PERÚ Ministerio de salud | Dirección General de Medicamentos, Insumos y Drogas | DIGEMID

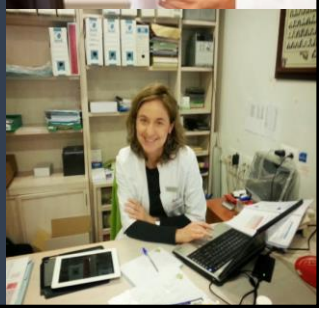
CenadIM
Centro Nacional de Documentación e Información de Medicamentos

Resolución de consultas

Taller N° 1

Reunión Técnica Nacional de la Red Peruana de Centros y Servicios de Información de Medicamentos "Información de medicamentos oncológicos: Actualización y casos clínicos"

Lima, 07 de Agosto de 2015



Funciones de Centro/Servicio de Información

INFORMACION PASIVA

- Resolución de las consultas recibidas.
- Elaboración de informes técnicos.
- Realización de búsquedas bibliográficas.

Resolución de las consultas recibidas

Especialmente aquellas con una orientación asistencial que pueden repercutir en la instauración, modificación o suspensión de un tratamiento farmacológico, identificación de las indicaciones de uso, dosificación, efectos adversos, interacciones, estabilidad, precauciones, contraindicaciones, etc, mejorando por tanto, el cuidado del paciente.

Proceso de la resolución de consultas

- Identificación del consultante
- Identificación del problema
- Recepción de la consulta
- Urgencia del problema
- Estrategia de búsqueda
- Elaboración de la respuesta
- Seguimiento

Recomendaciones para el diseño de una estrategia de búsqueda.

Recomendaciones para el diseño de una estrategia de búsqueda

A. Formule la pregunta a responder.

B. Estructure los componentes clave de la pregunta y defina los términos principales de la búsqueda.

C. Defina dónde buscar la mejor evidencia para responder a la pregunta.

D. Utilice los operadores booleanos pertinentes (AND – OR - NOT) y defina la opciones de campo dónde buscar (todo el texto, título, resumen).

A. Formule la pregunta a responder

Pregunta clínica:

Si en la terapia intraperitoneal de cáncer de ovario avanzado, paclitaxel y cisplatino se reconstituyen en solución salina normal a 37°C para ser administrados a través de un catéter peritoneal implantable; **¿la solución salina a 0.9% a 37°C puede afectar la estabilidad y en consecuencia la eficacia de estos medicamentos?**

B. Estructure los componentes clave de la pregunta y defina los términos principales de la búsqueda.

Estructurar los componentes claves de la pregunta clínica

- PICO es un acrónimo utilizado para identificar cuatro componentes principales de una pregunta clínica bien formulada.

P → Pacientes o problema (Patient)

I → Intervención (Intervention)

C → Comparación (Comparasion)

O → Resultados (Outcomes)

Componentes claves para precisar la información a buscar.

Pregunta clínica:

Si en la terapia intraperitoneal de cáncer de ovario avanzado, paclitaxel y cisplatino se reconstituyen en solución salina normal a 37°C para ser administrados a través de un catéter peritoneal implantable; **¿la solución salina a 0.9% a 37°C puede afectar la estabilidad y en consecuencia la eficacia de estos medicamentos?**

P → cáncer ovario

I → paclitaxel, cisplatino, solución salina, quimioterapia intraperitoneal hipertérmica

C → ----------

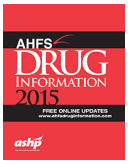
O → estabilidad, degradación, eficacia

C. Defina dónde buscar la mejor evidencia para responder a la pregunta.

Fuentes de Información

SCOPUS
Find out.

TRUVEN HEALTH ANALYTICS
MICROMEDEX SOLUTIONS®



BestPractice

MEDLINE

HINARI
ACCESS TO RESEARCH

DynaMed
Powered by EBSCOhost

PubMed

The NEW ENGLAND JOURNAL of MEDICINE

trip database

THE COCHRANE COLLABORATION®

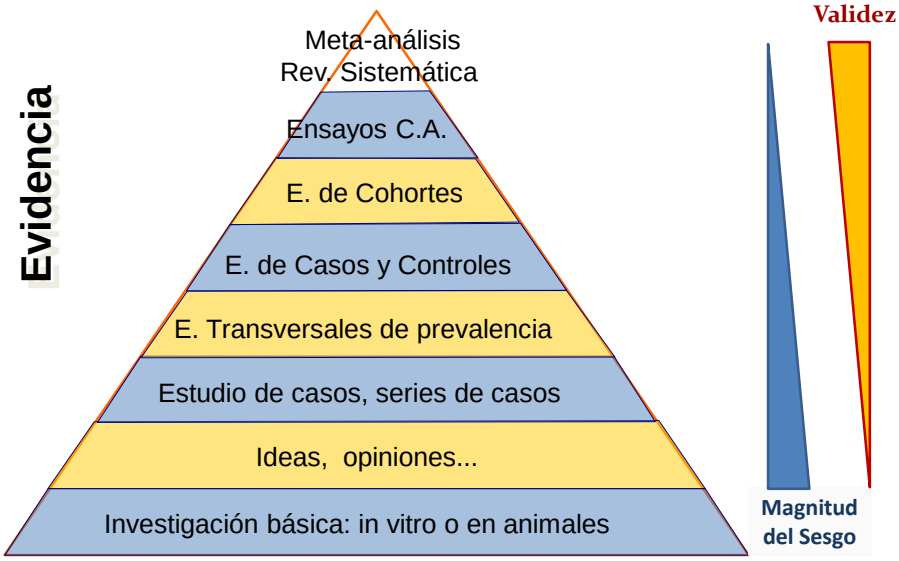
bvs biblioteca virtual en salud LILACS

UpToDate

ELSEVIER

JERARQUÍA DE LOS DISEÑOS DE INVESTIGACIÓN MEDICINA BASADA EN LA EVIDENCIA

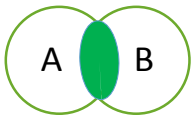
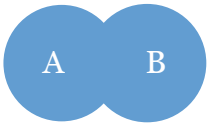
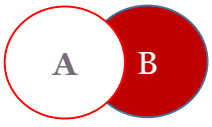
(en base a la validez interna)



