Supplementary materials

Rietveld P, et al.

A clinical pharmacological perspective on intraperitoneal chemotherapy

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Search strategy

Table S1. Search strategy

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	598	598
Embase	Embase.com	1971 - Present	1167	745
Web of Science Core Collection*	Web of Knowledge	1975 - Present	513	221
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	56	22
Total			**2334**	**1586**

*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

No other database limits were used than those specified in the search strategies

medline

(Ascitic Fluid / OR Peritoneum / OR Injections, Intraperitoneal / OR Peritoneal Cavity / OR (periton* OR intraperiton* OR Ascitic-Fluid*).ab,ti,kw.) AND (Plasma/ OR Serum/ OR Blood/ OR (plasma* OR serum* OR (blood* ADJ3 (concentration* OR level*))).ab,ti,kw.) AND (exp Pharmacokinetics / OR Pharmacokinetics.xs. OR (pharmacokinetic* OR Chronopharmacokinetic* OR ((drug* OR antineoplas* OR anti-neoplas* OR agent*) ADJ3 (absorption* OR accumulation* OR activation* OR adsorption* OR bioavailability* OR clearance* OR dialysability* OR diffusion* OR disposition* OR distribution* OR elimination* OR excretion* OR half-life* OR inactivation* OR metabolism* OR penetration* OR release* OR retention*)) OR (Concentration* ADJ3 time ADJ3 curve*) OR (dose* ADJ3 time* ADJ3 relation*)).ab,ti,kw. OR ((absorption* OR accumulation* OR activation* OR adsorption* OR bioavailability* OR clearance* OR dialysability* OR diffusion* OR disposition* OR distribution* OR elimination* OR excretion* OR half-life* OR inactivation* OR metabolism* OR penetration* OR release* OR retention*).ti. AND (Drug Therapy / OR exp * Antineoplastic Agents /))) AND (Combined Modality Therapy / OR exp Chemotherapy, Adjuvant / OR Antineoplastic Combined Chemotherapy Protocols / OR Antineoplastic Agents / OR exp * Antineoplastic Agents / OR exp Neoplasm/dt OR antineoplastic activity/ OR (chemotherap* OR antineoplas* OR anti-neoplas* OR anti-cancer* OR anticancer*).ab,ti,kw.) NOT (exp animals/ NOT humans/)

embase

('peritoneal fluid'/de OR peritoneum/de OR 'intraperitoneal drug administration'/exp OR 'peritoneal cavity'/de OR (periton* OR intraperiton* OR Ascitic-Fluid*):Ab,ti,kw) AND (plasma/de OR serum/de OR blood/de OR 'plasma concentration time curve'/de OR 'blood level'/de OR 'drug blood level'/de OR (plasma* OR serum* OR (blood* NEAR/3 (concentration* OR level*))):ab,ti,kw) AND (pharmacokinetics/exp OR (pharmacokinetic* OR Chronopharmacokinetic* OR ((drug* OR antineoplas* OR anti-neoplas* OR agent*) NEAR/3 (absorption* OR accumulation* OR activation* OR adsorption* OR bioavailability* OR clearance* OR dialysability* OR diffusion* OR disposition* OR distribution* OR elimination* OR excretion* OR half-life* OR inactivation* OR metabolism* OR penetration* OR release* OR retention*)) OR (Concentration* NEAR/3 time NEAR/3 curve*) OR (dose* NEAR/3 time* NEAR/3 relation*)):Ab,ti,kw OR ((absorption* OR accumulation* OR activation* OR adsorption* OR bioavailability* OR clearance* OR dialysability* OR diffusion* OR disposition* OR distribution* OR elimination* OR excretion* OR half-life* OR inactivation* OR metabolism* OR penetration* OR release* OR retention*):ti AND ('drug therapy'/de OR 'antineoplastic agent'/exp/mj))) AND (chemotherapy/exp OR 'antineoplastic agent'/de OR 'antineoplastic agent'/exp/mj OR 'neoplasm'/exp/dm_dt OR 'antineoplastic activity'/de OR (chemotherap* OR antineoplas* OR anti-neoplas* OR anti-cancer* OR anticancer*):Ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim)

