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Experimental Observations Regarding the Absorption of Cisplatin from an Ileal Segment Used as a Part of the Urinary Tract

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Abstract：Background：Metabolic abnormalities in patients with intestinal urinary diversion is caused by the re-absorption of urine solutes across the ileal segment. The reason for this is that some drugs excreted in the urine may also be re-absorbed. The purpose of the present study was to explore the possibility of cisplatin re-absorption from an ileal segment using a canine model with a unilateral ileal conduit.

Methods：Seven female mongrel dogs weighing 8.0 to 15.8 kg were used. After intravenous pentobarbital anesthesia, a 20-cm segment of the terminal ileum,（starting 10 cm from the ileocecal valve）was used to construct an ileal conduit. The right ureter was anastomosed to the oral end of the ileal segment, and the distal end was brought out through the abdominal wall to make an everted stoma. The left ureter was left intact. After an intravenous bolus injection of cisplatin（0.5 mg/kg B.W.), the urine from both ureters was collected for 3 hours. The urinary volume, pH, urinary components, and the cisplatin concentration were then determined and compared between the stomal urine and the contralateral control urine.

Results：The amount of excreted cisplatin in the control urine was 1.20±0.35 mg, while that of the stomal urine was 0.92±0.30 mg（$p<0.01$）. The re-absorption rate from the ileal conduit was 23.4±12.8%, and cisplatin was re-absorbed to a greater extent at a lower urinary pH（$r=-0.57$）.

Conclusions：We consider that excreted cisplatin is therefore significantly re-absorbed from the ileal segment which is part of the urinary tract.

Key words：**Cisplatin, Urinary diversion, Dogs, Re-absorption, Urinary pH**

Introduction

A radical cystectomy remains one of the most common types of therapy for invasive bladder cancer, and an intestinal segment has been preferably used as a urinary conduit or continent reservoir. Many patients who might have metastatic disease often undergo adjuvant chemotherapy after surgery, and cis-dichlorodiammineplatinum（cisplatin）and methotrexate play a major role in combination chemotherapy regimens, such as in Sternberg's M-VAC therapy.[1)2)] The major portion of these drugs is known to be excreted from the kidneys.[3)4)] In patients with intestinal urinary diversion, however, urine always come in contact with the intestinal mucosa, and thus the re-absorption of such drugs might occur. Although several studies have focused on methotrexate tolerance and/or toxicity in patients with intestinal urinary diversion,[5)-8)] the absorptive capacity of cisplatin in an intestinal segment which is part of the urinary tract has yet to be elucidated. If urinary cisplatin is significantly re-absorbed from the intestinal mucosa, then we may have to consider a modification of the cisplatin dosage. To answer this

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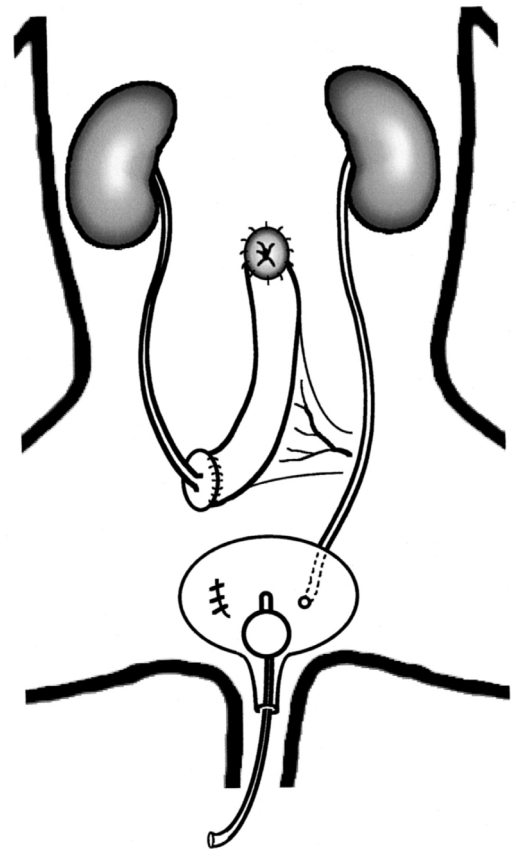

Fig. 1a. Canine model of unilateral ileal conduit urinary diversion. The right renal urine can be collected through the ileal stoma, while the left renal urine can be separately obtained via a urethral catheter.