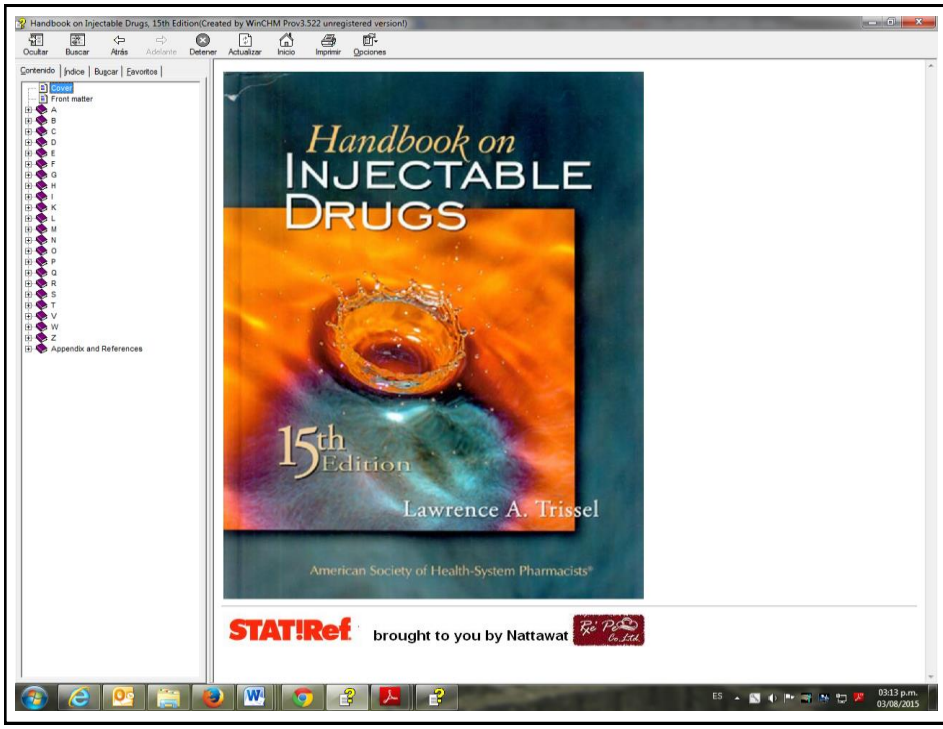
C. Utilice los operadores booleanos pertinentes (AND – OR - NOT).

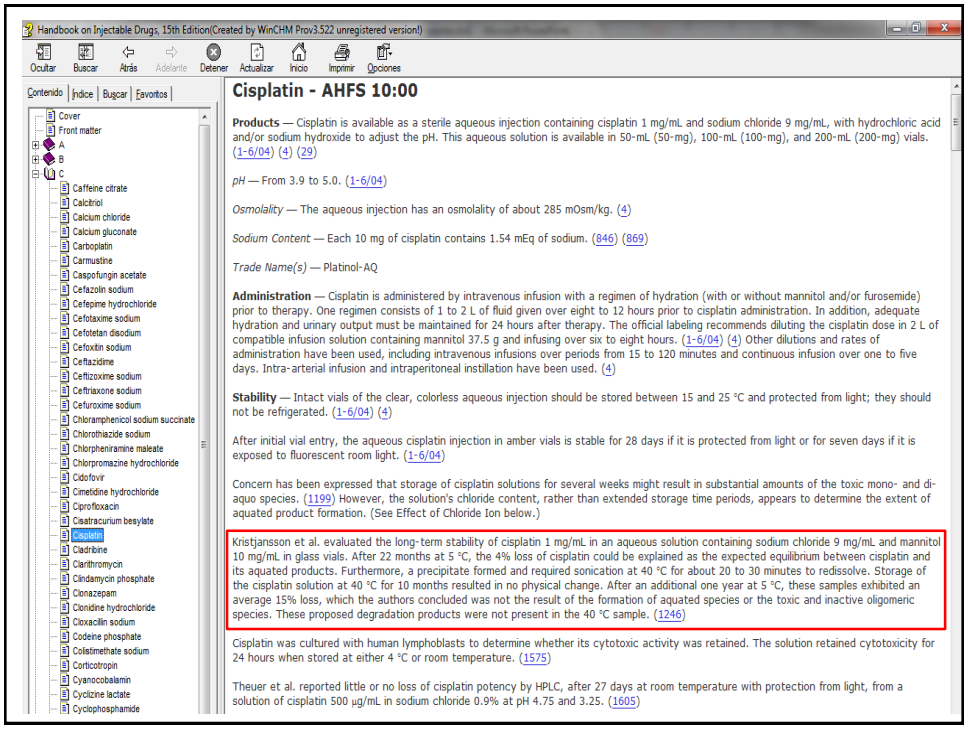
Operadores booleanos

Utilice los operadores booleanos para combinar diferentes términos.

Para combinar diferentes conceptos	AND	
Para combinar diferentes términos para un mismo concepto (SINÓNIMOS)	OR	
Excluye conceptos	NOT	

Búsqueda de información en fuentes terciarias





Kristjansson et al. evaluated the long-term stability of cisplatin 1 mg/mL in an aqueous solution containing sodium chloride 9 mg/mL and mannitol 10 mg/mL in glass vials. After 22 months at 5 °C, the 4% loss of cisplatin could be explained as the expected equilibrium between cisplatin and its aquated products. Furthermore, a precipitate formed and required sonication at 40 °C for about 20 to 30 minutes to redissolve. **Storage of the cisplatin solution at 40 °C for 10 months resulted in no physical change**. After an additional one year at 5 °C, these samples exhibited an average 15% loss, which the authors concluded was not the result of the formation of aquated species or the toxic and inactive oligomeric species. **These proposed degradation products were not present in the 40 °C sample**. (1246)

1246. Kristjansson F, Sternson LA. An investigation on possible oligomer formation in pharmaceutical formulations of cisplatin. *Int J Pharm*. 1988; 41:67-74.

International Journal of Pharmaceutics, 41 (1988) 67–74
Elsevier

IJP 01373

An investigation on possible oligomer formation in pharmaceutical formulations of cisplatin

Fjalar Kristjansson, Larry A. Sternson and Siegfried Lindenbaum

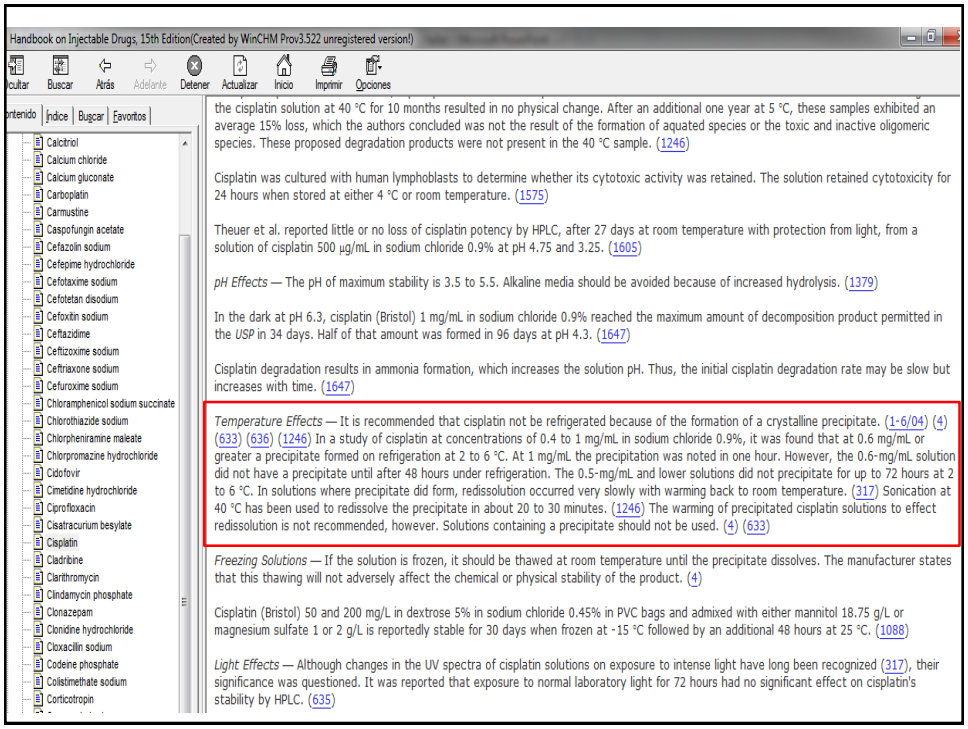
Department of Pharmaceutical Chemistry, The University of Kansas, Malott Hall, Lawrence, KS 66045 (U.S.A.)

