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Safety and efficacy of intraperitoneal injection of etoposide in oil suspension in mice with peritoneal carcinomatosis

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Abstract We compared the safety and efficacy in mice with peritoneal carcinomatosis of two etoposide formulations: an aqueous solution (Etp-sol) and particles suspended in oil (the addition products of iodine and the ethyl esters of the fatty acids obtained from poppy-seed oil (Lipiodol) or sesame oil; Etp-oil). We also investigated tissue distribution of etoposide in rats treated with Etp-oil and Etp-sol. Etoposide was injected intraperitoneally at concentrations ranging from 52 to 392 mg/kg (increasing geometrically by a factor of 1.4). The 50% lethal dose (LD_{50}), determined over a 2-week period of observation, was 135 mg/kg for Etp-oil and 108 mg/kg for Etp-sol. Autopsy findings included macroscopic intestinal bleeding, necrosis of the intestinal mucosa, and pulmonary congestion in mice from both treatment groups. In the efficacy trials. 10^6 P388 leukemia cells were transplanted into CDF_1 male mice, and Etp-oil and Etp-sol were injected at doses of 20 mg/kg and 80 mg/kg. In the groups receiving the 20 mg/kg dose, 11 of 19 mice in the Etp-oil group survived to day 60 compared with 3 of 20 mice in the Etp-sol group. Toxicity-related deaths occurred in 1 of 20 mice treated with 80 mg/kg Etp-oil and in 8 of 20 mice treated with 80 mg/kg Etp-sol. No cancer-related deaths were associated with the 80 mg/kg dose in either treatment group. Our findings showed that the Etp-oil was associated with a lower toxicity and a higher efficacy than the Etp-sol. To evaluate tissue distribution, rats were injected intraperitoneally with 5 mg/kg body weight of Etp-sol or Etp-oil. The tissue distribution of etoposide was subsequently analyzed by high performance liquid chromatography. Compared with Etp-sol, Etp-oil delivered significantly greater amounts of etoposide and for a longer period to the omentum, taken as representative of the intraperitoneal tissue, and the etoposide concentration in blood plasma was increased more slowly and decreased more gradually.

Key words Etoposide · Toxicity · Intraperitoneal administration

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Introduction

Etoposide, a semisynthetic derivative of podophyllotoxin which is extracted from certain plants of the genus *Podophyllum* [1, 2], has been used in treating small-cell bronchogenic carcinoma, malignant lymphoma, leukemia, bladder cancer, ovarian cancer, and other malignant diseases [3–6]. Etoposide has also been used to treat cancer of the digestive tract, mainly peritoneal carcinomatosis due to gastric cancer. However, etoposide's usefulness in cancer of the digestive tract has been limited by the toxicity associated with i.v. administration of high doses of the drug [7–9]. The mortality rate in patients with peritoneal carcinomatosis due to gastric cancer is about 50% and it is very difficult to obtain good results using etoposide by i.v. injection. However, in a previous study in mice, it has shown that an aqueous solution of etoposide (Etp-sol) for i.p. injection is more toxic than a solution for i.v. injection, and indeed clinically it is very difficult to administer high doses of Etp-sol intraperitoneally. We evaluated the safety and efficacy in mice with malignant peritonitis of two experimental dosage formulations of etoposide for i.p. injection, an oil suspension and a saline solution.

Materials and methods

A new dosage formulation of etoposide consisting of etoposide particles suspended in oil (Etp-oil) was prepared according to the following procedure. Pure etoposide powder (provided by Nippon

Kayaku, Tokyo, Japan) consisting of particles less than 0.2 mm in length as determined by a scanning electron microscope, was suspended in the addition product of iodine and the ethyl esters of fatty acids obtained from poppy-seed oil (Lipiodol; Kodama, Tokyo, Japan). The mixture was stirred with a magnetic stirrer for 6 h to form the Etp-oil. Etp-sol was used as the control formulation. Etp-sol was prepared by diluting etoposide for i.v. injection (Lastet; Nippon Kayaku, Tokyo, Japan) with saline. Etoposide is a water-insoluble drug and is administered clinically at concentrations of 0.6 mg/ml or less.

