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Specialist Interest Articles

Regional Pharmacokinetic Selectivity of Intrapleural Cisplatin

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The pharmacokinetics and toxicity of cisplatin were investigated in 3 patients affected by malignant mesothelioma who received 90 mg/m² of the drug intrapleurally. The mean area under the pleural Pt concentration versus time curve (AUC) [12.83 (S.D. 4.06) mg.min/ml] was about 50 times greater than that detected in plasma [0.27 (0.03) mg.min/ml], indicating a clear pharmacological advantage for this route of administration. The mean plasma total Pt concentration was 1.1 μg/ml and the apparent total body clearance was 268 (101) ml/min. Platinum plasma pharmacokinetic data measured following intrapleural cisplatin administration (4 patients) were compared with those observed in 7 patients treated intravenously with the same dose of cisplatin (90 mg/m²) under the same modalities of hydration. Intrapleural administration of cisplatin resulted in significantly lower plasma total partial AUC ($P < 0.05$) and prolonged plasma levels of filterable Pt compared with intravenous administration. No difference between the two routes of cisplatin administration in the renal clearance (S.D.) of filterable Pt [132 (64) ml/min and 122 (39) ml/min for intravenous and intrapleural cisplatin, respectively] were observed. None of the mesothelioma patients developed clinical symptoms or signs of pleural inflammation. The intrapleural treatment did not produce haemotoxicity and the emetic toxicity was lower compared with that observed in patients receiving cisplatin intravenously.
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INTRODUCTION

INTRACAVITARY CHEMOTHERAPY should be the most effective means of treating malignant mesothelioma and other neoplasms which remain mainly confined to body cavities. With this approach the cavity can be exposed to drug levels that are much greater than those following systemic administration. The pharmacokinetic advantage of the intraperitoneal route has been demonstrated with several drugs [1, 2]. Among these, cisplatin has been shown to be one of the safest and most active in the intracavitary treatment of malignant mesothelioma and ovarian carcinoma that has spread in the peritoneum [3, 4]. According to Howell *et al.* [5] the intraperitoneal concentration of cisplatin is 20–30 times greater than its peak plasma concentration.

When cisplatin was delivered intrapleurally alone [3, 6] or in combination regimens [7] it showed promising therapeutic activity as well as reduced undesired toxic effects. In order to define whether there is a real advantage of the intrapleural compared to the intravenous route of administration of cisplatin, the following study was conducted.

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MATERIALS AND METHODS

Patients

Cisplatin was administered intrapleurally to 4 patients, 2 men and 2 women, aged 70–78, affected by malignant mesothelioma of the pleura. The diagnosis of malignancy was made by pleuroscopy with multiple biopsies of the visceral and parietal pleura. None of the patients had previously undergone surgery or chemoradiotherapy and there was no evidence of extrathoracic metastases. All patients were symptomatic with thoracic pain or dyspnoea. Cisplatin (90 mg/m²) was diluted in 500 ml normal saline and administered in 30 min through a drainage catheter introduced into the pleural cavity. As much of the malignant pleural effusion as possible was drained before therapy. Following cisplatin treatment, all mesothelioma patients underwent a sclerosing treatment with instillation of tetracycline to prevent the reformation of the effusion.

Another group of 7 patients, 4 men and 3 women, aged 70–78, affected by osteosarcoma received intravenous 90 mg/m² cisplatin diluted in 500 ml normal saline in 30 min. The night before treatment all 11 patients received intravenous saline hydration (0.9% NaCl) at a rate of approximately 100 ml/h and after the infusion of the antineoplastic agent, systemic hydration was continued at the same rate for 24 h. Neither mesothelioma nor osteosarcoma patients had impaired renal or hepatic function and their haematological parameters were normal. Informed consent was given by all patients.

Specimen collection

Blood samples were collected in heparinised tubes prior to the administration of cisplatin and 15, 30 and 45 min and 1, 2, 4, 8, 24, 48 and 72 h after intrapleural or intravenous drug administration. Pleural fluid of 3 mesothelioma patients was drawn in heparinised tubes before drug administration and 15, 30 and 45 min and 1, 2 and 4 h after cisplatin administration. All samples were immediately centrifuged and duplicate 2 ml portions of plasma and pleural effusion were removed and centrifuged at 1000 *g* for 1 h in CF25 A Centriflow membrane cones (Amicon, Lexington) to obtain filterable platinum. Urine samples were collected before cisplatin administration and from 2, 4, 8, 24, 48 and 72 h pools, and the volume of urine for each collection period was recorded.