(Received 22 September 1986)
(Modified version received 21 May 1987)
(Accepted 10 July 1987)

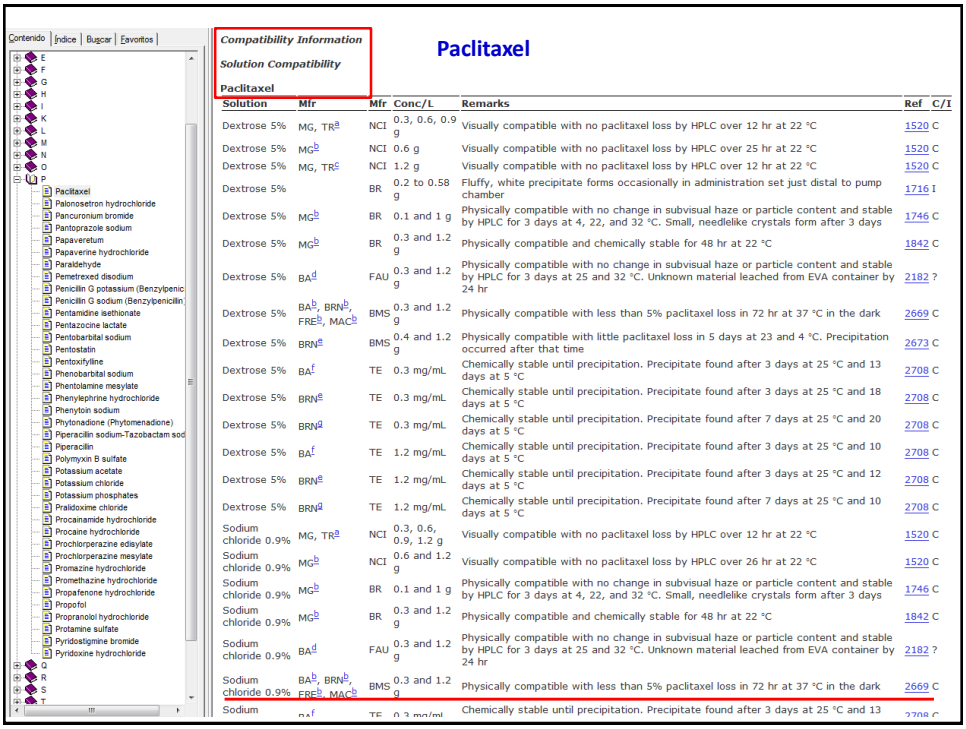
Key words: Cisplatin; *cis*-Dichlorodiammineplatinum(II); Di-μ-hydroxo-bis(cis-diammineplatinum(II)); Tri-μ-hydroxo-tris(*cis*-diammineplatinum(II)); (*cis*-Diamminediaquoplatinum(II); *cis*-diamminemonochloromonoaquoplatinum(II); Stability; Kinetics

Summary

Concern has been raised that the anti-neoplastic agent, cisplatin, when formulated in isotonic sodium chloride solution may degrade to di-μ-hydroxo-bis(*cis*-diammineplatinum(II)) (**4**) and tri-μ-hydroxo-tris(*cis*-diammineplatinum(II)) (**5**) which have been shown to be therapeutically inactive and highly toxic. The formation of **4** and **5** in pharmaceutical preparations of **1** is therefore of concern and was the subject of this study. Using HPLC procedures developed for the monitoring of *cis*-diamminemonochloro-monoaquoplatinum(II)) (**2**), *cis*-diamminediaquoplatinum(II) (**3**) and oligomeric species **4** and **5**, the long-term (1 year) stability of cisplatin (1 g/l) was investigated in 0.9% sodium chloride solution. Oligomeric products **4** and **5** were not found at the detection limits of 1 mg/l. The degradation of **2**, **3**, **4**, and **5** in aqueous sodium chloride solutions were also studied; all of these species degraded to cisplatin. Results stongly suggest that **4** and **5** are not formed in formulations in which cisplatin is dissolved in isotonic sodium chloride solution.



Temperature Effects .- It is recommended that cisplatin not be refrigerated because of the formation of a crystalline precipitate. (1-6/04) (4) (633) (636) (1246) In a study of cisplatin at concentrations of 0.4 to 1 mg/mL in sodium chloride 0.9%, it was found that at 0.6 mg/mL or greater a precipitate formed on refrigeration at 2 to 6 °C. At 1 mg/mL the precipitation was noted in one hour. However, the 0.6-mg/mL solution did not have a precipitate until after 48 hours under refrigeration. The 0.5-mg/mL and lower solutions did not precipitate for up to 72 hours at 2 to 6 °C. In solutions where precipitate did form, redissolution occurred very slowly with warming back to room temperature. (317) **Sonication at 40 °C has been used to redissolve the precipitate in about 20 to 30 minutes**. (1246) **The warming of precipitated cisplatin solutions to effect redissolution is not recommended, however. Solutions containing a precipitate should not be used.** (4) (633).



Contenido | Índice | Buscar | Favoritos

- E
- F
- G
- H
- I
- K
- L
- M
- N
- O
- P
  - Paclitaxel
  - Palonosetron hydrochloride
  - Pancuronium bromide
  - Pantoprazole sodium
  - Papaveretum
  - Papaverine hydrochloride
  - Paraldehyde
  - Pemetrexed disodium
  - Penicillin G potassium (Benzylpenic
  - Penicillin G sodium (Benzylpenicillin
  - Pentamidine isethionate
  - Pentazocine lactate
  - Pentobarbital sodium
  - Pentostatin
  - Pentoxifylline
  - Phenobarbital sodium
  - Phentolamine mesylate
  - Phenylephrine hydrochloride
  - Phenytoin sodium
  - Phytonadione (Phytomenadione)
  - Piperacillin sodium-Tazobactam sod
  - Piperacillin
  - Polymyxin B sulfate
  - Potassium acetate
  - Potassium chloride
  - Potassium phosphates
  - Pralidoxime chloride
  - Procainamide hydrochloride
  - Procaine hydrochloride
  - Prochlorperazine edisylate
  - Prochlorperazine mesylate
  - Promazine hydrochloride
  - Promethazine hydrochloride
  - Propafenone hydrochloride
  - Propofol
  - Propranolol hydrochloride
  - Protamine sulfate
  - Pyridostigmine bromide
  - Pyridoxine hydrochloride
- Q
- R
- S
- T