In the toxicity and efficacy studies, Etp-sol was administered intraperitoneally in a total volume of 1 ml within 1 h of preparation. The total volume of Etp-sol was limited to 1 ml because the mice used in the present study weighed 26–34 g. In a previous study, Etp-sol at a concentration of 0.6 mg/ml has been shown to form white crystals after being stored for 6 h at 22 °C. When Etp-sol was administered within 6 h of preparation, no white crystals were formed and the solution was fully absorbed in the peritoneal cavity.

Evaluation of toxicity

After 7 days of observation, 150 5-week-old male ICR mice (Shimizu Experimental Animals, Kyoto, Japan) were weighed. Mice weighing 26–34 g were selected for study and were maintained under specific pathogen-free conditions at an ambient temperature of 22 °C in an atmosphere at 60% humidity, and on a 12-h day-night cycle. They received water and a stock diet ad libitum.

Etp-oil and Etp-sol were each administered as a single 1-ml i.p. injection in doses ranging from 52 to 392 mg/kg (increasing geometrically by a factor of 1.4). Animals were observed for 2 weeks; general symptoms, changes in body weight, and survival were noted. Mice that died before day 14 were autopsied immediately. Mice surviving until day 14 were sacrificed by cervical dislocation on day 15 and autopsied. The acute 50% lethal dose (LD_{50}) value was determined by the Litchfield-Wilcoxon method.

Evaluation of efficacy

We evaluated the effects of two doses (20 and 80 mg/kg) of each formulation of etoposide. Etp-oil and Etp-sol were each prepared at concentrations of 0.4 and 1.6 mg/ml. Drugs were administered within 1 h of preparation. A cell suspension in saline was prepared from ascitic fluid that contained P388 leukemia cells which had been maintained intraperitoneally in male DBA_2 mice provided by the Sasaki Institute (Tokyo, Japan). Cell viability exceeded 95% as determined by the trypan blue exclusion test. After 1 day of observation, 120 5-week-old male CDF_1 mice weighing 20 g (Shimizu Experimental Animals, Kyoto, Japan) were inoculated intraperitoneally with 10^6 P388 leukemia cells per mouse (day 0). The mice were divided into six groups of 20 mice each.

Intraperitoneal bolus injections of etoposide were administered to the mice 48 h after inoculation. One group received a 1-ml bolus injection of 0.4 mg/ml Etp-oil, equivalent to 20 mg/kg body weight (Etp20-oil group). One group received a 1-ml bolus injection of 1.6 mg/ml Etp-oil, equivalent to 80 mg/kg body weight (Etp80-oil group). Two groups received the corresponding doses of Etp-sol (equivalent to 20 and 80 mg/kg body weight). One control group received an oil vehicle alone (1 ml/mouse) and another control group received no treatment.

The mice were observed for 60 days. Those that died were autopsied immediately and those that survived until day 60 were sacrificed by cervical dislocation and were autopsied on day 61. We examined mice macroscopically and microscopically to determine the cause of death and the number of residual cancer cells.

Differences in the number of surviving mice between groups were compared using the Chi-squared test. Survival times among the six groups in the efficacy study were compared using Student's paired t-test, with $P < 0.05$ accepted as statistically significant.