Web of science

TS=(((periton* OR intraperiton* OR Ascitic-Fluid*)) AND ((plasma* OR serum* OR (blood* NEAR/2 (concentration* OR level*)))) AND ((pharmacokinetic* OR Chronopharmacokinetic* OR ((drug* OR antineoplas* OR anti-neoplas* OR agent*) NEAR/2 (absorption* OR accumulation* OR activation* OR adsorption* OR bioavailability* OR clearance* OR dialysability* OR diffusion* OR disposition* OR distribution* OR elimination* OR excretion* OR half-life* OR inactivation* OR metabolism* OR penetration* OR release* OR retention*)) OR (Concentration* NEAR/2 time NEAR/2 curve*) OR (dose* NEAR/2 time* NEAR/2 relation*))) AND ((chemotherap* OR antineoplas* OR anti-neoplas* OR anti-cancer* OR anticancer*)))

Cochrane

((periton* OR intraperiton* OR Ascitic-Fluid*):Ab,ti,kw) AND ((plasma* OR serum* OR (blood* NEAR/3 (concentration* OR level*))):ab,ti,kw) AND ((pharmacokinetic* OR Chronopharmacokinetic* OR ((drug* OR antineoplas* OR anti-neoplas* OR agent*) NEAR/3 (absorption* OR accumulation* OR activation* OR adsorption* OR bioavailability* OR clearance* OR dialysability* OR diffusion* OR disposition* OR distribution* OR elimination* OR excretion* OR half-life* OR inactivation* OR metabolism* OR penetration* OR release* OR retention*)) OR (Concentration* NEAR/3 time NEAR/3 curve*) OR (dose* NEAR/3 time* NEAR/3 relation*)):Ab,ti,kw) AND ((chemotherap* OR antineoplas* OR anti-neoplas* OR anti-cancer* OR anticancer*):Ab,ti,kw)

Detailed drug characteristics and treatment variables

Table S2. Characteristics and treatment variables of drugs used in HIPEC

Study	Drug	Dose & volume	Route	N (PK)	Duration, temperature, flushing, pressure	Sample times range	Measurement	AUC IP	AUC IV	AUC or Cmax IP/IV ratio
Elias 2004 (1) & Elias 2002 (2)	Oxaliplatin	460 mg/m2 in 2L/m2	IP	20	30 min, IPCH, then washout	Plasma: 0-25h. IP: 0-40 min	UF Platinum		UF: 14.8 ug/ml*h	Cmax ratio 25
Elias 2002 (3)	Oxaliplatin	260-460 mg/m2 in 2 or 2.5L/m2	IP	16	30 min, IPCH, then washout	Plasma: 0-25h. IP: 0-40 min	Total and UF Platinum		Mean UF 14.8 ug/ml*h	
Ferron 2008 (4)	Oxaliplatin	460 mg/m2 or 360 mg/m2	IP	24	30 min, Heated intraoperative, coliseum technique, then washout	IP during HIPEC 0-30 min, IV: 0-8h	UF platinum		UF: 13.7 ug/ml*h	
Stewart 2008 (5)	Oxaliplatin	200 or 250 mg/m2	IP	15	2h ICPH, then washout	IP during IPCH 120 min, IV: 0-1440 min	Total platinum	49.6-62.7 mg/l*h	3.6-4.9 mg/l*h	12.8-13.8 (0-120 min)
Perez-Ruixo 2013 (6) & Perez-Ruixo 2014 (7)	Oxaliplatin	360 mg/m2 in 2.5-6L	IP	49	30-60 min, then washout	IP: 0-1h, IV: 0-28h	Total platinum (but transformed to oxaliplatin using the Mw)	132-150 mg/L*h	192-213 mg/L*h	
de Jong 2020 (8)	Oxaliplatin	460 mg/m2 in about 5L	IP	20	Oxaliplatin-based HIPEC was performed using the open coliseum technique at a dose of 460 mg/m2 , at a target temperature of 42–43 °C for a total duration of 30 min. One flushing and one non flushing group	IV 0-72h, IP: 0-0.5h	UF + total	± 75 ug/mL*h (0-0.5h)	10.5-28.0 ug/mL*h	
Chalretdurieu 2014 (9)	Oxaliplatin	360 mg/m2 or 460 mg/m2	IP	75	30 min HIPEC	IP: 0-0.8h, IV: 0-8h	UF (plasma) + Total (plasma+IP)	17000 ng/mL*h	3500 ng/mL*h	