Compatibility Information

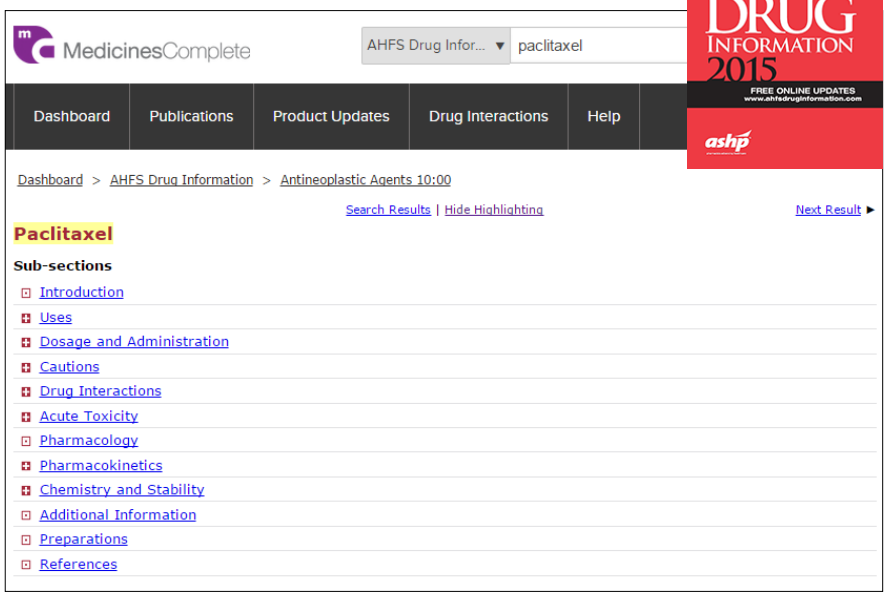
Solution Compatibility

Paclitaxel

Paclitaxel

Solution	Mfr	Mfr	Conc/L	Remarks	Ref	C/I
Dextrose 5%	MG, TR[a]	NCI	0.3, 0.6, 0.9 g	Visually compatible with no paclitaxel loss by HPLC over 12 hr at 22 °C	1520	C
Dextrose 5%	MG[b]	NCI	0.6 g	Visually compatible with no paclitaxel loss by HPLC over 25 hr at 22 °C	1520	C
Dextrose 5%	MG, TR[c]	NCI	1.2 g	Visually compatible with no paclitaxel loss by HPLC over 12 hr at 22 °C	1520	C
Dextrose 5%		BR	0.2 to 0.58 g	Fluffy, white precipitate forms occasionally in administration set just distal to pump chamber	1716	I
Dextrose 5%	MG[b]	BR	0.1 and 1 g	Physically compatible with no change in subvisual haze or particle content and stable by HPLC for 3 days at 4, 22, and 32 °C. Small, needlelike crystals form after 3 days	1746	C
Dextrose 5%	MG[b]	BR	0.3 and 1.2 g	Physically compatible and chemically stable for 48 hr at 22 °C	1842	C
Dextrose 5%	BA[d]	FAU	0.3 and 1.2 g	Physically compatible with no change in subvisual haze or particle content and stable by HPLC for 3 days at 25 and 32 °C. Unknown material leached from EVA container by 24 hr	2182	?
Dextrose 5%	BA[b], BRN[b], FRE[b], MAC[b]	BMS	0.3 and 1.2 g	Physically compatible with less than 5% paclitaxel loss in 72 hr at 37 °C in the dark	2669	C
Dextrose 5%	BRN[e]	BMS	0.4 and 1.2 g	Physically compatible with little paclitaxel loss in 5 days at 23 and 4 °C. Precipitation occurred after that time	2673	C
Dextrose 5%	BA[f]	TE	0.3 mg/mL	Chemically stable until precipitation. Precipitate found after 3 days at 25 °C and 13 days at 5 °C	2708	C
Dextrose 5%	BRN[e]	TE	0.3 mg/mL	Chemically stable until precipitation. Precipitate found after 3 days at 25 °C and 18 days at 5 °C	2708	C
Dextrose 5%	BRN[g]	TE	0.3 mg/mL	Chemically stable until precipitation. Precipitate found after 7 days at 25 °C and 20 days at 5 °C	2708	C
Dextrose 5%	BA[f]	TE	1.2 mg/mL	Chemically stable until precipitation. Precipitate found after 3 days at 25 °C and 10 days at 5 °C	2708	C
Dextrose 5%	BRN[e]	TE	1.2 mg/mL	Chemically stable until precipitation. Precipitate found after 3 days at 25 °C and 12 days at 5 °C	2708	C
Dextrose 5%	BRN[g]	TE	1.2 mg/mL	Chemically stable until precipitation. Precipitate found after 7 days at 25 °C and 10 days at 5 °C	2708	C
Sodium chloride 0.9%	MG, TR[a]	NCI	0.3, 0.6, 0.9, 1.2 g	Visually compatible with no paclitaxel loss by HPLC over 12 hr at 22 °C	1520	C
Sodium chloride 0.9%	MG[b]	NCI	0.6 and 1.2 g	Visually compatible with no paclitaxel loss by HPLC over 26 hr at 22 °C	1520	C
Sodium chloride 0.9%	MG[b]	BR	0.1 and 1 g	Physically compatible with no change in subvisual haze or particle content and stable by HPLC for 3 days at 4, 22, and 32 °C. Small, needlelike crystals form after 3 days	1746	C
Sodium chloride 0.9%	MG[b]	BR	0.3 and 1.2 g	Physically compatible and chemically stable for 48 hr at 22 °C	1842	C
Sodium chloride 0.9%	BA[d]	FAU	0.3 and 1.2 g	Physically compatible with no change in subvisual haze or particle content and stable by HPLC for 3 days at 25 and 32 °C. Unknown material leached from EVA container by 24 hr	2182	?
Sodium chloride 0.9%	BA[b], BRN[b], FRE[b], MAC[b]	BMS	0.3 and 1.2 g	Physically compatible with less than 5% paclitaxel loss in 72 hr at 37 °C in the dark	2669	C
Sodium	BA[f]	TE	0.3 mg/mL	Chemically stable until precipitation. Precipitate found after 3 days at 25 °C and 13	2708	C

AHFS Drug Information



Intraperitoneal Therapy

Sequential administration of IV paclitaxel, intraperitoneal (IP) cisplatin, and IP paclitaxel† is used for the treatment of optimally-debulked stage III ovarian cancer.[134] The National Cancer Institute (NCI), in conjunction with oncology groups, has issued a clinical announcement to recommend use of an IV/IP regimen for eligible patients with advanced ovarian cancer because of a substantial survival benefit.[345] [346] [347] Based on recent clinical trials, strong consideration should be given to use of a regimen containing IP cisplatin (100 mg/m^2) and a taxane (either IV only or IV plus IP) following primary surgery for optimally-debulked FIGO stage III ovarian cancer.[347]