Evaluation of tissue distribution

Male Wistar rats weighing 200 g (Shimizu Experimental Animals, Kyoto, Japan) received 20 mg/kg (equivalent to a drug volume of 10 ml/rat) of Etp-sol ($n = 33$) and Etp-oil ($n = 33$). Three rats from each group were sacrificed by cervical dislocation at 15 min and 30 min, at 1, 3, 6, 12 and 24 h, and on days 2, 4, 8 and 16. Blood samples, taken through a heart puncture up to day 16, were centrifuged at 3000 rev/min for 5 min and the supernatants (plasma) were stored at −100 °C until used in the etoposide assay. Samples of omentum were removed up to day 16 following etoposide administration. We selected the omentum as a representative intraperitoneal tissue. The samples of omentum were weighed with a microbalance and stored at −100 °C until used in the etoposide assay.

Etoposide concentrations in plasma and omentum were determined by high performance liquid chromatography and UV detection at a wavelength of 254 nm. The assay limits were 0.1 μg etoposide/g tissue and 0.04 μg etoposide/ml plasma. If the etoposide concentration was detectable in samples from all animals in the whole experiment we analyzed differences between groups at each time-point by analysis of variance. Differences were considered statistically significant for $P < 0.05$.

Results

Toxicity

Signs of toxicity, including a reduction in spontaneous movement, dishevelled fur, and a fall in temperature, were similar in the Etp-oil and Etp-sol groups. The severity of symptoms was dose-dependent. Mice that died of general asthenia exhibited bloody stools, alopecia, and loss of appetite. The death rate was also dose-dependent in both groups (Figs. 1 and 2). In the Etp-sol group, mice that had received doses of 200 mg/kg or higher died within 4 days of injection. Those that had received doses of 280 and 392 mg/kg died within a few hours of i.p. injection. Doses of 200 mg/kg or higher were associated with death in almost all mice in the Etp-oil group, but death in each dosage group occurred somewhat later than in the corresponding Etp-sol groups.

In mice that had received doses of 143 mg/kg or less of Etp-sol, the time needed to regain the lost weight increased in a dose-dependent manner (Fig. 3). Almost none of the mice that had received doses of 143 mg/kg or less of Etp-oil lost weight (Fig. 4). Most of the mice given doses of 200 mg/kg or more of Etp-oil and Etp-sol died without recovering their baseline body weight. The oil vehicle alone was not associated with weight loss.

Autopsy findings in mice from both treatment groups included inflammation of the abdominal wall, ascites without bleeding, and atrophy of the thymus. The severity of these effects was dose-dependent. Macroscopic evidence of intestinal bleeding, necrosis of the intestinal mucosa, and pulmonary congestion was found in most of the mice that died before postinjection day 7; these effects were severe in mice treated with high doses of etoposide. Mice that survived until day 14 showed only inflammation of the abdominal wall. The group treated with the oil vehicle showed no abnormalities.

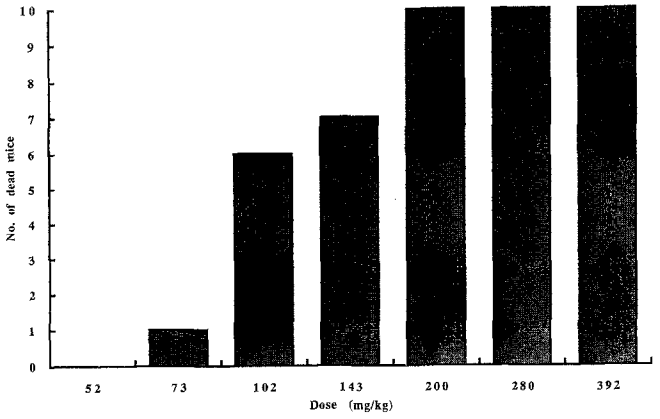

Fig. 1 Deaths in mice administered etoposide in aqueous solution (Etp-sol)