Assay methods

Platinum concentrations in plasma, pleural effusion and their ultrafiltrates as well as in urine were determined by flameless atomic absorption spectroscopy using an Hitachi Z-9000 spectrophotometer (W. Pabisch, Milan) [8]. Accuracy of the platinum determinations was verified by neutron activation analysis [9].

Pharmacokinetic analyses

Pharmacokinetic parameters for both plasma and pleural cavity were estimated by computer-assisted fitting of the data based on first-order kinetics.

Pleural clearance expressed as the permeability area product (*PA*) was calculated as

$$PA = -\ln [C_{i.pl(4\,h)}/C_{i.pl\,(0\,h)}] \times V_{i.pl}/4\,h$$

where $C_{i.pl}$ is the platinum concentration in the pleura and $V_{i.pl}$ is the volume of pleural fluid. The total body clearance of platinum was defined as milligrams of platinum absorbed from the pleura divided by the area under the plasma platinum concentration versus time curve (AUC) calculated for total platinum concentration up to 4 h. Renal clearance of filterable platinum was obtained by dividing the total platinum recovered in the urine during the first 4 h following cisplatin administration by the area under the plasma filterable platinum curve for the same time. The apparent pleural fluid half-life was calculated by dividing 0.693 (i.e. ln 2) by the platinum elimination rate constant. The apparent volume of the pleural compartment was calculated as the administered dose *D* divided by *A* (i.e. *D*/*A*), where *A* is the intercept term estimated by first-order kinetic regression analysis. The amount of platinum absorbed from the pleura (D_{abs}) was calculated as: $D_{abs} = D_0(1-e^{-\beta t})$, where D_0 is the estimated initial intrapleural amount of platinum and β is the pleural elimination rate constant. A computerised curve-fitting for non-linear regression analysis was applied to analyse the plasma and pleural fluid platinum data [10].

Statistical analyses

The significance of the differences between plasma pharmacokinetic parameters of patients receiving intrapleural cisplatin and patients receiving cisplatin intravenously, as well as the AUC values for total and filterable platinum in the pleural fluid of patients receiving intrapleural cisplatin, was assessed according to the Mann–Whitney (Wilcoxon) test statistics [11] at a significance level of $\alpha = 0.05$.

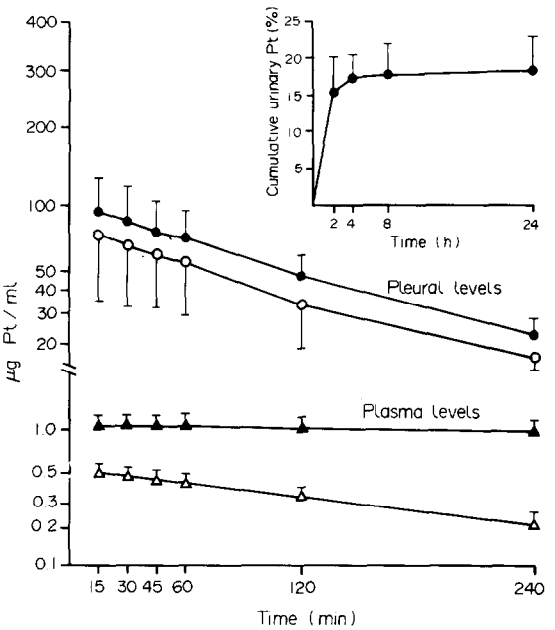

Fig. 1. Mean total and filterable plasma and pleural fluid concentrations and cumulative platinum recovery in the urine following intrapleural administration of 90 mg/m² cisplatin. Bars show S.D. (●) = total platinum in pleural fluid, (○) = filterable platinum in pleural fluid, (▲) = total platinum in plasma, (△) = filterable platinum in plasma.