In a randomized, phase III trial, patients with stage III ovarian carcinoma or primary peritoneal carcinoma, with no residual mass greater than 1.0 cm following surgery, received either IP therapy or IV therapy.[296] IP therapy consisted of IV paclitaxel 135 mg/m^2 by 24-hour infusion on day 1, followed by IP cisplatin 100 mg/m^2 on day 2, and IP paclitaxel 60 mg/m^2 on day 8.[296] IV therapy consisted of IV paclitaxel 135 mg/m^2 by 24-hour infusion on day 1 followed by IV cisplatin 75 mg/m^2 on day 2.[296] Treatment was administered in 3-week cycles for 6 cycles.[296]

Patients receiving IP therapy had longer median progression-free survival (24 versus 18 months) and longer median survival (66 versus 50 months) than those receiving IV therapy.[296] Severe or life-threatening (grade 3 or 4) toxicity occurred more frequently in patients receiving the IP regimen, including leukopenia, thrombocytopenia, GI toxicity, neurologic toxicity, infection, fatigue, adverse metabolic effects, and pain.[296] Only 42% of the patients in the IP group completed the assigned 6 cycles of IP therapy, and IP therapy often was discontinued because of catheter-related complications; patients who could not complete the IP regimen received IV therapy for the remaining treatment cycles.[296] Quality of life was worse before cycle 4 and at 3–6 weeks after completion of treatment for patients receiving IP therapy, but quality of life scores were similar for the groups at 1 year after completion of treatment except for the persistence of moderate paresthesias in patients receiving IP therapy.[296] [346]

For intraperitoneal therapy, the cisplatin dose was diluted in 2 L of 0.9% sodium chloride solution that was warmed to body temperature and infused through a surgically implanted peritoneal catheter.[296] [344] Following peritoneal infusion, the patient was asked to roll into a different position every 15 minutes for the next 2 hours to disperse the drug throughout the peritoneal cavity.[344] [347] The paclitaxel dose was diluted in a liter of saline solution that was warmed to body temperature and infused through the IP catheter, followed by IP infusion of an additional liter of warmed saline solution.[344] [347]

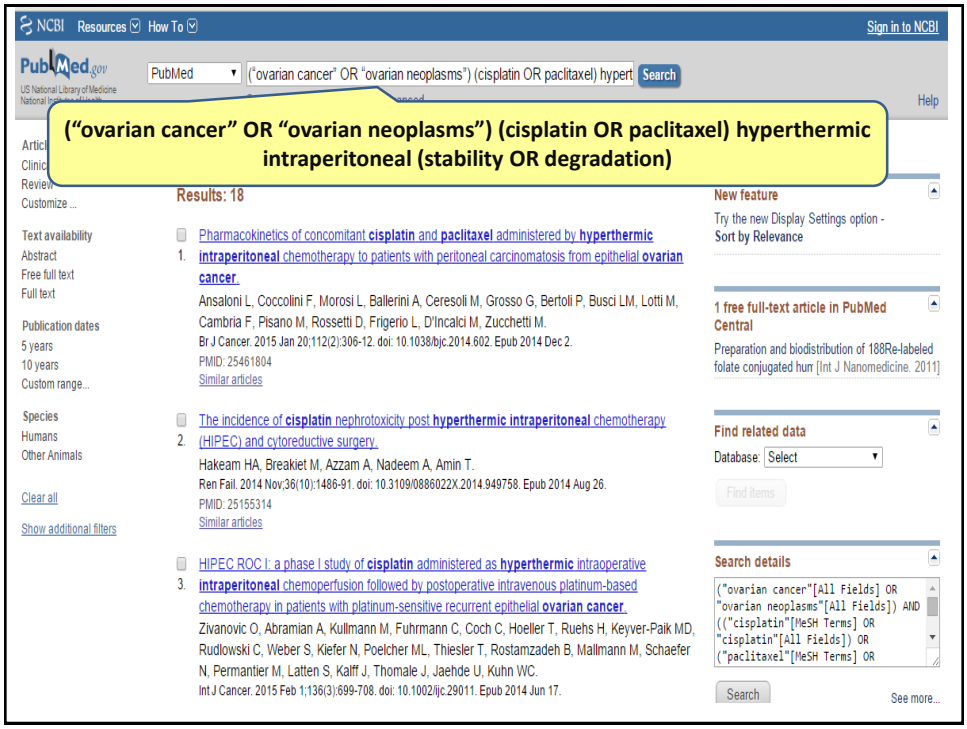
Catheter-related complications that caused discontinuance of IP therapy included infection and blockage.[344] Certain surgical procedures used to achieve optimal cytoreduction of ovarian cancer, such as rectosigmoid or left colon resection, may have contributed to catheter complications.[344] Most experts in the administration of IP chemotherapy recommend the use of a single-lumen venous catheter, such as a 9.6 French polyurethane venous access tubing, connected to a semi-permanent subcutaneous single-lumen venous access port.[344] [347] The IP catheter may be placed at the time of primary surgery as long as contamination of the peritoneal cavity has not occurred.[344] Timing of placement of the IP catheter (at the time of primary surgery versus delayed insertion) did not appear to affect tolerance of IP therapy.[344] The IP catheter should be removed as soon as IP therapy is completed to avoid catheter-related complications.[344] Supportive therapy should include

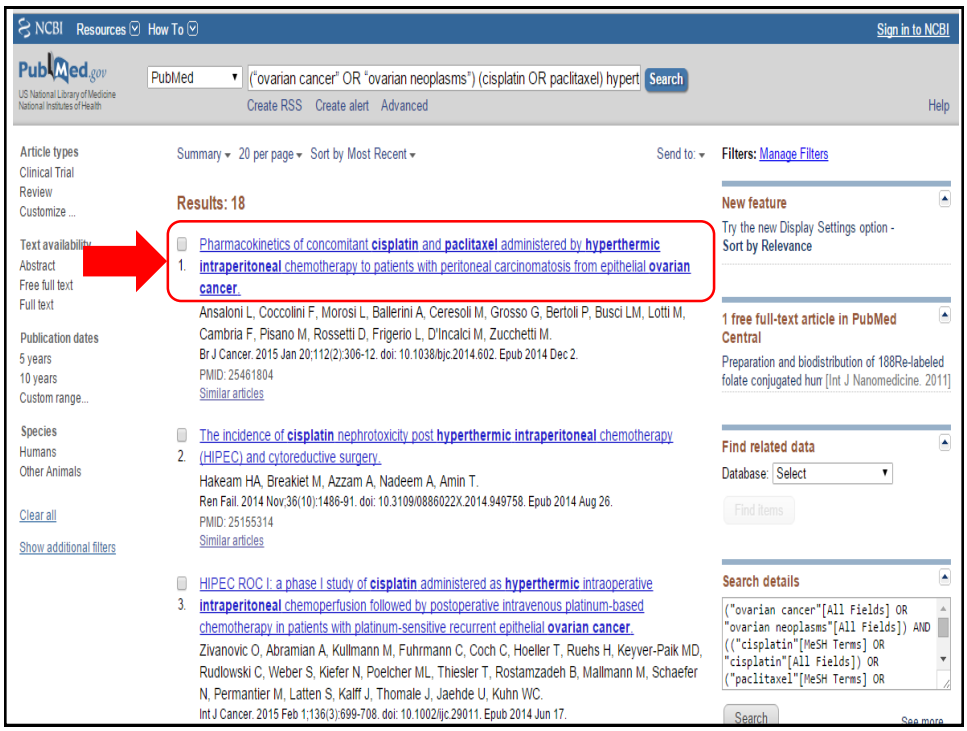
296. Armstrong DK, Bundy B, Wenzel L *et al*. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006; 354:34-43.