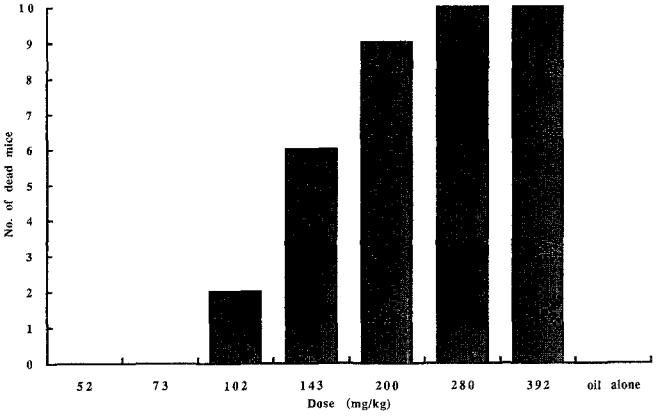

Fig. 2 Deaths in mice administered etoposide in oil suspension (Etp-oil)

Microscopic examinations showed bone marrow toxicity (Fig. 5) including a decreased number of bone marrow cells and necrotic and/or degenerative changes such as pycnosis or ballooning of the nuclei and abnormal structure or disappearance of the cytoplasm. These changes were found in mice treated with both formulations, although the changes were less pronounced in mice given Etp-oil than in mice given Etp-sol.

The acute LD_{50} value was 108 mg/kg (range 82–141 mg/kg, 95% confidence limits) in the Etp-sol group, and 135 mg/kg (range 110–166 mg/kg, 95% confidence limits) in the Etp-oil group.

Therapeutic efficacy

There were no toxicity-related deaths in either the Etp20-sol or the Etp20-oil group (Table 1). Significantly more mice in the Etp20-oil group than in the Etp20-sol group survived to day 60 ($P < 0.01$). The mean survival time was greater in the Etp20-oil group than in the Etp20-sol group,

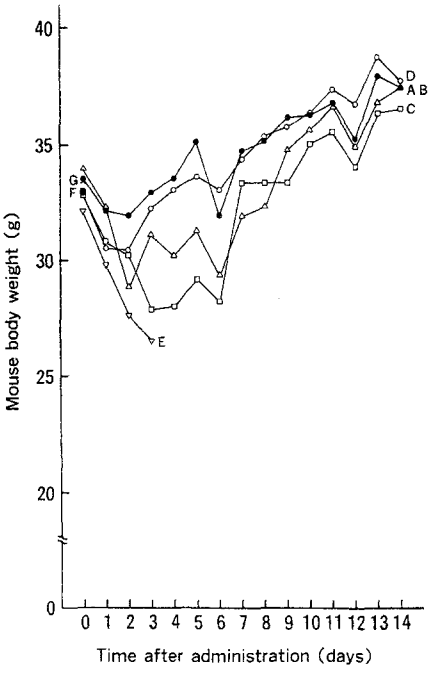

Fig. 3 Changes in body weight after intraperitoneal injection of etoposide in aqueous solution (Etp-sol). ● (*A*) 52 mg/kg, △ (*B*) 73 mg/kg, □ (*C*) 102 mg/kg, ○ (*D*) 143 mg/kg, ▽ (*E*) 200 mg/kg, ■ (*F*) 280 mg/kg, x (*G*) 392 mg/kg

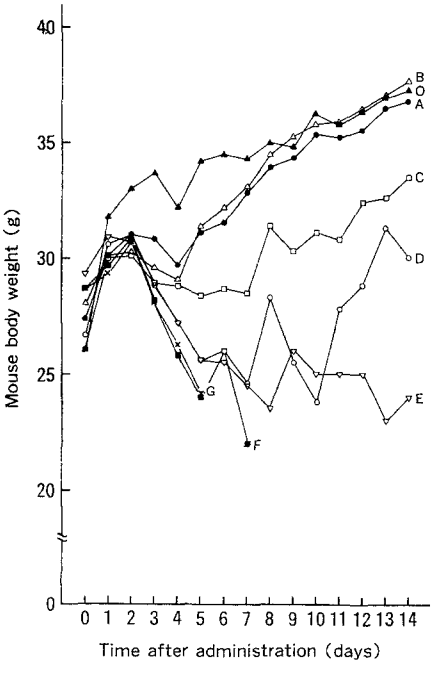

Fig. 4 Changes in body weight after intraperitoneal injection of etoposide in oil suspension (Etp-oil). ● (*A*) 52 mg/kg, △ (*B*) 73 mg/kg, □ (*C*) 102 mg/kg, ○ (*D*) 143 mg/kg, ▽ (*E*) 200 mg/kg, ■ (*F*) 280 mg/kg, x (*G*) 392 mg/kg, ▲ (*O*) oil alone