RESULTS

Toxicity

None of the 4 patients receiving intrapleural cisplatin complained of dyspnoea. 1 reported thoracic discomfort during the infusion and 2 had one episode of vomiting. Neither neurotoxicity nor haemotoxicity were observed. Serum creatinine levels remained normal in 3 patients, while 1 had a transient increase up to 1.5 mg/100 ml on the first day after cisplatin administration. All 7 patients receiving cisplatin intravenously showed the typical pattern of haemotoxicity and emetic toxicity as well as transient increases in the serum creatinine levels higher than 1.7 mg/100 ml.

Pharmacokinetics of intrapleural cisplatin

A semilogarithmic plot of the mean levels of total and filterable platinum measured in plasma and pleural fluid and cumulative platinum recovery in the urine following 90 mg/m² of cisplatin administered intrapleurally is shown in Fig. 1. During the first 4 h following administration data are well represented by a monocompartmental model. The estimated mean (S.D.) disappearance half-life (i.e. sum of absorption and binding to pleural tissue) of total platinum from the pleural fluid was 2.08 (0.65) h (Fig. 1). Platinum was apparently distributed in a pleural volume ranging from 0.65 to 1.7 litres with a mean (S.D.) value of 1.05 (0.59) litre. The mean (S.D.) value of the platinum elimination rate constant was 0.0060 (0.002) min^{-1} (range: 0.0043–0.0083). The intrapleural dose of 90 mg/m² of cisplatin produced a steady-state plasma total platinum concentration which averaged 1.11 μg/ml (Fig. 1). A high concentration of filterable platinum in pleural fluid was observed and no statistically significant difference was noted between total and filterable platinum AUC values [12.8 (4.0) and 9.2 (4.6) mg.min/ml for total and filterable pleural platinum, respectively; $P = 0.2752$]. The absolute value of the peak filterable plasma platinum varied between 0.43 and 0.61 μg/ml and was 33–46 times lower than the lowest platinum

Table 1. Regional pharmacokinetic selectivity for cisplatin following intrapleural administration of 90 mg/m²

Patient	AUC			Clearance (ml/min)		
	Pleural fluid	Plasma	Selectivity*	CL	RC	PA
1	8.41	0.26	31.8	239	137	7.50
2	16.40	0.24	69.2	380	153	5.49
3	13.69	0.30	45.3	184	65	4.06
Mean (S.D.)	12.83(4.06)	0.27(0.03)	48.7(18.9)	268(101)	118(47)	5.68(1.73)

*AUC pleural/AUC plasma.
AUC = area under concentration–time curve up to 4 h (mg.min/ml), CL = apparent total-body clearance, RC = renal clearance of filterable Pt, PA = pleural clearance.

level within the pleural effluent. The mean percentage of total platinum absorbed from the pleural cavity in 24 h was 97.5% (range: 92.7–100), and the amount of absorbed platinum excreted in 24 h was 18.5% (S.D. 4.2%) (Fig. 1).

Table 1 reports data on regional pharmacokinetic selectivity for cisplatin following intrapleural drug administration. The pharmacological advantage of the intrapleural administration of cisplatin consisted in an increased exposure to total platinum of the pleural cavity (AUC = 12.83 mg.min/ml) without increasing the exposure of systemic circulation (AUC = 0.27 mg.min/ml). Indeed, the mean area under the pleural platinum concentration versus time curve was about 50 times greater than that detected in plasma and a slower absorption of platinum from the pleura [PA = 5.7 (1.7) ml/min] relative to the elimination from the body [CL = 268 (101) ml/min] was noted (Table 1).

Pharmacokinetics by route of administration

Platinum plasma levels determined in 4 patients receiving 90 mg/m² cisplatin intrapleurally and in 7 patients who received the same dose intravenously are reported in Fig. 2 and Table 2.