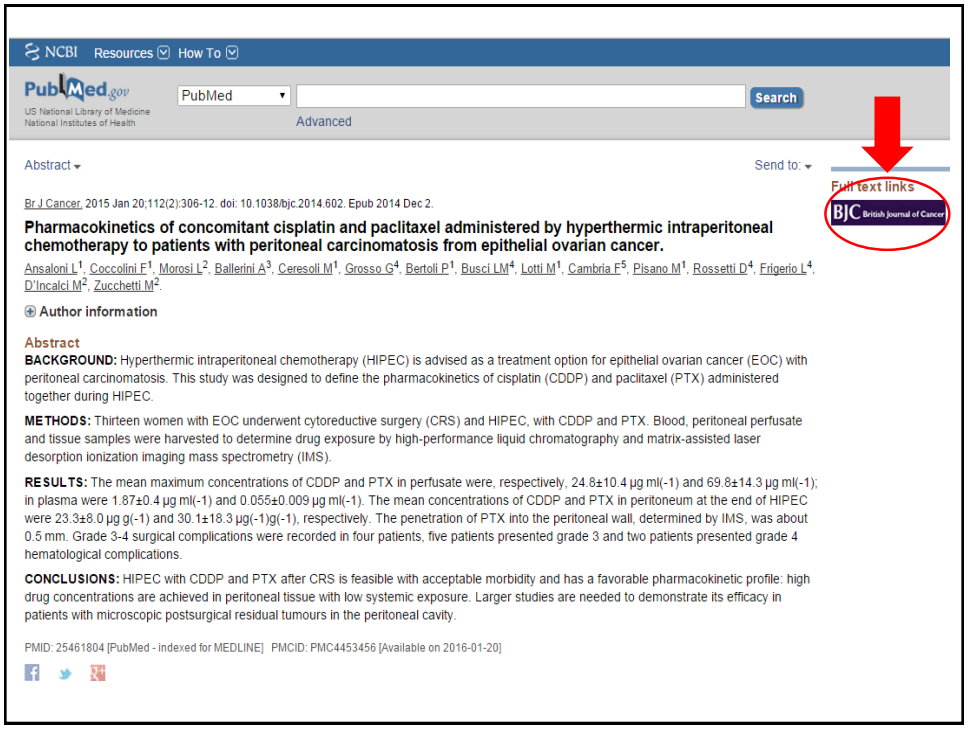
344. Walker JL, Armstrong DK, Huang HQ *et al*. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 2006; 100:27-32.

347. National Cancer Institute (NCI). NCI clinical announcement on intraperitoneal chemotherapy in ovarian cancer (January 5, 2006). From NCI web site.

Búsqueda de información en fuentes secundarias


NCBI Resources How To
Sign in to NCBI
PubMed
("ovarian cancer" OR "ovarian neoplasms") (cisplatin OR paclitaxel) hypert
Search
Help
("ovarian cancer" OR "ovarian neoplasms") (cisplatin OR paclitaxel) hyperthermic intraperitoneal (stability OR degradation)
Customize ...
Text availability
Abstract
Free full text
Full text
Publication dates
5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Show additional filters
Results: 18
1. Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer.
Ansaloni L, Coccolini F, Morosi L, Ballerini A, Ceresoli M, Grosso G, Bertoli P, Busci LM, Lotti M, Cambria F, Pisano M, Rossetti D, Frigerio L, D'Incalci M, Zucchetti M.
Br J Cancer. 2015 Jan 20;112(2):306-12. doi: 10.1038/bjc.2014.602. Epub 2014 Dec 2.
PMID: 25461804
Similar articles
2. The incidence of cisplatin nephrotoxicity post hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery.
Hakeam HA, Breakiet M, Azzam A, Nadeem A, Amin T.
Ren Fail. 2014 Nov;36(10):1486-91. doi: 10.3109/0886022X.2014.949758. Epub 2014 Aug 26.
PMID: 25155314
Similar articles
3. HIPEC ROC I: a phase I study of cisplatin administered as hyperthermic intraoperative intraperitoneal chemoperfusion followed by postoperative intravenous platinum-based chemotherapy in patients with platinum-sensitive recurrent epithelial ovarian cancer.
Zivanovic O, Abramian A, Kullmann M, Fuhrmann C, Coch C, Hoeller T, Ruehs H, Keyver-Paik MD, Rudlowski C, Weber S, Kiefer N, Poelcher ML, Thiesler T, Rostamzadeh B, Mallmann M, Schaefer N, Permantier M, Latten S, Kalff J, Thomale J, Jaehde U, Kuhn WC.
Int J Cancer. 2015 Feb 1;136(3):699-708. doi: 10.1002/ijc.29011. Epub 2014 Jun 17.
New feature
Try the new Display Settings option - Sort by Relevance
1 free full-text article in PubMed Central
Preparation and biodistribution of 188Re-labeled folate conjugated hum [Int J Nanomedicine. 2011]
Find related data
Database: Select
Find items
Search details
("ovarian cancer"[All Fields] OR "ovarian neoplasms"[All Fields]) AND (("cisplatin"[MeSH Terms] OR "cisplatin"[All Fields]) OR ("paclitaxel"[MeSH Terms] OR
Search
See more...