but the difference was not significant. There were no cancer-related deaths in either the Etp80-sol or the Etp80-oil group. Toxicity was responsible for significantly fewer deaths in the Etp80-oil group than in the Etp80-sol group.

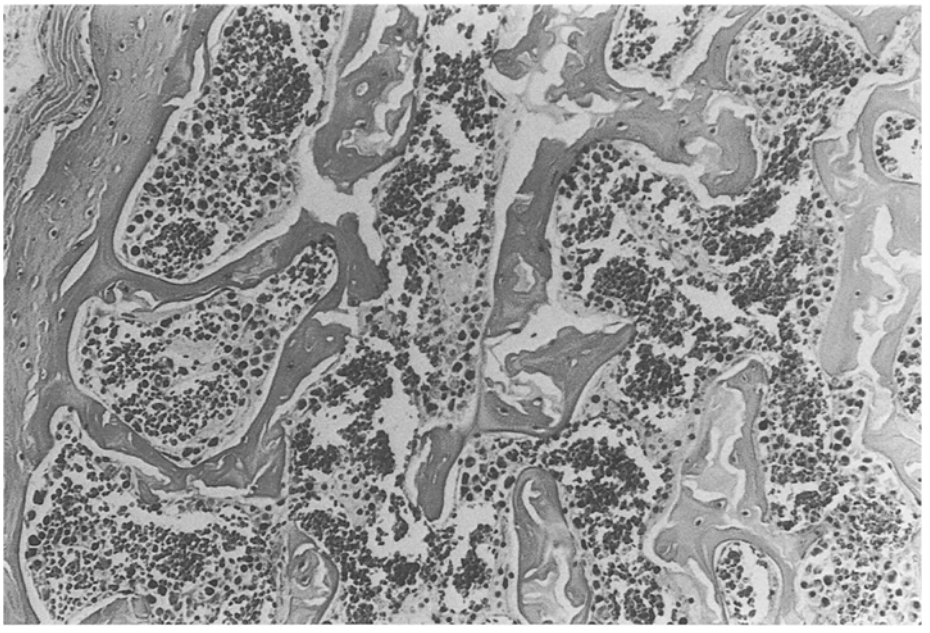

Fig. 5 Histological of bone marrow from a mouse that had received 280 mg/kg Etp-oil. This mouse died on day 6

Tissue distribution

Blood plasma

In the Etp-oil group, the plasma concentration of etoposide peaked at 1 h, and then gradually decreased, falling to undetectable levels 8 days after drug administration (Table 2). In the Etp-sol groups, the plasma concentration also peaked at 1 h. The peak plasma concentration in the Etp-sol group was ten times that in the Etp-oil group. The etoposide concentration decreased to undetectable levels by day 4 in the Etp-sol group. The plasma levels of etoposide in the Etp-oil group were significantly lower than in the Etp-sol group from 15 min to 3 h after administration, and were significantly higher than in the Etp-sol group from 12 h to 2 days after administration.

