Feasibility of using intraperitoneal epinephrine and cisplatin in patients with advanced peritoneal carcinomatosis

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Intraperitoneal epinephrine above 1 mg/l concentration has been shown to enhance the intratumoral accumulation and antitumor activity of intraperitoneal cisplatin in rats with advanced peritoneal carcinomatosis. The aim of this study was to determine the tolerance of intraperitoneal epinephrine combined with intraperitoneal cisplatin in patients with advanced peritoneal carcinomatosis (17 ovarian cancers, one peritoneal mesothelioma). Intraperitoneal epinephrine (1–5 mg/l) and cisplatin (50 mg/l; 100 mg total dose) were infused in 2 l of saline solution over 2 h. The maximal tolerated concentration of intraperitoneal epinephrine was not reached at 5 mg/l. Cardiovascular symptoms were infrequent and not strictly related to the epinephrine concentration. Tumor responses were obtained in some patients with disease resistant to intravenous platinum compounds. This work demonstrates for the first time that intraperitoneal epinephrine at sufficient concentration enhances the cisplatin effect and can be safely infused into the peritoneal cavity of patients with peritoneal carcinomatosis. The greatest limitation was abdominal pain and limited intraperitoneal distribution of the peritoneal fluid in this closed-abdomen procedure.
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Introduction

Ovarian cancer often remains confined to the peritoneal cavity even at a recurrent or advanced stage (peritoneal carcinomatosis). Peritoneal carcinomatosis is characterized by multiple metastatic deposits, varying in size from small granulomas to large masses, often invading the underlying organs and usually accompanied by ascitis. Most patients with stage III ovarian cancer relapse, despite a good initial response to standard intravenous (i.v.) chemotherapy (paclitaxel/carboplatin). As most of the relapses initially occur in the peritoneal cavity, the intraperitoneal (i.p.) administration of cytotoxic agents could, theoretically, improve their therapeutic activity. Intraperitoneal chemotherapy is based on the dose–effect relationship at the local level. For example, the i.p. administration of cisplatin yielded an i.p. concentration that was 12–15-fold higher than the plasma concentration [1]. Despite this theoretical advantage, the clinical efficacy of i.p. chemotherapy is limited to patients whose residual tumor nodules are less than 5 mm in diameter after surgical debulking [2]. The failure of i.p. administered drugs to cure larger tumor masses is mainly attributed to their poor penetration from the peritoneal cavity into the tumor tissue. That is, when compared with i.v. infusion, i.p. administration of cisplatin enhances the average platinum concentration in the tumor mass, but the increase is limited to the outer 1–2 mm of the tumor [3]. Owing to technical difficulties and the relatively limited increase in disease control over standard i.v. treatment, i.p. chemotherapy is not yet an accepted modality for the treatment of ovarian cancer, despite some encouraging results [4–8].

New methods to increase the depth of penetration of anticancer agents into the metastatic peritoneal nodules are needed. We previously demonstrated that i.p. epinephrine increased the penetration of cisplatin and oxaliplatin into metastatic peritoneal tumor nodules in rats [9–11]. This improved drug penetration led to a greater antitumor efficacy, allowing for the cure of millimeter-sized peritoneal tumor nodules that could not be obtained with i.p. cisplatin or i.p. oxaliplatin used

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alone. Epinephrine was thought to improve the depth of platinum compound diffusion, both by limiting the drainage of the drug through the peritoneal and tumor vasculature (the draining off hypothesis), and by decreasing the high interstitial pressure in solid tumors [12]. Increase of platinum accumulation in rat peritoneal nodules was half-maximal at 1 mg/l and maximal at 2.5 mg/l epinephrine concentration in the peritoneal liquid [10]. These encouraging experimental results led us to design a feasibility study, aiming to determine whether such epinephrine concentrations are achievable in human patients with refractory peritoneal carcinomatosis.

Patients and methods

Eligibility criteria

Patients over 18 years old, with peritoneal carcinomatosis, were eligible for the study, provided they did not have extra-abdominal tumors at computed tomography (CT) scan. Except the patient with peritoneal mesothelioma, who was treated as first-line therapy in the study (patient 6), all other patients had ovarian tumors that were considered resistant to carboplatin (progression or early relapse < 6 months after treatment). The 'Comité Consultatif pour la Protection des Personnes Soumises aux Recherches Biologiques de Bourgogne' approved the protocol and informed consent was obtained from all the patients. Patients had adequate hematological (white blood cell count > 3000 cells/mm^3; platelets $> 10^5$ cells/mm^3), renal (serum creatinine < 1.5 mg/dl) and hepatic (bilirubin, aminotransferase and alkaline phosphatase less than twice the upper limit of normal) function. The World Health Organization performance status was 0–2. Patients were excluded if peripheral neuropathy was grade 2 or higher, or if they had any contraindication to i.p. therapy, such as intra-abdominal infection. Strictly normal cardiovascular function was checked by history and physical examination, an electrocardiogram (ECG), a 24-h heart rhythm recording, heart echocardiography, and Doppler sonographic examination of cervical, renal and inferior limb arteries.