Kusamura 2021 (10)	Cisplatin	42 mg/L in 4000-6000L	IP	38	closed abdomen 60 min HIPEC, different abdominal pressure	IV+IP: 0-60 min	Total + UF platinum	35 (UF), 42 (total), (unit not reported)		28 (UF), 24 (total)
Zivanovic 2015 (11)	Cisplatin	60, 80, 100 mg/m2	IP	12	90 min HIPEC	IP: 0-1.5h, IV: 0-72h	Total platinum	27 (100mg/m2) ug/mL*h	1.83 (100mg/m2) ug/mL*h	19.5 (0-90 min)
Cotte 2011 (12)	Cisplatin	0.8-1.5 mg/kg in 4-6L	IP	40	closed adbomen HIPEC, 90 minutes, drained afterwards	IP:0-120h, IV:0-240h	Total platinum		63 mg/mL*h	5.9 (0-1.5h)
Royer 2008 (13)	Cisplatin	90 mg in 3L (2 times)	IP	27	HIPEC 1h, then washout and then again 1h chemotherapy and washout	IP: 0-2h, IV: 0-24h	Total + UF platinum, total protein concentrations	20 (UF), 24 (total) mg/L*h (for 2 baths)	5.9 (UF), 25.2 (total) mg/L*h (for 2 baths)	3.4 (UF), 1 (total) (for 2 baths)
Royer 2005 (14)	Cisplatin	50 mg/m2 in 3L	IP	11	HIPEC open procedure, 2h, then washout	IP: 0-120min, IV: 0-inf	Total + UF platinum, total protein concentrations, albumin concentrations	11.73 mg/L*h (total), 10.23 mg/L*h (UF)	46.26 mg/L*h (total), 4.02 mg/L*h (UF)	0.25 (total), 2.5 (UF)
Ansaloni 2015 (15)	Cisplatin	100 mg/m2 in 2.3L/m2	IP	13	HIPEC, 90 minutes, drained and washed afterwards	IV: 0-90min, IP:geen auc	Total platinum (omgerekend naar cisplatin voor concentraties)		128.5 ug/mL*min	
Mikkelsen 2020 (16)	Carboplatin	800 mg/m2 in 5L, max 1600 mg	IP	15	HIPEC open abdominal technique, perfusion time 90 min then drainage	IP: 0-90 min, IV: 0-48h	Total carboplatin			12.3 (90 min)
de Bree 2008 (17)	Paclitaxel	175 mg/m2 in 3.5-7L	IP	10	HIPEC 2 hours, closed perfusion, fluid was drained after	IV+IP: 5 days	Paclitaxel	145 (0-2h), 736.4 (0-120h) mg/L*h	0.109 (0-2h), 2.2 (0-120h) mg/L*h	1462 (0-2h), 366 (0-120h) (AUC), 1178 (Cmax)
Elias 2004 (1)	Irinotecan	300 to 700 mg/m2 in 2L/m2	IP	35	30 min, IPCH, then washout	IV: 0 to 24h, IP: 30 min	Irinotecan		16.8 ± 3.8 ug/mL*h	
Jacquet 1998 (18)	Mitomycin C	22.5 +-7.1 mg in 3L	IP	18	2h lavage, then all was collected, 48 degrees,	IP+IV: 0-120 min		340.1 ± 138.5 ug/ml*min	15.1 ± 4.0 ug/ml*min	23.5 ± 10.3
Van der Speeten 2010 (19)	Mitomycin C	15 mg/m2 in 1.5 l/m2	IP	145	HIPEC for 90 min, 42 degrees	IP+IV:0-90 min				27