Omentum

Concentrations of etoposide in the omentum were assayed as a measure of intraperitoneal tissue distribution (Table 3). In the Etp-oil group, the etoposide concentration in the omentum was in the range of 168.5–86.0 μg/g during the first 2 days after administration, and was 2.32 μg/g even on day 8. Conversely, in the Etp-sol group, a concentration of 94.0 μg/ml recorded at 30 min was the highest mean value achieved, and this value decreased rapidly to about 1.0 μg/g

Table 1 Therapeutic efficacy of etoposide for treatment of peritoneal carcinomatosis induced by P388 leukemia cells

Group (no. of mice)	Treatment	MST ± SD* (days)	T/C (%)**	Toxicity***	Survival**** (to day 60)
Etp20-oil (19)	Etp-oil 20 mg/kg i.p.	23.8±4.4	202	0/19	11/19
Etp20-sol (20)	Etp-sol 20 mg/kg i.p.	21.6±2.0	183	0/20	3/20
Etp80-oil (20)	Etp-oil 80 mg/kg i.p.	7.0±0	–	1/20	19/20
Etp80-sol (20)	Etp-sol (80 mg/kg i.p.	7.4±0.5	–	8/20	12/20
Oil alone (19)	Oil, 1 ml i.p.	12.6±1.1	107	0/19	0/19
No treatment (19)	–	11.8±1.8	100	0/19	0/19

MST ± SD*, mean survival time ± standard deviation of dead mice in a group
T/C (%)**, MST of mice treated with Etp-oil or Etp-sol/MST of mice treated without etoposide (No treatment group)
Toxicity***, number of mice died of toxicity/number of mice in a group
Survival****, number of mice surviving to day 60/number of mice in a group

Table 2 Etoposide concentration in blood plasma. Values are means of three experiments ± SE (*NS* not significant, *ND* not detectable)

Time after administration	Etoposide concentration (μg/ml)		Statistical significance (*F*-ratio)
	Etp-oil	Etp-sol	
15 min	0.58±0.03	6.40±1.02	$P < 0.005$ (32.4)
30 min	0.85±0.11	9.04±0.96	$P < 0.005$ (72.4)
1 h	1.15±0.18	13.1 ±5.0	$P < 0.025$ (15.2)
3 h	0.71±0.05	2.26±0.70	$P < 0.025$ (14.2)
6 h	0.32±0.03	0.14±0.04	NS
12 h	0.23±0.03	0.05±0.01	$P < 0.005$ (48.6)
24 h	0.12±0.01	0.05±0.01	$P < 0.005$ (45.1)
2 days	0.13±0.01	0.05±0.01	$P < 0.01$ (24.0)
4 days	0.06±0.01	ND	–
8 days	ND	ND	–

Table 3 Etoposide concentration in the omentum. Values are means of three experiments ± SE (*NS* not significant, *ND* not detectable)

Time after administration	Etoposide concentration (μg/g)		Statistical significance (F-ratio)
	Etp-oil	Etp-sol	
15 min	158.2 ±12.8	68.5 ±13.1	$P < 0.01$ (24.0)
30 min	168.5 ±9.1	94.0 ±5.9	$P < 0.005$ (47.0)
1 h	165.0 ±19.9	36.5 ±5.0	$P < 0.005$ (39.0)
3 h	136.1 ±9.4	7.5 ±1.3	$P < 0.005$ (185)
6 h	156.5 ±7.3	0.98±0.27	$P < 0.005$ (456)
12 h	86.0 ±21.2	0.92±0.11	$P < 0.025$ (16.0)
24 h	96.0 ±16.4	1.07±0.25	$P < 0.005$ (33.4)
2 days	94.5 ±3.7	0.64±0.04	$P < 0.005$ (638)
4 days	3.70±0.55	0.35±0.15	$P < 0.005$ (34.4)
8 days	2.32±0.12	0.46±0.15	$P < 0.005$ (90.3)
16 days	0.55±0.02	ND	–

by 6 h. The concentration in the Etp-oil group was significantly greater from 15 min to 8 days after administration than in the Etp-sol group ($P < 0.01-0.005$).