Treatment schedule

Except for the first three patients who were treated via a percutaneous needle in the first period of the trial, all other i.p. treatments were using an i.p. catheter and a subcutaneous device, which was surgically placed under general anesthesia. Patients were treated in a special unit for investigative clinical trials, under continuous surveillance. In order to prevent cisplatin nephrotoxicity, patients received 1.5 l of i.v. isotonic saline solution (9 g/l NaCl) for 3 h before the delivery of i.p. chemotherapy, and 2 l of i.v. saline with potassium (2 g/l) and magnesium (1 g/l) for 18 h after the i.p. treatment. Premedication consisted of antiemetics (setrons and methylprednisone) and analgesics (paracetamol and/or morphine). The i.p. treatment consisted of 2 h of i.p. infusion of 2 l saline solution with 50 mg/l cisplatin (100 mg total dose) and various escalated concentrations (1, 2, 3, 4 or 5 mg/l) of epinephrine. Epinephrine was diluted in 50 ml saline and i.p. infused parallely with cisplatin, through an electric pump, so that it can be immediately stopped if predefined abnormal events occurred. The peritoneal cavity was not drained at the end of i.p. treatment. An abdominal ultrasonography was performed in most patients to study the distribution of peritoneal fluid. The presence or absence of liquid was checked in eight abdominal areas (peri-hepatic, subhepatic, peri-splenic, subsplenic, right and left lateral flanks, Douglas recessus, and centro-mesenteric). Diuresis, blood pressure, pain evaluation and continuous ECG were monitored during and 24 h after epinephrine administration. The first i.p. chemotherapy was given at least 4 weeks after a previous systemic chemotherapy and recovery of all toxicities. Cycles were repeated every 4 weeks for a total of six courses, unless progression or toxicity occurred. A complete physical examination, measurement of blood pressure and weight, basal ECG, blood counts, serum electrolytes, renal function, and serum CA 125 levels were performed before each new cycle.

Toxicity assessment

The predefined upper limits for deciding whether or not to stop epinephrine i.p. infusion were heart rate above 130/min, systolic blood pressure above 190 mmHg, ventricular extrasystoles over 2/min or any abnormal cardiovascular event, such as angina pectoris or malaise. For the evaluation of systemic toxicity, standard National Cancer Institute Common Toxicity Criteria 2 criteria were applied and scored after every cycle. Abdominal pain was scored grade 3 when oral or i.v. morphine was required and grade 4 if pain persisted more than 72 h, despite the use of morphine-based analgesics.

Efficacy assessment

Despite the fact that the assessment of response was not the main objective of this feasibility study, several clinical and biological responses were encountered and were scored. The evaluation of response was performed according to Response Evaluation Criteria in Solid Tumors in patients with measurable tumor deposits (≥ 2 cm), with a CT scan every three cycles. Serum CA 125 levels were determined at each cycle. A 100% increase of marker levels above normal, the appearance of new lesions or an increase of tumor measurement $\geq 20\%$ were considered as signs of tumor progression. A partial response was defined as a sustained decrease of serum CA 125 greater than 50%, confirmed at 1-month interval, when the disease was not measurable by CT scan. Stable disease required no clinical and biological change for a minimum of two cycles (8 weeks).

