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Lack of effect of cisplatin on i.v. L-PAM plasma pharmacokinetics in ovarian cancer patients*

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Summary. Melphalan (L-PAM) pharmacokinetics were investigated in nine ovarian cancer patients before and after cisplatin (DDP) treatment. When L-PAM was given 24 h before DDP, the elimination half-life ($t_{½\beta}$), plasma clearance (Clp), and volume of distribution (Vd_β) of L-PAM were, respectively: 46.4 ± 6.7 min, 20.5 ± 3.7 l/m^2, and 306.8 ± 34.4 ml/min per square meter. When L-PAM was inoculated 24 h after DDP, $t_{½\beta}$, Clp, and Vd_β were 47.5 ± 6.3 min, 20.4 ± 2.8 l/m^2, and 322.0 ± 54.1 ml/min per square meter. Thus, DDP pretreatment does not significantly affect L-PAM pharmacokinetics. Regression analysis showed a significant correlation between the L-PAM elimination rate constant (β) and renal function assessed by creatinine clearance. One patient who received this sequence of treatment for six courses showed a threefold decrease of L-PAM Clp after the last treatment. The reported high myelotoxicity of the combination of DDP and L-PAM when DDP was given 24 h before L-PAM cannot be attributed to DDP-induced changes in L-PAM kinetics but might to some extent be related to a loss of renal function consequent to many courses of treatment.

Introduction

It has been reported that melphalan (L-PAM) given i.v. causes a significantly higher frequency of severe leukopenia in multiple myeloma patients with moderate renal failure than in patients with normal renal function [8]. Alberts et al. [3] have studied the disposition and bone marrow toxicity of i.v. L-PAM in dogs with severe renal impairment due to unilateral total nephrectomy and controlateral partial nephrectomy; they found prolonged plasma half-life, lower renal clearance, and greater myelosuppression than in controls with normal renal function.

L-PAM and cisplatin (DDP), used in combination chemotherapy in the treatment of ovarian cancer, have been reported to induce unexpectedly severe and prolonged myelosuppression in a significant number of patients [11]. A possible explanation might be that DDP, given 24 h before L-PAM, could have induced renal damage [10], resulting in slower L-PAM elimination. This hypothesis is supported by the recently reported relationship between the L-PAM elimination rate constant or AUC (area under the plasma L-PAM concentration time curve) and creatinine clearance [1, 5, 6].

To verify whether L-PAM pharmacokinetics was modified by DDP pretreatment, we compared the kinetics of L-PAM during the first two courses of treatment in the same patients given the drug either 24 h before or 24 h after DDP.

Patients and methods

Nine previously nontreated patients with advanced epithelial ovarian cancer (FIGO stages III and IV) were given a combination of L-PAM (12 mg/m^2 as a 2-min injection) and DDP (80 mg/m^2 as 30-min infusion), with a 24-h interval between the two drugs. Table 1 shows their main characteristics before each inoculation. For the first cycle, patients 1–4 received L-PAM on day 2, 24 h after DDP treatment (schedule A), whereas patients 5–9 received L-PAM on day 1, followed 24 h later by DDP (schedule B). The sequence was reversed in each patient for the second cycle. The pharmacokinetics of L-PAM were studied in patient 9 after six cycles, all but the first given according to schedule A.

Sample collection. After L-PAM injection, 8-ml blood samples were drained through an indwelling cannula from the arm that did not receive the drug, immediately put into heparinized tubes, and spun down at 2000 rpm. Samples were taken at the end of injection and 5, 10, 15, 30, 45, 60, 120, 150, 180, 240, 360, 480 and 720 min after the injection.

Drug assay. The method of drug assay, previously described in detail elsewere [7], can be summarized as follows: 1 ml plasma, with 5 µg dansyl proline added as internal standard, and 1 ml methanol (0° C) were mixed for 20 s and cooled to −70° C (acetone and dry ice) for 3 min. The plasma-methanol mixture was then centrifuged in a refrigerated centrifuge, and 20–25 µl clear methanolic solution was injected directly into the column (µ-Bondapack C18, purchased from Waters Associates, New York, N. Y., USA) of a Waters model 6000A HPLC equipped with a 254 nm absorbance detector. Separation was achieved using an isocratic solvent system of water (55%) and methanol (45%) with 1% acetic acid at the flow rate of 1.2 ml/min.