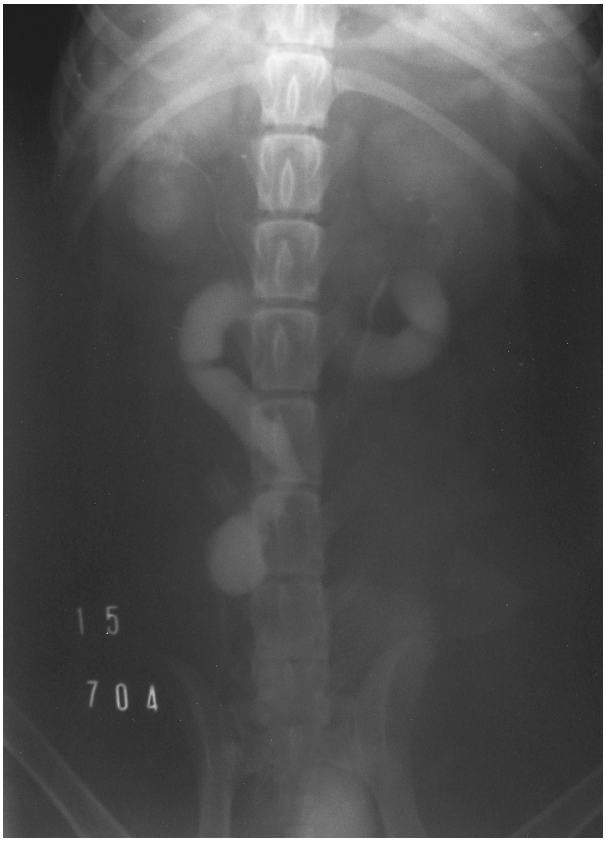

Fig. 1b. Intravenous urography findings for this model

question, we made experimental observations of the absorptive capacity of the ileal mucosa for cisplatin in a canine model with unilateral ileal conduit urinary diversion.

Methods

Operative Procedure：This study was done under the approval of the Committee of Ethics at Fukuoka University. Seven female mongrel dogs weighing 8.0 to 15.8 kg were used. After intravenous pentobarbital anesthesia, a 20-cm segment of the terminal ileum, (starting 10 cm from the ileocecal valve) was taken to construct an ileal conduit. The right ureter was anastomosed to the oral end of the ileal segment, and the distal end was brought out through the abdominal wall to make an everted stoma. The left ureter was left intact (Fig. 1a). An antibiotic was administered for 7 days after the operation. Two weeks later, intravenous urography was done to confirm the morphological and functional symmetry of the bilateral nephroureteral units (Fig. 1b). As a result, the right renal urine, which passed through the ileal segment, could be collected from the ileal stoma (stomal urine) and the left renal urine could be separately collected through a urethral catheter (control urine).

Separate renal urine study：The night before the experiment, the animals were restricted to an intake of water alone. Following the induction of anesthesia with intravenous ketamine hydrochloride at a rate of 25 mg/kg B.W., inhalation anesthesia with halothane and nitrous oxide was initiated and maintained under the control of a respirator. The right femoral artery was connected to a monitor system (Nihon Kohden RM-6000, Tokyo, Japan) to record the mean arterial blood pressure. Next, the dogs were fixed to a dog sling for the collection of the two separate urine samples.