Pharmacokinetics study

Pharmacokinetic analysis of epinephrine was carried out in most of the patients when it was possible to withdraw

peritoneal liquid from the i.p. catheter. The initial 5 ml of fluid was discarded and then 5 ml was collected in ethylene glycol-bis(*b*-aminoethyl ether)/glutathione-containing vials for the determination of epinephrine concentration. At the same time, blood samples were collected and centrifuged at 4°C. Samples were kept frozen at −80°C until assay. Plasma and peritoneal samples were analyzed for epinephrine using high-pressure liquid chromatography and electrochemical detection [13]. Briefly, this involved adding 50 mg of acid-washed alumina to the sample, neutralizing with 1 mol/l Tris base and letting the alumina settle. After washing the alumina twice with ultrapure water, epinephrine was eluted from the alumina by adding 100 µl of 0.1 mol/l perchloric acid. This elute was analyzed on a 5-µm C18 reverse-phase column (equilibrated with 0.08 mol/l sodium phosphate, pH 4.2, 0.27 mmol/l ethylenediamine tetraacetic acid, 3% acetonitrile, 3.7 mmol/l octan-1 sulfonic acid) coupled to a Waters high-pressure liquid chromatograph equipped with a Waters 460 (Waters, Saint Quentin en Yvelines, France) electrochemical detector set at +850 mV. Recovery of the sample was corrected using dihydroxybenzylamine as an internal standard.

Results

Population and treatment

Eighteen patients (17 women/one man) were included in this feasibility study between February 2000 and June 2003. The median age was 64 years (range 52–77 years). All female patients initially had stage III ovarian cancer, the majority of them with papillary serous histology (13/17). The male patient had peritoneal mesothelioma. All patients with ovarian cancer received carboplatin and paclitaxel therapy as the primary treatment. Two or more lines (median 2; range 1–4) of systemic chemotherapy (liposomal doxorubicin, topotecan, gemcitabine) were allowed before inclusion. Only the patient with peritoneal mesothelioma was first-line treated, owing to refractory ascitis. The median time from the first surgical treatment was 316 days.

The study was initially designed for an intrapatient escalation of i.p. epinephrine concentration, starting from 1 mg/l, then increasing in steps of mg/l at each new cycle up to 5 mg/l, if well tolerated (patients 1–6). The 5 mg/l epinephrine concentration was considered as the maximum level to reach in regard to the animal studies, which showed that a maximum potentiating effect on platinum penetration and antitumor effect was obtained for a 2.5-mg/l concentration in rats, and that a 5-mg/l concentration was well tolerated in pigs [10]. The study was transiently stopped at the request of Autorité Française de Sécurité Sanitaire des Produits de Santé owing to a serious adverse event, which was not epinehrine related (bowel perforation and peritonitis because of the percutaneous needle). The regulatory agency then required that a Port-a-Cath subcutaneous device be used and recommended a fixed concentration for all the cycles in a given patient (patients 7–18). Despite this intermediary modification of the study design, a pooled analysis of both periods of the study could be performed, considering each cycle as an independent event. So, 59 cycles of i.p. chemotherapy (mean 3.05; range 1–11; six cycles with cisplatin alone and 53 cycles with various concentrations of epinephrine) were analyzed from 18 patients.

Safety

Cardiovascular events owing to epinephrine, peritoneal toxicity owing to an increased cisplatin tissue penetration and systemic toxicity owing to cisplatin were anticipated when the study was designed. The cardiovascular effect related to epinephrine was encountered at various concentration levels, but was always reversible a few minutes after stopping the infusion (Table 1). No event required the use of antiarrhythmic or antihypertensive drugs. The main cardiac side-effect was a transitory and noncomplicated episode of angina pectoris of a short, 5-min duration, which led to the ultimate withdrawal of i.p. epinephrine for this patient. This problem occurred at the fourth i.p. infusion at a concentration of 1 mg/l, whereas three previous cycles at 1 mg/l had been well tolerated in the patient. Few patients (3/53 cycles with epinephrine) complained of adrenergic malaise with sweating and anxiety, irrespective of whether or not associated to tachycardia (2/53), or increased systolic blood pressure (4/53). These effects were quickly reversible after transient withdrawal of infusion. No clear relationship was seen between the occurrence of cardiovascular effects and the epinephrine dose. The maximal tolerated concentration of i.p. epinephrine was not reached at 5 mg/l. It was decided not to increase further the dose of i.p epinephrine, as rat studies clearly showed a maximal potentiating effect on platinum accumulation at 2.5 mg/l and pig studies showed signs of cardiac intolerance above 10 mg/l i.p. epinephrine.