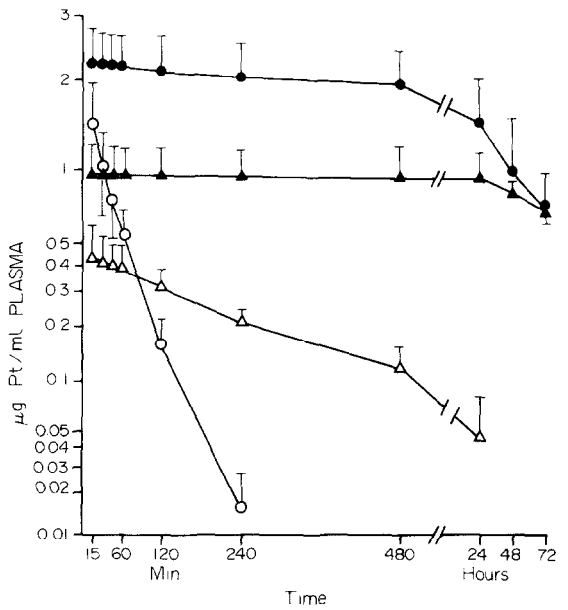

Fig. 2. Mean total and filterable platinum in the plasma of patients following intravenous or intrapleural administration of 90 mg/m² cisplatin. Bars show S.D. total platinum after intravenous (●) or intrapleural treatment (▲); filterable platinum after intravenous (○) or intrapleural treatment (△).

Table 2. Plasma pharmacokinetic parameters and renal clearance for platinum after intravenous (n = 7) and intrapleural (n = 4) administration of 90 mg/m² cisplatin

	Route of administration		
	intravenous	intrapleural	*P*
Maximum [Pt] total (μg/ml)	2.25 (0.58)	0.96 (0.35)	< 0.01
Maximum [Pt] filterable (μg/ml)	1.45 (0.55)	0.42 (0.18)	< 0.01
[Pt] total exposure up to 72 h (mg.min/ml)	5.78 (2.31)	4.47 (0.52)	NS
[Pt] total exposure up to 4 h (mg.min/ml)	0.52 (0.14)	0.27 (0.03)	< 0.05
[Pt] filterable exposure up to 4 h (mg.min/ml)	0.094 (0.031)	0.086 (0.012)	NS
Renal clearance of filterable Pt (ml/min)	132 (64)	122 (39)	NS

Mean (S.D.)
NS = not significant.

The peak plasma levels for total and filterable platinum following intravenous therapy were respectively 2.3 and 3.4 times higher than those observed after intrapleural administration. Prolonged plasma levels of filterable platinum were observed following intrapleural administration of cisplatin compared to those noted after intravenous treatment (Fig. 2). Similar mean (S.D.) values of total plasma AUC up to 72 h were found in patients receiving cisplatin intravenously [5.78 (2.31) mg.min/ml] and intrapleurally [4.47 (0.52) mg.min/ml]. Conversely, partial AUC mean values were approximately doubled following intravenous therapy [0.52 (0.14) mg.min/ml] compared to that observed following intrapleural therapy [0.27 (0.03) mg.min/ml, $P < 0.05$]. There was no difference between the two routes of cisplatin administration in the renal platinum clearance [132 (64) ml/min and 122 (39) ml/min for intravenous and intrapleural treatment, respectively].

DISCUSSION

The results of this study confirm that a single dose of 90 mg/m² of cisplatin can be administered safely by intrapleural infusion, without producing local toxicity. No patients developed clinical symptoms or signs of inflammation of the pleural surface. The emetic toxicity was lower following intrapleural than intravenous treatment. A consistently higher concentration of platinum in the pleura than in plasma could be achieved after intrapleural administration. Intrapleural platinum concentrations were 73–141 times higher than those observed in plasma. The AUC, which is a more accurate measure of drug exposure, was 32–69 times greater in pleura than in plasma while the level of total platinum in plasma was maintained constant. Such an increased exposure of the pleural cavity along with the slower absorption (clearance) of platinum from the pleura relative to the elimination from the body, formed the rationale for the therapeutic advantage of intrapleural therapy.

The comparative intrapleural and intravenous therapy of the same dose of cisplatin (90 mg/m²) resulted in significantly lower plasma total partial AUC and prolonged plasma levels of filterable platinum following intrapleural administration. Indeed, filterable platinum could be detected in plasma at times up to 24 h after treatment. The prolonged plasma levels of filterable platinum observed in intrapleurally treated patients

might be due to different rates of irreversible binding of cisplatin or Pt containing species to proteins and/or other reactive nucleophyles (e.g. sulphydryl-containing molecules). This could account for the lower systemic toxicity that was observed in mesothelioma patients. No statistically significant difference was noted by comparing the AUCs for total platinum up to 72 h.