van Ruth 2004 (20)	Mitomycin C	35 mg/m2 in three divided doses in 3L	IP	47	semi-open abdomen, basic perfusate volume of 3L, perfusion rate of 1 L/min, abdominal temperature of 40°C, 90 minutes of perfusion and three additions of drug (50% at beginning of perfusion, and further additions of 25% at 30 and 60 minutes). Excess fluid was drained afterwards	IP:0-90 min, IV: 0-18h (AUC IV 0-inf)		630 mg/L*min	71 mg/L*min	10.1
Cerretani 2005 (21)	Mitomycin C	20 mg/m2 in 4-6L	IP	28	ICPH, 60 min, 42 degrees, flow rate: 700-800 ml/min	IP:0-60 min, IV: 0-360 min (AUC IV 0-inf)		332.16 mg/L*min	15.8 mg/L*min	~21
Jacquet 1998 (18)	Mitomycin C	22.5 mg/m2 in 3L (30 mg in 3L)	IP	18	2h HIPEC 42 degrees, then drainage	IP+IV:0-120 min		340 ug/mL*min	15 ug/mL*min	23.5
Choi 2023 (22)	nal-IRI	70-280 mg/m2 in 3 L	IP	18	HIPEC 30 minutes, closed procedure, 41 degrees, nal-IRI evacuated afterwards and residual chemotherapy washed out	IP: 0-30 min, IV: 0-72h	Total IRI and SN-38		22.62 ug/mL*h (IRI) (280 mg/m2), 167.8 ug/mL*h (SN-38) (280 mg/m2)	
Sugarbaker 2021 (23)	PLD	50 or 100 mg/m2, 1.5L/m2 or 2L	IP	14	90 or 180 minutes HIPEC open technique	IP+IV:0-90/0-180min	PLD			600 (90 min, 50 mg/m2, 1.5L/m2), 1200 (180 min, 100 mg/m2, 1.5L/m2), 1390 (180 min, 100mg/m2, 2L)
Salvatorelli 2012 (24)	PLD	in 4 L	IP	17	HIPEC (closed) for 1 hour, 42 degrees, abdominal cavity washed afterwards	IP:0-1h, IV:	PLD (no free doxorubicin detected)			≥1000

Table S3. Characteristics and treatment variables of drugs used in catheter-based IP therapy

Study	Drug	Dose & volume	Route	N (PK)	Duration, temperature, flushing, pressure	Sample times range	Measurement	AUC IP	AUC IV	AUC or Cmax IP/IV ratio
Jaquet 1998 (18)	5-FU	15 mg/kg (mean 700 mg) in 1L	IP	18	Early postoperative IP chemotherpay	0-180 min	5-FU	733 ug/ml*min*	2.14 ug/ml*min*	18
Seymour 2008 (25)	5-FU	Week 1&2: 400 mg/m2 IP in 1500 and 1500 ml, week 4: IV bolus FU 400 mg/m2 + FU 400 mg/m2 IP in 1500ml	IP + IV	12	Week 1+2: 40 min IP instillation, week 4: 5 min IV bolus plus 1 h later a 40 min IP instillation	IP+IV: 0-20h	5-FU	~ 1000 ug/mL*h	~ 1 ug/mL*h	~1000
de Jong 2023 (26)	Cisplatin	100 mg/m2	IP	11	Instillation over 1h	0-24h	UF platinum + total platinum		10.1 mg/L*h	29 (Cmax ratio)
Leopold 1993 (27)	Cisplatin	20-120 mg/m2 in 1L after administration of 1L normal saline	IP	15	60 minutes (not removed after)	IP+IV: 0-24h	UF platinum			30-35
Jandial 2017 (28)	Carboplatin	AUC 4 in 2L	IP	10	IP bolus instillation	IV: 5h, IP: 2h	UF platinum	21.6 mg/mL*min	1.45 mg/mL*min	14.9
Miyagi 2005 (29)	Carboplatin	AUC 6 in 500 ml	IP	11	IP bolus instillation	IV+IV:0-24h	UF platinum	53.32 mg/mL*min	2.86 mg/mL*min	
De Jong 2023 (26)	Paclitaxel	60 mg/m2	IP	11	IP instillation	IP: only one sample at the end of IP instillation. IV: 0-24h	Paclitaxel		0.06 ug/mL (gmean concentration)	972 (gmean concentration)

