ABSTRACT

The toxicity and pharmacokinetics of cis-diaminedichloroplatinum (cisplatin) (90 mg/sq m) administered as a single 4-hr peritoneal dialysis, with or without concurrent i.v. infusion of sodium thiosulfate, 0.43 or 2.13 g/sq m/hr for 12 hr, were studied on 20 courses of treatment. When given without thiosulfate, the toxicity of cisplatin was systemic rather than local, and the peritoneal cavity/plasma ratio of the area under the curve was 12. Addition of i.v. thiosulfate significantly reduced the nephrotoxicity. The concentration of cisplatin in the peritoneal cavity was sufficiently greater than that in the plasma to prevent thiosulfate, which equilibrated into the cavity, from interfering with the antitumor activity of cisplatin in the peritoneum. This study demonstrates a pharmacokinetic advantage of i.p. chemotherapy with cisplatin.

INTRODUCTION

It has been amply demonstrated both in experimental murine systems and in humans that some tumors which are sensitive to a drug in vitro do not respond when treated in vivo (32, 33). Inadequacy of drug delivery is probably the most important reason for the failure of chemotherapy in these tumors (20). Intracavitary chemotherapy has the potential of markedly increasing total drug delivery for at least 2 major groups of human tumors, ovarian carcinoma and mesothelioma, and possibly for others. The usefulness of intracavitary chemotherapy is already well established for the treatment of meningeal leukemia (1, 16), and the intravesicular route is used routinely in the management of early-stage bladder carcinoma (22, 31).

In cases where drugs are administered by peritoneal dialysis, the ratio of the total drug exposure (area under the concentration x time curve, AUC) for the peritoneal cavity to that for the systemic circulation is determined by the relative clearances of the drug from these 2 compartments (9). Pharmacokinetic modeling predicts that, when the drug is slowly removed from the peritoneal cavity and rapidly eliminated from the rest of the body, or when the drug is extensively metabolized during passage from the cavity to plasma, the concentration in the cavity can be maintained at a level several orders of magnitude higher than in plasma (9). This prediction has been confirmed in initial studies of 5-fluorouracil (27-29), methotrexate (13, 17, 18), and doxorubicin (23, 24). Under conditions where the cavity/plasma concentration ratio is sufficiently high, the i.v. infusion of a competitive neutralizing agent may potentially further improve the therapeutic index by blocking the toxicity of the drug reaching the plasma. The success of this approach depends both on the rate at which the neutralizing agent equilibrates into the peritoneal cavity and on how the degree of neutralization changes as a function of the concentration of the chemotherapeutic agent. If the slope of this interaction is steep enough, then, when just enough neutralizing agent is infused i.v. to block systemic toxicity, even if the agent equilibrates into the cavity it will not be able to interfere with the cytotoxic activity of the higher concentration of chemotherapeutic agent at the surface of the tumor. We have successfully used this approach to increase the duration of peritoneal exposure to very high concentrations of methotrexate to as long as 5 days (13).

Cisplatin is one of the most effective drugs currently available for the treatment of ovarian carcinoma (26, 30, 34, 35). When it is administered i.v., its dose is limited to 100 to 120 mg/sq m by nephrotoxicity. We have previously demonstrated that concurrent administration of sodium thiosulfate can protect against nephrotoxicity in mice (15). In this clinical trial, we have studied the pharmacokinetics and toxicity of cisplatin administered i.p. and have examined the effect of concurrent i.v. infusion of sodium thiosulfate on these parameters. We have also investigated the relationship between drug exposure and the survival of clonogenic human ovarian carcinoma cells in vitro over a range of total drug exposure encompassing that which can be achieved with i.p. therapy.

PATIENTS AND METHODS

The subjects were patients with malignant ascites and a positive cytology or patients whose tumor was entirely confined to the peritoneal cavity. Seven patients received a total of 20 courses of i.p. cisplatin. There were 2 males and 5 females with a median age of 51 (range, 31 to 60). Four patients had ovarian carcinoma and one each had mesothelioma, melanoma, and malignant carcinoid. Entrance criteria included a serum creatinine of less than 1.5 mg/dl, a blood urea nitrogen of less than 40 mg/dl, a leukocyte count of greater than 100,000/cu mm, a platelet count of greater than 100,000/cu mm, a life expectancy of greater than 1 month, and recovery from all toxicities due to prior treatment.