The known technical problems of i.p. chemotherapy were encountered (one catheter migration into the bowel lumen, one subcutaneous drug extravasation owing to catheter leakage, one infection of the subcutaneous device leading to its withdrawal). A case of bowel perforation with peritonitis requiring surgical intervention was observed in the third patient, when chemotherapy was given through a percutaneous needle. Five patients were removed from the study: one for peritonitis owing to a bowel perforation, one for aggravation of a cisplatin-induced neuropathy, two for mild grade 1 renal toxicity and one for refusal. Abdominal discomfort and pain was the most frequent side-effect (53% grade 3, 15% grade 4) and could persist up to 7 days after i.p. infusion. Nausea and vomiting were moderate owing to the

Table 1 Toxicity and outcome

Patient no.	No. of cycles	Epinepherine concentration (mg/l)	Toxicity			Additional comments
			Cardiovascular	Abdominal pain	Other	
1	2	0	–	3		
		1	–	4	grade 3 neuropathy	exit of study owing to neuropathy
2	4	0	–	3	fever, vomiting	
		1	–	4		SD
		2	HSBP	4	ileus >72 h	
		3	–	4	malaise, increase in creatinine	
3	2	0	–	3	bowel perforation and peritonitis	PR, decrease of CA 125 >50%
		1	–	4	weight gain, nausea	SD
4	5	0	–	0		
		1	–	3		
		2	–	3		
		3	VES	3	weight gain, nausea	
		3	–	3	weight gain, nausea	
5	5	0	–	0	weight gain, nausea	SD
		1	–	2	weight gain, nausea	
		1	HSBP	3	weight gain, nausea	
		2	tachycardia	3	nausea	
		2	VES	4	nausea	
6	11	0	–	4	nausea	
		1	–	3	malaise	SD
		1	–	3		
		1	–	3	nausea	
		2	–	3		
		3	–	3	intraparietal perfusion	
		4	–	3		
		4	–	4	malaise, ileus >72 h	
		5	–	4		
		5	–	3		
		5	–	3		
7	4	1	–	2		SD
		1	–	1		
		1	–	2		
		1	angina	2		
8	1	1	–	3	ileus >72 h	Exit owing to refusal
9	3	1	–	2	extravasation	SD
		2	–	2		
		1	tachycardia	3	dyspnea	
10	2	1	–	3		PD
		1	–	3		
11	6	1	–	0	weight gain	PR: drying of a refractory ascitis
		1	–	0	weight gain	
		2	–	0	weight gain	
		2	–	0		
		2	HSBP	0		
		2	HSBP	0		
12	2	2	–	3	malaise	PD
		2	–	3	migration of the catheter	
13	3	2	–	3	nausea	PD
		2	–	3	nausea	
		2	–	3	nausea	
14	1	2	–	2	increased creatinine	PR, decrease of CA 125 >50%
15	1	2	–	3	infection of subcutaneous device	PR, decrease of CA 125 >50%
16	3	3	–	3		
		3	–	2	ileus >72 h	PD
		3	–	3	nausea	
17	3	3	–	3	ileus >72 h, weight gain	PR, decrease of CA 125 >50%
		3	–	3	weight gain	
		3	–	3	weight gain	
18	1	3	–	3	nausea	PR: drying of a refractory ascitis

HSBP, high systolic blood pressure >190 mmHg; VES, ventricular extrasystoles >2/min; PR, partial response; PD, progessive disease; SD, stable disease.

systematic use of setrons and corticosteroids as anti-emetic agents. Constipation with transient ileus was observed in almost all patients for few days but was reversible in less than 1 week with the use of an osmotic laxative (lactulose). Weight gain > 2 kg, with or without limb edema, was related to the slow elimination of both i.v. hydration and peritoneal liquid over several days. A moderate and transitory increase in serum creatinine level was registered in two patients (16 and 19 mg/l), which prompted the removal of both patients from the study. A severe worsening of a pre-existing neuropathy was recorded. This patient had a residual grade 1 neuropathy

from the primary paclitaxel/carboplatin therapy. No significant hematological or other unexpected toxicities occurred. The median hospital duration time was 4 days/cycle (range 3–14).

An abdominal ultrasonography was performed in 31/59 cycles. Fluid distribution i.p. was considered fairly homogenous in 24/31 cycles (presence of liquid in five or more of eight predefined abdominal compartments). In seven cured patients, peritoneal liquid was seen in less than five areas. Even when the fluid was well distributed in the lateral flanks, the peri-hepatic and peri-splenic zones, the centro-mesenteric area, and the intestinal loops were poorly bathed. In one patient, who was further operated on for a bowel obstruction, mesenteric and intestine loops were tightly aggregated around a mass of tumor nodules without peritoneal nodules on the parietal peritoneum.