Imano 2012 (30)	Paclitaxel	80 mg/m2 in 1L	IP	11	IP therapy, drinage tubes clamped for 24 or 48h, then drained	IV+IP:0-48h	Paclitaxel	23237758 ng/mL*h	3893.3 ng/mL*h	596.9 (AUC), 2917.5 (Cmax)
Hofstra 2002 (31)	Paclitaxel	75 mg/m2 in 1 L	IP	25	Instillation IP chemotherapy, infused over 2h	IV+IP:0-24h	Paclitaxel		922 (0-inf) ug/L*h	1350
Markman 1992 (32)	Paclitaxel	25-175 mg/m2 in 1 or 2L	IP	17	Instillation IP chemotherapy, infused as rapidly as possible	IV+IP: 0-48h	Paclitaxel			996 (range: 336-2890), 1000 (Cmax)
Badgwell 2024 (33)	Paclitaxel	40-100 mg/m2 in 0.5L. Before IP treatment, 0.5L NaCl was instilled in the IP cavity.	IP	16	Instillation IP chemotherapy, infused over 0.5h	IV: 0-72h	Paclitaxel		13,955 ng/mL*h	658 (Cmax)
Taylor 2019 (34)	Docetaxel	50, 75, 100 mg/m2	IP	12	Instillation IP chemotherapy	IP+IV: 0-72h (AUC0-inf)	Docetaxel	215,718.5 (50 mg) ng/mL*h, 872,981.3 (75 mg), 732,660.7 (100 mg) ng/mL*h	1,173.5 (50 mg) ng/mL*h, 4,230.3 (75 mg) ng/mL*h, 3189.3 (100 mg) ng/mL*h	AUC: 229 (179 at 50mg/m2, 284 at 75 mg/m2 and 247 at 100 mg/m2). Cmax: 571 (50 mg), 235.3 (75 mg), 428.8 (100 mg)
Morgan 2003 (35)	Docetaxel	40, 80, 100, 125 mg/m2 in polysorbate 80 and 2L NaCl 0.9%. Before IP treatmen, 500 mL NaCl was instilled in the IP cavity.	IP	18	implanted IP catheter (instillation IP therapy). Polysorbate 80 diluent.	IP+IV: 0-24h (AUC 0-inf)	Docetaxel			152 (median) 181 (mean)
Fushida 2008 (36)	Docetaxel	25, 35, 45 and 60 mg/m2 in 1 L	IP	15	1 hour infusion	IP+IV: 0-24h	Docetaxel	473.6 ug/mL*h		515 (range 22-1773)

Choi 2011 (37)	Irinotecan	50-300 mg/m2 in 1L	IP	17	IP instillation	Up to 56h	Irinotecan	450 h*mg/L	12.77 h*mg/L	~ 35
Choi 2011 (37)	Irinotecan	50-300 mg/m2 in 1L	IP	17	IP instillation	Up to 56h	SN-38	1.12 h*mg/L	0.57 h*mg/L	~ 2
Eerden 2023 (38)	Irinotecan	50, 75 or 100 mg in 1L	IP	18	1.5 hour IP infusion	IP+IV: 0-48h (AUC 0-24h)	Irinotecan		892.8 ng.h/ml (50 mg), 1947.1 ng.h/ml (75 mg) dose, and 2391.7 ng.h/ml (100 mg)	
Eerden 2023 (38)	Irinotecan	50, 75 or 100 mg in 1L	IP	18	1.5 hour IP infusion	IP+IV: 0-48h (AUC 0-24h)	SN-38	242 ng.h/ml (50 mg), 160 ng.h/ml (75 mg), and 284 ng.h/ml (100 mg)	26.5 ng.h/ml (50 mg), 47.5 ng.h/ml (75 mg), and 41.2 ng.h/ml (100 mg)	4.8
Cristea 2019 (39)	NAB-PTX	35-175 mg/m2	IP	16	IP catheter infusion	IP+IV: 0-48h	Total PTX	259.1 mg/L*h (140 mg/m2)	4.4 mg/L*h (140 mg/m2)	147
Sugarbaker 2021 (23)	PLD	50 mg in 2L	IP	14	Early postoperative IP chemotherapy	IP+IV:0-24h	PLD			
Williamson 2015 (40)	nanoparticle paclitaxel (Nanotax®)	50-275 mg/m2 in 2 L	IP	21	IP instillation, infused over 30-60 minutes, not drained afterwards	IP+IV: 0-336h	Total PTX		2.996 umol/L*h (mean all doses)	

Table S4. Characteristics and treatment variables of drugs used in PIPAC

Study	Drug	Dose & volume	Route	N (PK)	Duration, temperature, flushing, pressure	Sample times range	Measurement	AUC IP	AUC IV	AUC or Cmax IP/IV ratio
Lurvink 2021 (41)	Oxaliplatin	92 mg/m2	IP	20	PIPAC	0-24h	UF + total		49-59.5 ug/mL*h, UF: 9.6-11.7 ug/mL*h	
Dumont 2020 (42)	Oxaliplatin	90-140 mg/m2	IP	10	PIPAC	0-48h	UF		6106-9028 ug/l*h	
Ceelen 2022 (43)	NAB-PTX	35-140 mg/m2	IP	20	PIPAC 30 minutes	IV: 0-24h	Total PTX		1904 ng/mL*h (140 mg/m2)	

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