Patients were hydrated with 0.9% NaCl solution i.v. for 12 hr prior to treatment. The abdomen was drained completely through either a previously placed Tenckhoff catheter or a percutaneously inserted peritoneal dialysis catheter. The requisite dose of cisplatin (Bristol Laboratories, Syracuse, N. Y.) was diluted to isotonicity with sterile water, suspended in 2 liters of warm 0.9% NaCl solution, and instilled into the peritoneal cavity by gravity flow over 10 min. After a single 4-hr dwell, the cavity was again drained as completely as possible. Concurrent with the instillation of cisplatin, a bolus of 12.5 g mannitol was given i.v. followed by 30 g of mannitol in 1 liter 0.9% NaCl solution infused over 6 hr. If urine flow was less than 100 ml/hr prior to

1 Supported by Grant CA 23100 from the National Cancer Institute, by Grant RR-00827 from the NIH/Division of Research Resources. This work was conducted in part by the Clayton Foundation for Research—California Division.

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3 The abbreviations used are: AUC, area under the concentration x time curve; cisplatin, cis-diaminedichloroplatinum; DDTC, diethylthiocarbamate.

Received July 28, 1982; accepted December 2, 1982.
the growth rate of these representative nonmalignant cells to sulfate/cisplatin ratios of 280 to 950 were required to restore concentration of cisplatin. Thiosulfate is excreted primarily by the kidney, and its clearance closely approximates that of creatinine (3, 10). Based on calculations using Equation A, which relates the plasma concentration at steady state (C_{ss}) to the infusion rate and clearance, it was estimated that continuous sodium thiosulfate infusions of 0.43 and 2.13 g/sq m/hr would yield steady-state plasma concentrations of approximately 94 and 471 µg/ml, respectively, in patients with normal renal function, and these dose rates were selected for clinical trial.

\[ C_{ss} = \frac{\text{Infusion rate}}{\text{Clearance}} \]  

(A)

**Effect of Thiosulfate on Cisplatin Toxicity.** Chart 2 shows the effect of thiosulfate on the nephrotoxicity of cisplatin as measured by the maximum percentage of change in serum creatinine during the 3-week period following treatment on 19 evaluable courses. When cisplatin was administered by the i.p. route without thiosulfate, the mean increase in serum creatinine was 42 ± 41% (S.D.). The addition of an i.v. thiosulfate infusion of 0.43 g/sq m/hr produced a peak creatinine change of −11 ± 31% (p < 0.05) and, when a thiosulfate dose rate of 2.13 g/sq m/hr was used, the maximum change was 11 ± 19% (p < 0.1). Thus, the lower thiosulfate dose rate significantly reduced the nephrotoxicity of cisplatin. Although the effect of the higher dose rate of thiosulfate was not statistically significant

![Chart 1. Dose-response curves for the antagonism by sodium thiosulfate of cisplatin-induced decrease in the growth rate of WI-L2 cells in vitro. Cisplatin concentrations: 1 µM (○), 4 µM (■), and 10 µM (×). Antagonism was quantitated by growth rate. Point, mean of triplicate cultures.](image)

![Chart 2. Nephrotoxicity of cisplatin, 90 mg/sq m i.p., as a function of sodium thiosulfate dose. Nephrotoxicity was quantitated as the maximum percentage of change in serum creatinine during the 3 weeks following treatment. Bars, geometric mean.](image)
any significant nephrotoxicity (14) confirming that this dose rate of thiosulfate is in fact protective.

Table 1 presents data on the hematological toxicity of i.v. cyclophosphamide alone and in combination with i.v. thiosulfate on 18 evaluable courses. Cyclophosphamide at a dose of 90 mg/sq m i.v. by itself caused a decrease in the leukocyte count which averaged only 2% but produced an average 31% decrease in the platelet count (p < 0.05, t test for paired observations). The addition of thiosulfate had no effect on the changes in the leucocyte count, but at a dose rate of 0.43 g/sq m/hr it reduced, and at a dose rate of 2.13 g/sq m/hr it completely eliminated, the reduction in platelet count (p > 0.05, t test for paired observations).