Pharmacokinetic study

Owing to a one-way valve effect, which prevented aspiration of peritoneal fluid or patient refusal, pharmacokinetic data on blood and peritoneal epinephrine were available only for 22 cycles (Fig. 1). Epinephrine concentration in peritoneal liquid was always above 1 mg/l with large intercycle variations (Fig. 1a). A nonlinear relationship was found between the epinephrine plasma level and the i.p. infused concentration, with a plasma level that increased suddenly between the 1- and 2-mg/l infused doses (Fig. 1b).

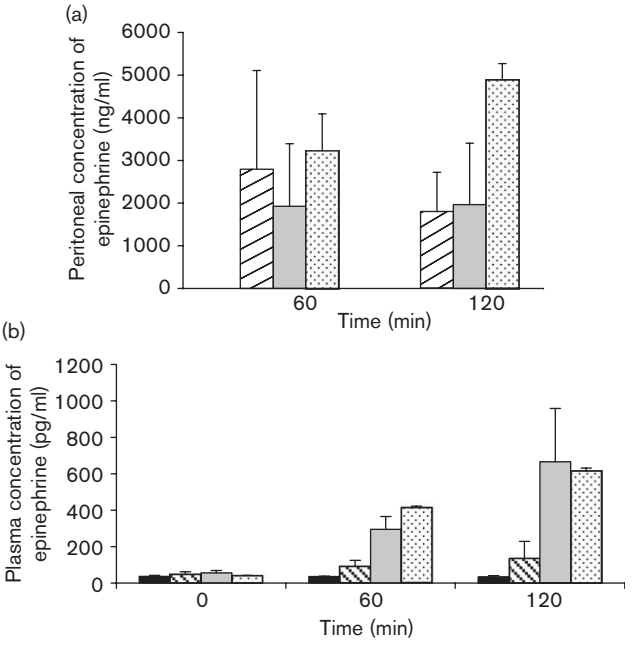
Tumor response

Of the 18 patients, 16 completed at least two cycles and were assessable for tumor response (Table 1). One patient refused treatment after the first cycle because of persistent abdominal pain and one had a severe worsening of a pre-existing neuropathy after the first cycle. Definitive drying of a refractory ascitis was obtained in two patients, one with ovarian cancer and the other with peritoneal mesothelioma. Four of 15 patients with progressive ovarian cancer had a sustained decrease (> 50%) in CA 125 levels. Six patients had a stable disease and four progressed on study. The median time to disease progression of the intent-to-treat population was 5.1 months (range 0–12 months) with a median overall survival of 17 months. Most of the patients received various salvage regimens of i.v. non-platinum-based chemotherapy after this investigational study.

Discussion

In the present clinical study, epinephrine concentrations from 1 to 5 mg/l have been safely given with i.p. cisplatin in patients with refractory peritoneal carcinomatosis. Such concentrations potentiated the accumulation and antitumor efficacy of cisplatin in a rat model [9–11]. Pharmacokinetic study showed a sudden increase in the epinephrine plasma level when the infused dose passed from 1 to 2 mg/l, but not between 2 and 3 mg/l epinephrine. A clear-cut relationship, however, was not seen between the occurrence of cardiovascular symptoms and the epinephrine infused dose. Some patients displayed signs of cardiovascular intolerance (angina pectoris, tachycardia, increased blood pressure) for the 1-mg/l epinephrine starting i.p. concentration, whereas others had no symptoms, even when the epinephrine serum concentration was as high as 600 pg/ml. For three cycles, 5 mg/l epinephrine was given with only a feeling of malaise, but without objective signs of cardiac intolerance. Epinephrine is a physiological catecholamine, which is released by the adrenal medulla upon stress (e.g. exercise, heart failure, hemorrhage, emotional stress or excitement, pain). Epinephrine is also released at a high level in pheochromocytoma, a chromaffin cell tumor that can lead to a fatal hypertensive crisis. Epinephrine increases heart rate and inotropy (β_1-adrenoceptor mediated) and leads to vasoconstriction in most systemic arteries and veins through postjunctional α_1- and α_2-adrenoceptors. The overall cardiovascular response is increased cardiac output and systemic vascular resistance, which results in an elevation of arterial blood pressure. During a wide variety of situations that can be considered stressful, epinephrine release from the adrenal medulla causes detectable increases in the circulating concentration of epinephrine. Stress, such as cold pressure testing,

Fig. 1



Peritoneal (a) and plasma (b) concentrations of epinephrine in patients who received intraperitoneal treatment with 0 (dark bar), 1 (dashed bar), 2 (grey bar) or 3 mg/l (dotted bar) of epinephrine and 50 mg/l of cisplatin in 2 l of saline solution for 2 h.