Discussion

The i.p. administration of etoposide has been limited by toxicity. In the present study, i.p. injection of etoposide was also limited by toxicity. We developed a suspension of etoposide in oil (Lipiodol) with an acute LD_{50} by i.p. injection of 135 mg/kg, a lower toxicity than previously reported [8, 10]. At doses below its LD_{50}, Etp-oil caused little or no loss of body weight, whereas Etp-sol produced a weight loss at doses below its LD_{50} values.

When Etp-sol is administered intraperitoneally, it is readily absorbed from capillaries in the peritoneum into the circulation, making it difficult to maintain a high concentration of etoposide in the abdominal cavity. When an oil suspension of etoposide is injected peritoneally, it is absorbed slowly via the lymph system [11, 12]. Thus, it is possible to maintain a high concentration in the abdominal cavity because the oil suspension formulation acts as a slow-release preparation in the peritoneum [13–15].

To prepare the aqueous solution of etoposide, we diluted Lastet (etoposide for intravenous infusion) in saline. High concentrations of Etp-sol form white crystals after a few hours at 22 °C [15, 16] in indirect light.

We previously evaluated aqueous solutions of etoposide prepared by dissolving the drug either in a solution of DMSO and Tween 80 or in a solution of polyethylene glycol 300, ethanol and Tween 80. Intraperitoneal injection of the solvent alone produced death in a few hours. In the high-dose groups in this study (280, 392 mg/kg), death occurred after day 4 in the Etp-oil group, but within a few hours of injection in the Etp-sol group, indicating that the mice may have experienced a toxic reaction to the solvent (mainly DMSO and Tween 80) as well as to the drug.

In the present study, Etp-sol and Etp-oil exhibited a therapeutic effect at a dose of 20 mg/kg. The survival rate was higher in the Etp-oil group (11 of 19 mice) than in the Etp-sol group (3 of 20 mice). No cancer deaths occurred in the groups given the 80 mg/kg dose, but toxicity-related death occurred in 1 mouse in the Etp80-oil group and in 8 mice in the Etp80-sol group. These findings indicate that Etp-oil was less toxic and had greater efficacy than Etp-sol [12]. In the clinical setting, continuous or divided doses of etoposide have been found to be more effective than a single dose [17–21].

In this study, we found that when an aqueous solution of etoposide was administered intraperitoneally to mice, the drug was absorbed promptly from the peritoneal capillaries into the circulating blood. In a recent approach to treating peritoneal carcinomatosis involving the direct i.p. administration of anticancer drug. Los et al. [22] found that the drug concentration in intraperitoneal tumors was higher after i.p. injection than after i.v. injection. When Zimm et al. [14] administered etoposide with cisplatin by peritoneal dialysis to 39 patients with intraperitoneal malignancies, they found that etoposide was cleared rapidly from the peritoneal cavity, with 80% of the drug eliminated by the end of a 4-h dwell time, but plasma levels of etoposide were equivalent to plasma levels detected after i.v. administration of the same dose. Thus, the amount of drug delivered to the tumor by capillary blood flow was identical to that delivered by i.v. drug administration. The peak free drug concentrations in the peritoneal cavity were 188-fold higher, resulting in much greater i.p. tumor exposure to etposide than systemic tissue exposure. These findings are in agreement with our tissue distribution study in rats.

Etoposide concentrations in the omentum were much higher and remained high for a longer period in rats given Etp-oil than in those given Etp-sol. The plasma level of etoposide peaked relatively early and decreased rapidly in the Etp-sol group, whereas plasma levels remained low in the Etp-oil group over a longer period. These findings suggest that when etoposide is injected intraperitoneally in the Etp-oil formulation, etoposide is released slowly from the peritoneum. The present findings, as well as those of previous studies, suggest that Etp-oil has a lower toxicity and a superior therapeutic effect than Etp-sol [12, 14, 15]. Etp-oil appears to be a promising etoposide

formulation for the treatment of intraperitoneal malignancies in the clinical setting.

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