Instillation of cyclophosphamide i.p. did not produce any local toxicity within the peritoneal cavity. No patient in this study developed clinical symptoms or signs of peritonitis. Pretreatment peritoneal fluid cell counts were often abnormal, but cell counts were not increased when measured at 3 weeks after treatment, and they showed no tendency to increase with serial courses of therapy. Since initiation of the i.p. cyclophosphamide treatment program at this institution, we have had the opportunity to directly examine the serosal surfaces in 5 patients either at laparoscopy or autopsy within 4 weeks of the last course of treatment, and in no case were there any changes in the serosal surfaces that could be attributed to treatment. In patients with documented i.p. adhesions, none of whom were included in this study, we have observed mild-to-moderate abdominal pain during filling of the abdomen, and this has been attributed to mesenteric traction. The amount of nausea and vomiting produced by i.p. instillation of cyclophosphamide was less intense and of shorter duration than that produced by equivalent i.v. doses; however, nausea and vomiting were still significant and universal.

**Effect of Thiosulfate on Cisplatin Pharmacokinetics.** Non-protein-bound cyclophosphamide was measured with an assay that detects only those forms of cyclophosphamide in the plasma that are still capable of reacting with nucleophilic sites on other molecules, in this case DDTC (2). Data were sufficient for pharmacokinetic analysis on 18 of the 20 courses. Chart 3 shows the DDTC-reactive cyclophosphamide kinetics in a representative patient with ovarian carcinoma receiving 90 mg/sq m. There was a nearly exponential decrease in the peritoneal cyclophosphamide concentration with time. The pharmacokinetic data is presented in Table 2. The i.p. instillation of 90 mg/sq m of cyclophosphamide produced an AUC for the peritoneal cavity of 97.1 μg·hr/ml and a plasma AUC of 8.1 μg·hr/ml when measured using the DDTC assay. Thus, the AUC for the peritoneal cavity was 12-fold greater than that for the plasma following i.p. instillation of cyclophosphamide.

The data in Table 2 also demonstrate the impact of the concomitant i.v. infusion of thiosulfate at 0.43 and 2.13 g/sq m/hr on the cyclophosphamide kinetics. The lower dose rate produced no reductions in any of the pharmacokinetic parameters for either the peritoneal cavity or plasma. The higher thiosulfate dose rate produced a 23 to 32% decrease in the mean values for the peak peritoneal cyclophosphamide concentration, (p < 0.05) and the peritoneal (p < 0.05) and plasma (p < 0.20) AUC, but changes in peritoneal AUC were matched by proportional changes in plasma AUC so that the mean AUC ratio did not vary with thiosulfate dose rate. Thiosulfate did not change the peritoneal clearance of the cyclophosphamide, reflecting the fact that neither dose rate of thiosulfate affected the half-life of 0.85 ± 0.26 hr for DDTC-reactive cyclophosphamide in the peritoneal cavity.

**Pharmacokinetics of Sodium Thiosulfate.** Serial plasma and peritoneal measurements of thiosulfate concentration were available from 13 courses of treatment in 8 patients receiving thiosulfate at a dose rate of 2.13 g/sq m/hr. The insensitivity of the thiosulfate assay precluded accurate measurements in patients receiving 0.43 g/sq m/hr. Chart 4 shows that the i.v. loading dose of 4 g/sq m followed by a constant infusion of 2.13 g/sq m/hr produced a steady-state plasma thiosulfate concentration which averaged 410 μg/ml, reflecting a total body clearance of 85 ml/min/sq m. Even at the time of the first measurement immediately after instillation of the cyclophosphamide, measurable concentrations of thiosulfate were already present in the peritoneal cavity, and within 2 hr the peritoneal thiosulfate...
concentration had reached steady state at a value that was 81% of the plasma level. Thus, thiosulfate introduced into the systemic circulation entered the peritoneal cavity rapidly, and significant differences in the availability of thiosulfate for the neutralization of cisplatin in the 2 compartments existed only during the first hr after the start of i.v. thiosulfate infusion.