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Table 1. Patient characteristics

Patient Number	Age (years)	L-PAM total dose[a] (mg)	Creatinine clearance (ml/min)	
			L-PAM day 1	L-PAM day 2
1	60	19.2	67	73
2	69	18.0	60	38
3	62	20.0	75	74
4	28	18.6	118	103
5	64	19.0	52	48
6	56	20.3	106	79
7	33	23.4	172	109
8	66	17.0	61	44
9	46	19.8	–	96
				67[b]

[a] The dose corresponded to 12 mg/m² for all patients
[b] Patient 9: 6th cycle of therapy

Pharmacokinetic calculations. The plasma concentrations of L-PAM vs time for each patient were fitted to the standard equation for a two-compartment model using a non-linear fitting computer program [14]. AUC was determined by the trapezoidal rule. The elimination half-life ($t_{½\beta}$), plasma clearance (Clp) and volume of distribution (Vd_β) were calculated using the equation

$t_{½\beta} = 0.693/\beta$ (elimination half-life)
$Clp = Dose/AUC_{0-\infty}$ (plasma clearance)
$Vd_\beta = Clp/\beta$ (volume of distribution)

Statistical correlation of the data was done by regression analysis.

Results

Figure 1 shows the plasma decay curves of L-PAM given before (*A*) or after DDP (*B*) to the same patients. The drug levels at the end of injection varied widely in both schedules, but the intrapatient variability was low in most

Table 2. Pharmacokinetic parameters of L-PAM given i.v. to ovarian cancer patients

Patient Number	L-PAM given 24 h before DDP			24 h after DDP		
	$t_{1/2\beta}$ min	Clp ml/min/m²	Vd_β l/m²	$t_{1/2\beta}$ min	Clp ml/min/m²	Vd_β l/m²
1	38	210	11.5	30	566	24.5
2	64	416	38.5	80	222	27.7
3	41	236	13.9	54	213	16.6
4	23	416	13.8	29	406	17.6
5	46	230	15.3	43	220	13.7
6	–	–	–	32	281	13.0
7	37	371	20.0	–	–	–
8	76	269	29.5	64	157	14.5
9	–	–	–	48	515	35.8
				59[a]	164	14.1
X	46.4	306.8	20.5	47.5	322.0	20.4
±SE	6.7	34.4	3.7	6.3	54.1	2.8