This study further strengthens the rationale for the intrapleural cisplatin treatment schedule given the very high levels of filterable reactive platinum detected in the pleura, the prolonged plasma levels of filterable platinum, and the absence of haematological toxicity and the contained emetic toxicity despite the fact that cisplatin was absorbed systematically up to therapeutic levels.

1. Markman M. Intraperitoneal antineoplastic agents for tumors principally confined to the peritoneal cavity. *Cancer Treat Rev* 1986, **13**, 219–242.
2. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978, **62**, 1–11.
3. Pfeifle CE, Howell SB, Markman M. Intracavitary cisplatin chemotherapy for mesothelioma. *Cancer Treat Rep* 1985, **69**, 205–207.
4. Markman M. Intraperitoneal cisplatin chemotherapy in the management of ovarian carcinoma. *Semin Oncol* 1989, **16**, 79–82.
5. Howell SB, Pfeifle CE, Wung WE, *et al.* Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med* 1982, **97**, 845–851.
6. Markman M, Cleary S, Pfeifle C, Howell SB. Cisplatin administered by the intracavitary route as treatment for malignant mesothelioma. *Cancer* 1986, **58**, 18–21.
7. Markman M, Howell SB, Green MR. Combination intrapleural chemotherapy for malignant pleural disease. *Proc Am Ass Cancer Res* 1984, **25**, 172.
8. Pera MF, Harder HC. Analysis for platinum in biological material by flameless atomic absorption spectrometry. *Clin Chem* 1977, **23**, 1245–1249.
9. Esposito M, Collecchi P, Oddone M, Meloni S. Platinum assay by neutron activation analysis and atomic absorption spectroscopy in cisplatin treated pregnant mice. *J. Radioanal Nucl Chem* 1987, **113**, 437–443.
10. Draper NR, Smith H. *An Introduction to Non-linear Estimation. Applied Regression Analysis.* New York, Wiley, 1981.
11. Dixon JW, ed. *BMDP Statistical Software.* Berkeley, University of California Press, 1988.

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Low-dose Cytarabine for Acute Myeloid Leukaemia and Myelodysplastic Syndromes: *in vivo* and *in vitro* Cytotoxicity

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14 patients with acute myeloid leukaemia (AML) and 7 with myelodysplastic syndrome (MDS) were treated with cytarabine in low dosage. In AML a complete remission rate of 43% was found and in all patients profound cytopenia was noticed without any sign of maturation induction. In MDS no effect of low-dose cytarabine could be detected. We also studied the effect of low-dose cytarabine *in vitro* in freshly isolated leukaemic cells of 10 patients with AML. Maturation induction was measured by a comprehensive panel of quantitative and qualitative markers of maturation. No differentiation inducing effect of low-dose cytarabine could be found. We conclude on the basis of our own results and after reviewing the literature that low-dose cytarabine exerts its effect by cytotoxicity instead of maturation induction.
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INTRODUCTION

CYTARABINE IS one of the most effective agents in the treatment of acute myeloid leukaemia (AML). Regimens of 100-200 mg/m^2 per day for 7 days induce complete remissions (CR) in 60-80% of patients [1]. Recently, low-dose cytarabine has been introduced as an effective but less toxic treatment. In 846 patients low-dose cytarabine induced a CR in 32% [2]. The CR rate for patients older then 50 years was 56%. The mechanism through which cytarabine in small doses exerts its effect is not clear. Several authors have suggested that low-dose cytarabine promotes differentiation of leukaemic cells [3]. However, our group as well as others showed a cytotoxic effect of low-dose cytarabine without an obvious maturation-inducing effect [4, 5]. We report on *in vivo* data of 21 patients with AML and myelodysplastic syndrome (MDS) treated with low-dose cytarabine together with the *in vitro* effects of low-dose cytarabine in freshly isolated leukaemic cells.

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PATIENTS AND METHODS

Patients

14 patients with AML and 7 patients with MDS were treated with cytarabine in a dose of 10 mg/m^2 twice a day subcutaneously over 21 days. After reaching a CR or considerable blast reduction