**In Vitro Cisplatin Dose-Response Curve.** The pharmacokinetic results presented above indicate that, by instilling cisplatin via the i.p. route, the peritoneal cavity received a total drug exposure that was approximately 12-fold greater than the systemic circulation. In order to determine the significance of this greater AUC for the killing of tumor cells, primary tumors from 3 patients with ovarian carcinoma and samples of 2 human ovarian carcinoma xenografts growing in nude mice were tested in vitro for their sensitivity to cisplatin using the soft agar colony assay of Hamburger et al. (11). All the tumors tested had been exposed to prior therapy with cisplatin. Chart 5 indicates that the logarithm of the surviving fraction is linearly related to the logarithm of the AUC (r = 0.93; p = 0.005). An AUC of 8.1 µg-hr/ml for DDTC-reactive cisplatin, which is close to the maximum tolerated plasma exposure in the absence of thiosulfate, yielded a surviving fraction of 0.27. A 12-fold greater AUC, such as was achieved in the peritoneal cavity, produced a surviving fraction of 0.17. Thus, it is apparent that, because of the logarithmic nature of the dose-response curve, even the large increase in peritoneal AUC that was achievable with i.p. instillation of cisplatin would not necessarily be expected to increase tumor cell kill by more than approximately 0.1 log unit over that attainable with AUCs associated with conventional routes of cisplatin infusion.

**Responses.** Table 3 presents information on the 6 patients who were evaluable for response, including 4 with ovarian carcinoma, one with mesothelioma, and 1 with malignant carcinoid. All patients had had extensive prior therapy, and the ovarian carcinoma patients had failed combination chemotherapy programs. All evaluable patients received treatment with cisplatin alone on some courses and cisplatin with thiosulfate on others. In some patients, the dose of cisplatin was escalated to tolerance after treatment at the 90-mg/sq m level (14). The patient with carcinoid responded with a >50% decrease in the volume of his ascites and normalization of a markedly elevated 5HIAA lasting 5 months. The patient with mesothelioma had a decrease in his ascites to the point where it was not clinically detectable, and disappearance of an abdominal wall mass that lasted until he was lost to follow-up after 4 months. One of the patients with ovarian carcinoma who had residual micronodular disease and a positive peritoneal fluid cytology after debulking surgery converted her cytology to negative and has remained free of disease for 12+ months while receiving continued therapy.

**DISCUSSION**

When administered by the i.v. route, cisplatin is rapidly delivered by capillary flow to the bone marrow and the kidneys but is much less effectively delivered to free-floating tumor cells in the peritoneal cavity or poorly vascularized small serosal nodules. The results of this study suggest that, for these components of tumors confined to the peritoneal cavity, the i.p. route of cisplatin administration appears to be much more advantageous than the i.v. route, even when used without thiosulfate. Instillation of cisplatin via the i.p. route resulted in a 12-fold greater exposure for the peritoneal cavity than for the plasma. In addition, at the relatively large 90-mg/sq m dose of cisplatin, sufficient drug leaked into the plasma so that even those components of the tumor supplied only by capillary flow received a cytotoxic exposure to cisplatin. Thus, by utilizing the i.p. route, one can markedly increase the total drug expo-
sure for free-floating tumor cells and small nodules for which there is no limitation of drug diffusion, while at the same time delivering significant amounts of drug by capillary flow. However, it is apparent that by itself the use of the i.p. route would not permit much escalation in the total amount of cisplatin actually administered to the patient since renal damage was still the major toxicity.

The addition of i.v. sodium thiosulfate to the program of i.p. cisplatin administration had the effect of reducing nephrotoxicity, and at the higher dose rate it also reduced the degree of thrombocytopenia. In a separate study, we have shown that the degree of protection against nephrotoxicity was quite dramatic, and that even cisplatin doses of 270 mg/sq m did not produce nephrotoxicity when thiosulfate was administered concurrently (6, 14). The mechanism of this protective effect remains uncertain. Cisplatin reacts readily with nucleophilic sites on a variety of sulfur-containing molecules (4, 36), and in all probability thiosulfate can react covalently with cisplatin to form a complex that has no toxicity for either normal or malignant tissues (15). This inactive cisplatin/thiosulfate complex is not measured by the assay used for cisplatin in this study. However, despite the presence of thiosulfate in the plasma, DDTC-reactive cisplatin was paradoxically readily detected in amounts equivalent to those present in the absence of thiosulfate infusion. Thus, the protection against nephrotoxicity was not due to a major decrease in the delivery of active drug to the kidneys. Thiosulfate is not a very potent neutralizing agent for cisplatin, as evidenced by the fact that the thiosulfate concentration must be 280 to 950 times higher than that of the cisplatin in order to reverse toxicity to a lymphoblastoid cell line, and the fact that the rate constant for the reaction is low. One likely explanation for the ability of thiosulfate to protect without decreasing the plasma AUC is that thiosulfate may be concentrated extensively in the kidneys (3, 10), possibly producing sufficiently high local concentrations of thiosulfate to neutralize cisplatin reaching the renal tubules.

