166E+01 1.1289E+00 -6.1984E+00 -2.3276E+01

0ITERATION NO.: 20 OBJECTIVE VALUE: -752.241304739523 NO. OF FUNC. EVALS.: 21
CUMULATIVE NO. OF FUNC. EVALS.: 263
PARAMETER: -1.1431E-01 -1.1123E+00 -5.5836E-02 1.6058E-01 -6.9308E-01 6.7554E-01 -1.0222E-02 2.1139E-01 2.0008E-01 3.1513E-01 2.7869E-01 9.9627E-01
GRADIENT: -1.6080E-01 -2.9546E-01 -4.6773E-01 -3.3183E-01 -5.2655E-02 -3.8795E-01 -7.3910E-01 -5.1289E-02 -1.6200E-01 3.9799E-02 -6.1903E-02 -1.9511E-02

0ITERATION NO.: 25 OBJECTIVE VALUE: -752.250929092566 NO. OF FUNC. EVALS.: 18
CUMULATIVE NO. OF FUNC. EVALS.: 367
PARAMETER: -1.0805E-01 -1.0988E+00 -4.6202E-02 1.6988E-01 -6.8173E-01 6.8981E-01 -9.8545E-03 2.1168E-01 2.0081E-01 3.1290E-01 2.7895E-01 9.9361E-01

GRADIENT: -3.9161E-03 2.6518E-03 -4.0053E-03 5.9828E-03 -6.6694E-03 1.9270E-04 2.5804E-03 1.8954E-03 1.4160E-03 -5.9150E-03 2.5006E-03 -1.6751E-04

0MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 367
NO. OF SIG. DIGITS IN FINAL EST.: 3.3 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.
ETABAR: -4.6579E-03 0.0000E+00 0.0000E+00 -1.7100E-02 0.0000E+00 3.1072E-02 0.0000E+00 0.0000E+00
P VAL.: 9.1848E-01 1.0000E+00 1.0000E+00 7.3011E-01 1.0000E+00 7.6039E-01 1.0000E+00 1.0000E+00
MINIMUM VALUE OF OBJECTIVE FUNCTION -752.251

FINAL PARAMETER ESTIMATE
THETA - VECTOR OF FIXED EFFECTS PARAMETERS

TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 7	TH 8	TH 9	TH10
3.25E+00	1.51E-01	8.64E-01	5.36E+01	3.66E+00	5.41E+01	2.00E+01	3.14E+01	1.34E-01	1.99E-01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS

	ETA1	ETA2	ETA3	ETA4	ETA5	ETA6	ETA7	ETA8
ETA1	1.53E-01							
ETA2	0.00E+00	0.00E+00						
ETA3	0.00E+00	0.00E+00	0.00E+00					
ETA4	0.00E+00	0.00E+00	0.00E+00	1.43E-01				
ETA5	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00			
ETA6	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	5.97E-01		
ETA7	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	
ETA8	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

	EPS1	EPS2
EPS1	1.00E+00	
EPS2	0.00E+00	1.00E+00

STANDARD ERROR OF ESTIMATE

THETA - VECTOR OF FIXED EFFECTS PARAMETERS

TH 1	TH 2	TH 3	TH 4	TH 5	TH 6	TH 8	TH 9	TH10
5.31E-01	2.87E-02	9.72E-02	7.17E+00	1.04E+00	1.91E+01	8.45E-01	1.23E-02	1.59E-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS -

	ETA1	ETA2	ETA3	ETA4	ETA5	ETA6	ETA7	ETA8
ETA1	6.66E-02							

ETA2	0.00E+00	0.00E+00						
ETA3	0.00E+00	0.00E+00	0.00E+00					
ETA4	0.00E+00	0.00E+00	0.00E+00	7.01E-02				
ETA5	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00			
ETA6	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	2.57E-01		
ETA7	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	
ETA8	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

	EPS1	EPS2
EPS1	1	
EPS2		1