NCBI Resources How To
Sign in to NCBI
PubMed
("ovarian cancer" OR "ovarian neoplasms") (cisplatin OR paclitaxel) hypert
Search
Create RSS Create alert Advanced
Help
Article types
Clinical Trial
Review
Customize ...
Text availability
Abstract
Free full text
Full text
Publication dates
5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Show additional filters
Summary 20 per page Sort by Most Recent
Send to:
Filters: Manage Filters
Results: 18
1. Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer.
Ansaloni L, Coccolini F, Morosi L, Ballerini A, Ceresoli M, Grosso G, Bertoli P, Busci LM, Lotti M, Cambria F, Pisano M, Rossetti D, Frigerio L, D'Incalci M, Zucchetti M.
Br J Cancer. 2015 Jan 20;112(2):306-12. doi: 10.1038/bjc.2014.602. Epub 2014 Dec 2.
PMID: 25461804
Similar articles
2. The incidence of cisplatin nephrotoxicity post hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery.
Hakeam HA, Breakiet M, Azzam A, Nadeem A, Amin T.
Ren Fail. 2014 Nov;36(10):1486-91. doi: 10.3109/0886022X.2014.949758. Epub 2014 Aug 26.
PMID: 25155314
Similar articles
3. HIPEC ROC I: a phase I study of cisplatin administered as hyperthermic intraoperative intraperitoneal chemoperfusion followed by postoperative intravenous platinum-based chemotherapy in patients with platinum-sensitive recurrent epithelial ovarian cancer.
Zivanovic O, Abramian A, Kullmann M, Fuhrmann C, Coch C, Hoeller T, Ruehs H, Keyver-Paik MD, Rudlowski C, Weber S, Kiefer N, Poelcher ML, Thiesler T, Rostamzadeh B, Mallmann M, Schaefer N, Permantier M, Latten S, Kalff J, Thomale J, Jaehde U, Kuhn WC.
Int J Cancer. 2015 Feb 1;136(3):699-708. doi: 10.1002/ijc.29011. Epub 2014 Jun 17.
New feature
Try the new Display Settings option - Sort by Relevance
1 free full-text article in PubMed Central
Preparation and biodistribution of 188Re-labeled folate conjugated hum [Int J Nanomedicine. 2011]
Find related data
Database: Select
Find items
Search details
("ovarian cancer"[All Fields] OR "ovarian neoplasms"[All Fields]) AND (("cisplatin"[MeSH Terms] OR "cisplatin"[All Fields]) OR ("paclitaxel"[MeSH Terms] OR
Search
See more...



NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed Search
Advanced

Abstract Send to:

Full text links
BJC British Journal of Cancer

Br J Cancer. 2015 Jan 20;112(2):306-12. doi: 10.1038/bjc.2014.602. Epub 2014 Dec 2.

Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer.

Ansaloni L[1], Coccolini F[1], Morosi L[2], Ballerini A[3], Ceresoli M[1], Grosso G[4], Bertoli P[1], Busci LM[4], Lotti M[1], Cambria F[5], Pisano M[1], Rossetti D[4], Frigerio L[4], D'Incalci M[2], Zucchetti M[2].

Author information

Abstract

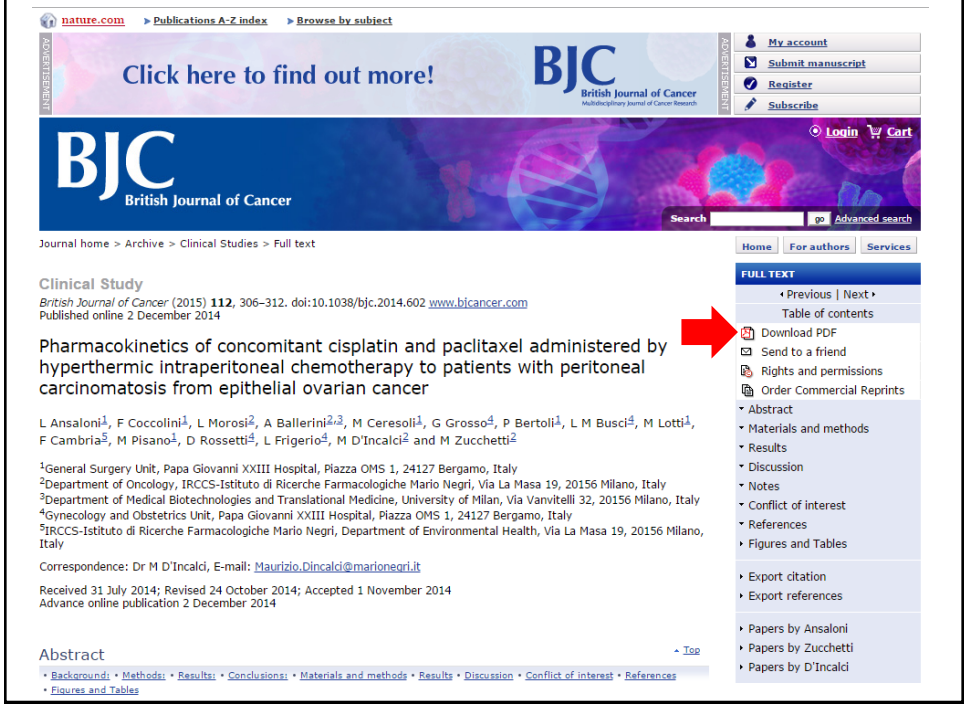
BACKGROUND: Hyperthermic intraperitoneal chemotherapy (HIPEC) is advised as a treatment option for epithelial ovarian cancer (EOC) with peritoneal carcinomatosis. This study was designed to define the pharmacokinetics of cisplatin (CDDP) and paclitaxel (PTX) administered together during HIPEC.

METHODS: Thirteen women with EOC underwent cytoreductive surgery (CRS) and HIPEC, with CDDP and PTX. Blood, peritoneal perfusate and tissue samples were harvested to determine drug exposure by high-performance liquid chromatography and matrix-assisted laser desorption ionization imaging mass spectrometry (IMS).

RESULTS: The mean maximum concentrations of CDDP and PTX in perfusate were, respectively, 24.8±10.4 μg ml(-1) and 69.8±14.3 μg ml(-1); in plasma were 1.87±0.4 μg ml(-1) and 0.055±0.009 μg ml(-1). The mean concentrations of CDDP and PTX in peritoneum at the end of HIPEC were 23.3±8.0 μg g(-1) and 30.1±18.3 μg(-1)g(-1), respectively. The penetration of PTX into the peritoneal wall, determined by IMS, was about 0.5 mm. Grade 3-4 surgical complications were recorded in four patients, five patients presented grade 3 and two patients presented grade 4 hematological complications.

CONCLUSIONS: HIPEC with CDDP and PTX after CRS is feasible with acceptable morbidity and has a favorable pharmacokinetic profile: high drug concentrations are achieved in peritoneal tissue with low systemic exposure. Larger studies are needed to demonstrate its efficacy in patients with microscopic postsurgical residual tumours in the peritoneal cavity.

PMID: 25461804 [PubMed - indexed for MEDLINE] PMCID: PMC4453456 [Available on 2016-01-20]



nature.com Publications A-Z index Browse by subject

Click here to find out more!