The average clearance of DDTC-reactive cisplatin from the peritoneal cavity of 0.77 liters/sq m/hr was somewhat greater than that predicted on the basis of molecular weight alone (approximately 0.2 liters/sq m/hr) (8). This was probably due in part to the fact that cisplatin can be cleared not only by diffusion into capillaries and lymphatics but also by reaction with nucleophilic sites on proteins and other compounds present in peritoneal fluid to form inactive complexes (5, 12, 19). It is noteworthy that the peritoneal clearance of cisplatin did not vary with serial courses of treatment, which is in agreement with the observation that it produced no evidence of chemical peritonitis, and no changes in the serosal membranes were observed in 5 patients by direct visualization.

The steady-state concentration of thiosulfate in the plasma (410 μg/ml) was very close to that predicted on the basis of Equation A. Thiosulfate distributes in the total extracellular fluid (10), and a significant differential in peritoneal and plasma thiosulfate concentration was observed only for the first hr of infusion. However, the concentration differential for cisplatin between the 2 compartments was well above the 10-fold difference that, based on in vitro data, should be sufficient to prevent thiosulfate from interfering with the antitumor activity of cisplatin in the peritoneal cavity. Several other compounds in addition to sodium thiosulfate can reduce the systemic toxicity of cisplatin in animals (4, 34), and thiosulfate may not be the ideal neutralizing agent. However, the facts that it is readily available for use in humans, that it produces little toxicity, and that there has been a long period of experience with the clinical use of the agent for the treatment of cyanide poisoning (7, 8) recommends it for further study.

The adequacy of drug distribution in the abdomen, the penetration of the drug into the tumor from its free surface, and the intrinsic sensitivity of the tumor are all important considerations that bear on the potential clinical utility of i.p. cisplatin with or without thiosulfate. Little information is available on what fraction of the tumor surface can be exposed to drug when the abdomen is distended with 2 liters of fluid or on the ability of cisplatin to penetrate the tumor by diffusion. One can anticipate that, in patients with ovarian carcinoma, mesothelioma, or other tumors, loculation of fluid may be a frequent problem, and that because of its reactivity the diffusion coefficient of cisplatin in tissue may be quite low. These difficulties can be circumvented in part by using a large enough dose administered into the peritoneal cavity that the amount of drug that leaks into the plasma is equivalent to a maximum tolerated dose of drug given i.v.

The problem of intrinsic drug resistance on the part of the tumor may not be as easily surmounted. Our data indicate that tumors obtained from patients previously treated with cisplatin are highly resistant when tested in vitro. The dose–response curve for the killing of colony-forming cells in these tumors was very shallow, so that for each 1-log increase in AUC there was...
only a 0.2-log additional tumor cell kill. Untreated tumors can be expected to have steeper dose-response curves (11) than were observed for previously treated tumors in this study, and this suggests that the increased AUC achievable with the i.p. route should be of much greater value to the patient with a previously untreated tumor than for patients with prior cisplatin exposure. Nevertheless, at present there is little information on how many logs of in vitro clonogenic cell kill are required per course for a treatment program to be effective in vivo, and we have observed excellent responses in several patients even when macronodular disease was present (14). Thus, we believe that at this point in its development intracavitary chemotherapy merits further investigation for both early and untreated, and late and previously treated disease.

ACKNOWLEDGMENTS

The authors would like to thank Bristol Laboratories and Eli Lilly and Co. for providing the drugs used in this study. In addition, they would like to thank Kathy Price for preparation of the manuscript.

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Intraperitoneal cis-Diamminedichloroplatinum with Systemic Thiosulfate Protection

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