[a] Patient 9: 6th cycle of therapy not included in the mean

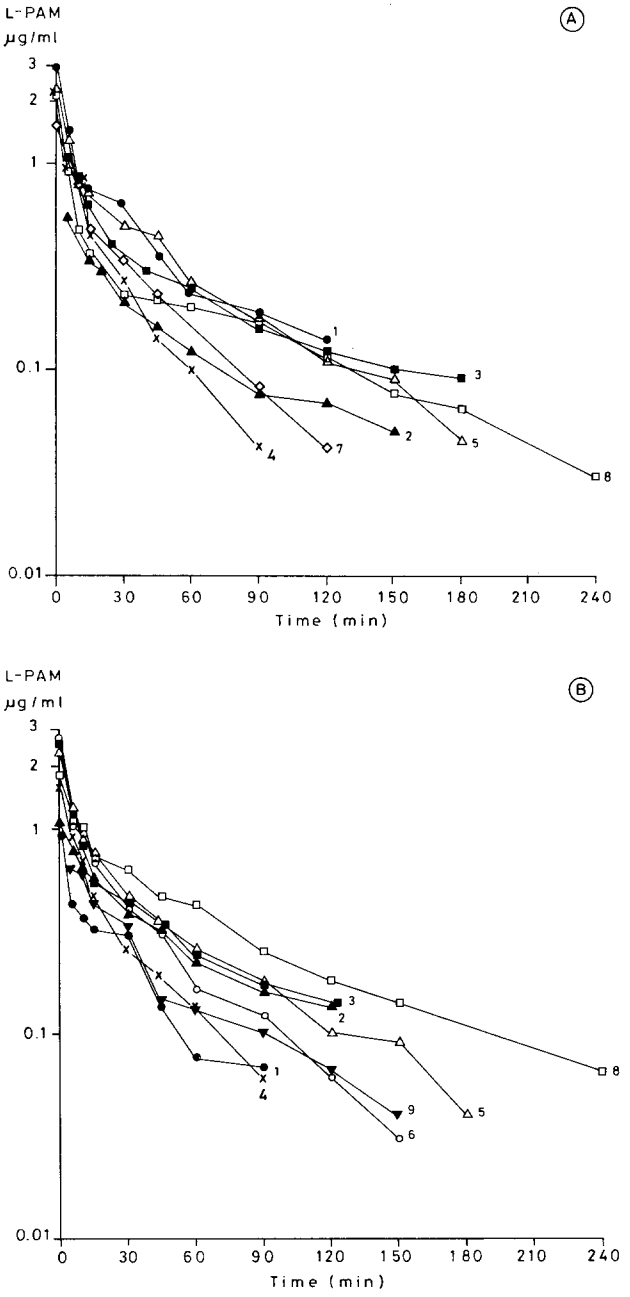

Fig. 1. Plasma decay curves of L-PAM given before (*A*) or after DDP (*B*) in the same patients

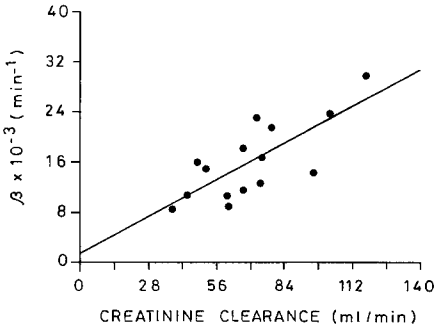

Fig. 2. Relationship between L-PAM β and creatinine clearance as assessed by linear regression analysis ($r = 0.76$; $P = 0.00097$)

cases. The data for all patients was adequately described by a two-compartment model.

Table 2 summarizes the main pharmacokinetic parameters. Beta half-life, Clp, and Vd_β values were very similar regardless of whether L-PAM was given before or after DDP. Patient 9 showed a decrease in L-PAM clearance to less than one-third of the initial value after six courses of treatment. The relationship between creatinine clearance (CrCl) and β in a total of 16 courses was statistically significant ($r = 0.76$, $P = 0.00097$) as evaluated by regression analysis (Fig. 2).

Discussion

DDP pretreatment did not significantly modify L-PAM kinetics after one course of treatment. Pharmacokinetic parameters were in fact similar whether L-PAM was given before or after DDP. The L-PAM kinetic parameters found in the present study appear similar to those previously reported after equal [2, 5, 6, 9, 13] or much higher doses given in combination with bone marrow transplant [4, 12, 15].

Although conflicting reports have been published [1, 4, 6, 15], some studies have shown a highly significant correlation between CrCl and the L-PAM elimination rate. The present study confirms this, but the coefficient of correlation, though statistically significant, was not particularly high. Alberts et al. [2] have analyzed the in vitro half-life of L-PAM dissolved in plasma (at 37° C) of nine cancer patients and found a more than twofold difference (in vitro half-life ranged between 1.3 and 2.5 h). Therefore, considering that chemical degradation plays an important part in L-PAM plasma elimination and its interpatient variation, it is not surprising that correlations between drug Clp and renal function may be unsatisfactory and may vary in different groups.

It is worth noting that in patient 9, who was investigated after six courses of treatment and who showed a reduction of about 30% of the CrCl value between the 1st and 6th courses, a parallel decrease of L-PAM Clp and a slight increase in $t_{½\beta}$ were found. Altogether these findings do not suggest that the inoculation of DDP 24 h before L-PAM is responsible for a reduction of L-PAM Clp, which in turn might lead to the greater hematological toxicity previously reported in myeloma patients [8]. Nevertheless, DDP-induced renal dysfunction, particularly after repeated treatment, could conceivably slightly modify L-PAM elimination, possibly resulting in higher toxicity.

Factors other than pharmacokinetics (i.e., pharmacodynamic factors) probably play more important roles in the unexpectedly high myelotoxicity observed after treatment with this drug combination.

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