BJC British Journal of Cancer

My account
Submit manuscript
Register
Subscribe

Login Cart

BJC British Journal of Cancer

Search go Advanced search

Journal home > Archive > Clinical Studies > Full text

Home For authors Services

FULL TEXT
Previous | Next
Table of contents
Download PDF
Send to a friend
Rights and permissions
Order Commercial Reprints
Abstract
Materials and methods
Results
Discussion
Notes
Conflict of interest
References
Figures and Tables
Export citation
Export references
Papers by Ansaloni
Papers by Zucchetti
Papers by D'Incalci

Clinical Study

British Journal of Cancer (2015) **112**, 306–312. doi:10.1038/bjc.2014.602 www.bjcancer.com
Published online 2 December 2014

Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer

L Ansaloni[1], F Coccolini[1], L Morosi[2], A Ballerini[2,3], M Ceresoli[1], G Grosso[4], P Bertoli[1], L M Busci[4], M Lotti[1], F Cambria[5], M Pisano[1], D Rossetti[4], L Frigerio[4], M D'Incalci[2] and M Zucchetti[2]

[1]General Surgery Unit, Papa Giovanni XXIII Hospital, Piazza OMS 1, 24127 Bergamo, Italy
[2]Department of Oncology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, 20156 Milano, Italy
[3]Department of Medical Biotechnologies and Translational Medicine, University of Milan, Via Vanvitelli 32, 20156 Milano, Italy
[4]Gynecology and Obstetrics Unit, Papa Giovanni XXIII Hospital, Piazza OMS 1, 24127 Bergamo, Italy
[5]IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Department of Environmental Health, Via La Masa 19, 20156 Milano, Italy

Correspondence: Dr M D'Incalci, E-mail: Maurizio.Dincalci@marionegri.it

Received 31 July 2014; Revised 24 October 2014; Accepted 1 November 2014
Advance online publication 2 December 2014

Abstract Top

Background: • Methods: • Results: • Conclusions: • Materials and methods • Results • Discussion • Conflict of interest • References • Figures and Tables

BJC

British Journal of Cancer (2015) 112, 306–312 | doi: 10.1038/bjc.2014.602

Keywords: peritoneal carcinomatosis; intraperitoneal chemotherapy; HIPEC; pharmacokinetics; MALDI imaging

Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer

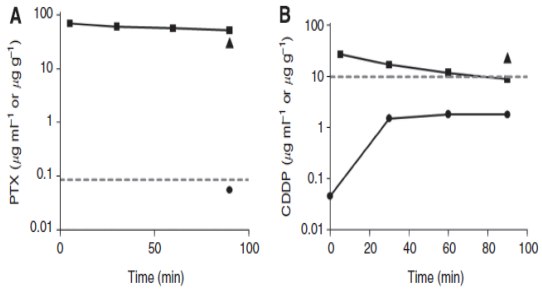


Figure 1. Mean concentrations of PTX (A) and CDDP (B) in plasma (●), perfusate (■) and peritoneal tissue (▲) during HIPEC. The dashed line indicates the lowest cytotoxic concentration of these drugs.

ELABORACIÓN DE LA RESPUESTA

Respecto a la consulta: **¿la solución salina a 0.9% a 37°C que se utiliza en la reconstitución de paclitaxel y cisplatino puede afectar la estabilidad y en consecuencia la eficacia de estos medicamentos en pacientes con cáncer de ovario avanzado que reciben quimioterapia intraperitoneal?,** se informa lo siguiente:

En la monografía de paclitaxel del *Drug Information* de la *American Society of Health-System Pharmacists* se reporta que la administración secuencial de paclitaxel IV, intraperitoneal (IP) cisplatino y paclitaxel IP se utiliza para el tratamiento de cáncer de ovario en estadio III con cito-reducción óptima. No obstante, se debe tener en cuenta que el uso de paclitaxel y cisplatino en la quimioterapia IP en cáncer de ovario avanzado es un uso "*off-label*". En los estudios realizados con la terapia IP, la dosis de cisplatino se diluyó en 2 L de solución de cloruro de sodio al 0,9% que se calentó a la temperatura corporal y se infunde a través de un catéter peritoneal implantado quirúrgicamente. Después de la infusión peritoneal, se pide al paciente rodar en una posición diferente cada 15 minutos durante las siguientes 2 horas para dispersar el medicamento por toda la cavidad peritoneal. La dosis de paclitaxel se diluyó en un litro de solución salina que se calentó a la temperatura corporal y se infunde a través del catéter IP, seguido de una infusión IP de un litro adicional de solución salina calentada (1).

En el *Handbook of Injectable Drugs* de la American Society of Health-System Pharmacists se menciona que en el estudio realizado por Kristjansson *et al.* se evaluó la estabilidad a largo plazo de cisplatino 1 mg/ml en una solución acuosa que contiene 9 mg/ml de cloruro de sodio y 10 mg/ml de manitol en viales de vidrio, en donde se reportó que después de almacenar la solución a 40 °C durante 10 meses no se observó ningún cambio físico; sin embargo, después de almacenar un año adicional a 5 °C, estas muestras mostraron una pérdida promedio del 15% de cisplatino. Asimismo, no se reportó la presencia de productos de degradación en las muestras almacenadas a 40 °C (2).

En un estudio de cisplatino en concentraciones de 0,4 a 1 mg/mL en cloruro de sodio al 0,9%, se encontró que a partir de las concentraciones de 0,6 mg/ml se formó un precipitado cuando se almacena de 2 a 6 °C. En las soluciones donde se formó el precipitado, la redisolución se dio muy lentamente con el calentamiento a temperatura ambiente. La sonicación a 40 °C se usó para volver a disolver el precipitado en unos 20 a 30 minutos, sin embargo se menciona que no se recomienda el calentamiento de soluciones de cisplatino para efectuar la redisolución de los precipitados (2).

Según el *Handbook of Injectable Drugs* de la American Society of Health-System Pharmacists se evaluó la estabilidad de paclitaxel diluido con 5% de dextrosa y cloruro de sodio 0,9% a concentraciones finales de 0,3 y 1,2 mg/ml en cuatro bolsas de poliolefina (Viaflo, Freeflex, Ecoflac y Macoflex N) reportando que paclitaxel es físicamente compatible con la pérdida de menos de 5% en 72 horas a 37 ° C en la oscuridad (2).

En el estudio farmacocinético realizado en 13 pacientes por Ansoloni *et al.* se evidencia que la quimioterapia intraperitoneal hipertérmica (de 41 a 43°C) con cisplatino y paclitaxel después de la cirugía citorreductora tiene un perfil farmacocinético favorable alcanzando altas concentraciones de los fármacos en el tejido peritoneal con baja exposición sistémica. Sin embargo, se necesitan estudios más amplios para demostrar su eficacia en pacientes con tumores residuales posquirúrgicos microscópicos en la cavidad peritoneal (3).

Referencias bibliográficas:

1. AHFS Drug Information. American Society of Health-System Pharmacists. In: MedicinesComplete © The Pharmaceutical Press 2014 [acceso 18 marzo 2015]. Disponible en: https://www.medicinescomplete.com
2. *Handbook of Injectable Drugs*. American Society of Health-System Pharmacists. In: MedicinesComplete © The Pharmaceutical Press 2014 [acceso 18 marzo 2015]. Disponible en: https://www.medicinescomplete.com
3. Ansaloni L, Coccolini F, Morosi L, Ballerini A, Ceresoli M, Grosso G, Bertoli P, Busci LM, Lotti M, Cambria F, Pisano M, Rossetti D, Frigerio L, D'Incalci M, Zucchetti M. Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitonealchemotherapy to patients with peritoneal carcinomatosis from epitelial ovarian cancer. Br J Cancer. 2015 Jan 20;112(2):306-12.