caffeine ingestion and upright tilt or standing, leads to modest increases in plasma epinephrine, < 100 pg/ml [14]. Other conditions, such as mental stress [15], can lead to an intermediate elevation in plasma epinephrine (100–300 pg/ml). More dramatic increases in plasma epinephrine (> 300 pg/ml) have been noted with severe hypoglycemia [16] and dynamic supine or upright exercise [17]. During dynamic exercise, the magnitude of increase in plasma epinephrine is related to the relative workload and the mean plasma epinephrine levels can be as high as 600 pg/ml. The plasma concentrations produced by our three epinephrine doses (on an order of 600 pg/ml for 3 mg/l) thus span the normal physiological range noted in humans. Stratton *et al.* [18] studied the hemodynamic effects of three different infusion rates of epinephrine (25, 50 or 100 ng kg/min for 14 min) in 10 normal individuals. The graded increase in plasma epinephrine caused dose-dependent hemodynamic changes. At the highest plasma concentration, 484 ± 69 pg/ml, which was close to the highest level observed in our study, epinephrine produced modest changes in heart rate (24 ± 3%), systolic pressure (26 ± 4%) and mean arterial pressure (– 10 ± 2%). The systemic vascular resistance decreased by 48 ± 1% at the highest infusion rate. As a matter of fact, the cardiovascular toxicity was not the limiting toxicity in this study and the occurrence of cardiovascular events was not strictly related to the epinephrine dose. The main cardiac problem was a transient episode of angina pectoris in a woman without known antecedents. The other events were short episodes of malaise and anxiety with or without transient increase in heart rate and/or blood pressure, which regressed in less than 15 min after the withdrawal of i.p. epinephrine. A previous experimental study has shown that a 5-mg/l i.p. epinephrine concentration did not modify heart rate and blood pressure in anesthetized and laparotomized pigs [10]. A significant increase in the cardiovascular parameters was obtained only for the 10- and 20-mg/l concentrations, but no lethal toxicity was seen in pigs. There was quick normalization of heart rate and blood pressure after epinephrine withdrawal, and the animals survived without aftereffects. The short half-life of epinephrine in the peritoneal cavity (20.8 ± 3.6 min in the pig) explained the quick reversibility of the cardiovascular problems. So, the risk of dangerous cardiovascular events seems limited when the epinephrine concentration does not exceed 5 mg/l in the infused i.p. liquid.

The major problem was grade III or IV abdominal pain, which occurred in most of the patients (42/59 cycles), and even led to refusal of treatment by one patient. Pain is often mentioned in studies that evaluated postoperative i.p. chemotherapy. For example, grade II abdominal pain was recorded in 26% of patients who received i.p. carboplatin in combination with i.v. paclitaxel [19]. Sabbatini *et al.* [20] reported that 17% of patients returned to the operating room for evaluation of abdominal pain after the i.p. gemcitabine/cisplatin combination, two patients had recurrence, and all had areas of fibrous tissue with encasement of the bowel and obstruction. Pain was also frequent, but generally graded as mild, with i.p. mitoxantrone [21] or i.p. paclitaxel and cisplatine [22]. In our study, abdominal pain could be related partly to postoperative peritoneal adhesions as all the patients but one, the one with a peritoneal mesothelioma, had been previously operated on. Moreover, adhesions were probably involved in the inability to distribute adequately, throughout the peritoneal cavity, the drug-containing fluid as previously shown [23]. The peritoneal fluid was distributed in most of the abdominal compartments in only 24/31 cycles in our patients. The centro-abdominal area, however, was almost never correctly bathed in patients who were lying down and that could be a critical cause of i.p. chemotherapy failure.

In conclusion, 1–5 mg/l of epinephrine could be infused into the peritoneal cavity of patients with peritoneal carcinomatosis. Such concentrations are probably sufficient for maintaining a constant vasoconstriction of the peritoneal and tumoral microvascular bed, and this enhances the penetration of cisplatin into the peritoneal tumor nodules. A clinical and/or biological response was obtained in some patients with a disease resistant to i.v. platinum compounds, but the greatest limitation of this closed-abdomen technique was the poor distribution of the peritoneal fluid into the whole peritoneal cavity. To avoid this limitation, we are now conducting a feasibility trial with the open-abdomen peri-operative administration of epinephrine at increasing doses and cisplatin at a fixed dose after maximum surgical debulking in patients with ovarian carcinoma.

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