Beginning 1 or 2 hours before cisplatin admi-

Table The measurement results of the urinary volume and cisplatin concentration in the control urine and the stomal urine

	Control urine	Stomal urine	p value
Mean urine volume (ml)	42.3±20.6	44.3±22.5	0.56
Mean cisplatin concentration in urine (mg/ml)	0.034±0.019	0.029±0.025	0.09

nistration, the dogs were hydrated intravenously with 5% glucose in water at a rate of 15 ml/kg/hour. After the establishment of a constant urine flow, a bolus of cisplatin at a dose of 0.5 mg/kg B.W. was intravenously administered, and urine samples were thereafter collected separately from the ileal conduit stoma and the urethral catheter for exactly 3 hours. The urinary volume, pH and urinary components were determined. The cisplatin concentration was measured as platinum with an atomic absorption spectrophotometer (Hitachi Z-8000, Tokyo, Japan). The experiment was repeated at an interval of at least 4 weeks.

Statistical Analysis: All data were expressed as the mean and standard deviation. The data regarding the total excretion of cisplatin were analyzed using the paired Student's *t* test. Correlation coefficients were examined between the re-absorption rate of cisplatin and other factors such as the urinary volume, urinary pH, water movement (re-absorption or the excretion of water from the ileal segment), and the cisplatin concentration. The results were statistically analyzed using the StatView J-5.0 software package (SAS Institute Inc., North Carolina, U.S.A.). A P value of less than 0.05 was considered to be significant.

Results

A total of 17 samplings of separate urine were obtained made from 7 dogs. There were no differences in the urinary volume and the cisplatin concentration between the control urine and the stomal urine (Table). The total cisplatin excretion for 3 hours was 35.4±10.1% of the administered dose. Separate cisplatin excretion in the urine was 0.92±0.30 mg in the stomal urine and 1.20 ±0.35 mg in the control urine, and the difference was significant ($p<0.01$, Fig. 2). Assuming that

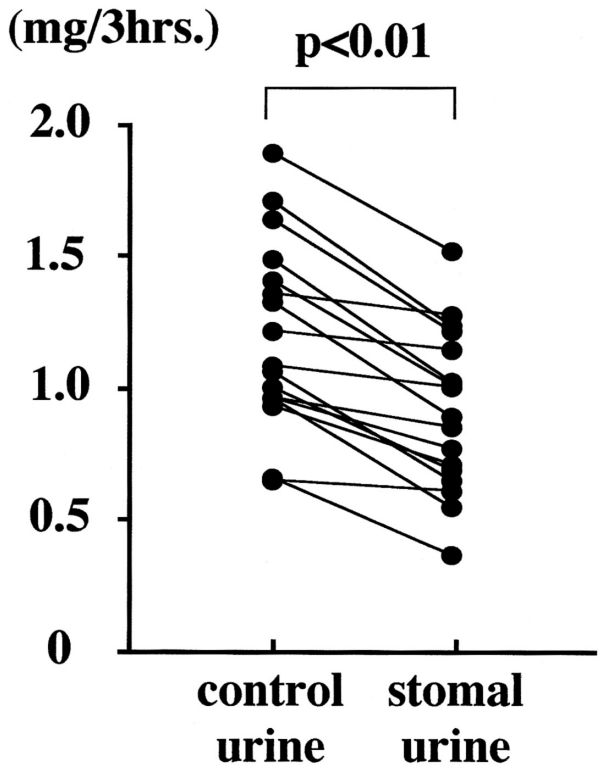

Fig. 2. Total excretion of cisplatin

the bilateral renal function was equal, the diminished cisplatin excretion in the stomal urine could be attributed to re-absorption from the ileal segment which is part of the right upper urinary tract. The re-absorption rate of cisplatin was calculated by means of the following formula:

Re-absorption rate of cisplatin
$$= (Pc - Ps)/Pc \times 100(\%)$$

Pc: Cisplatin (mg) in control urine, Ps: Cisplatin (mg) in stomal urine

The cisplatin re-absorption rate was 23.4±12.8%, and cisplatin was re-absorbed to a greater extent

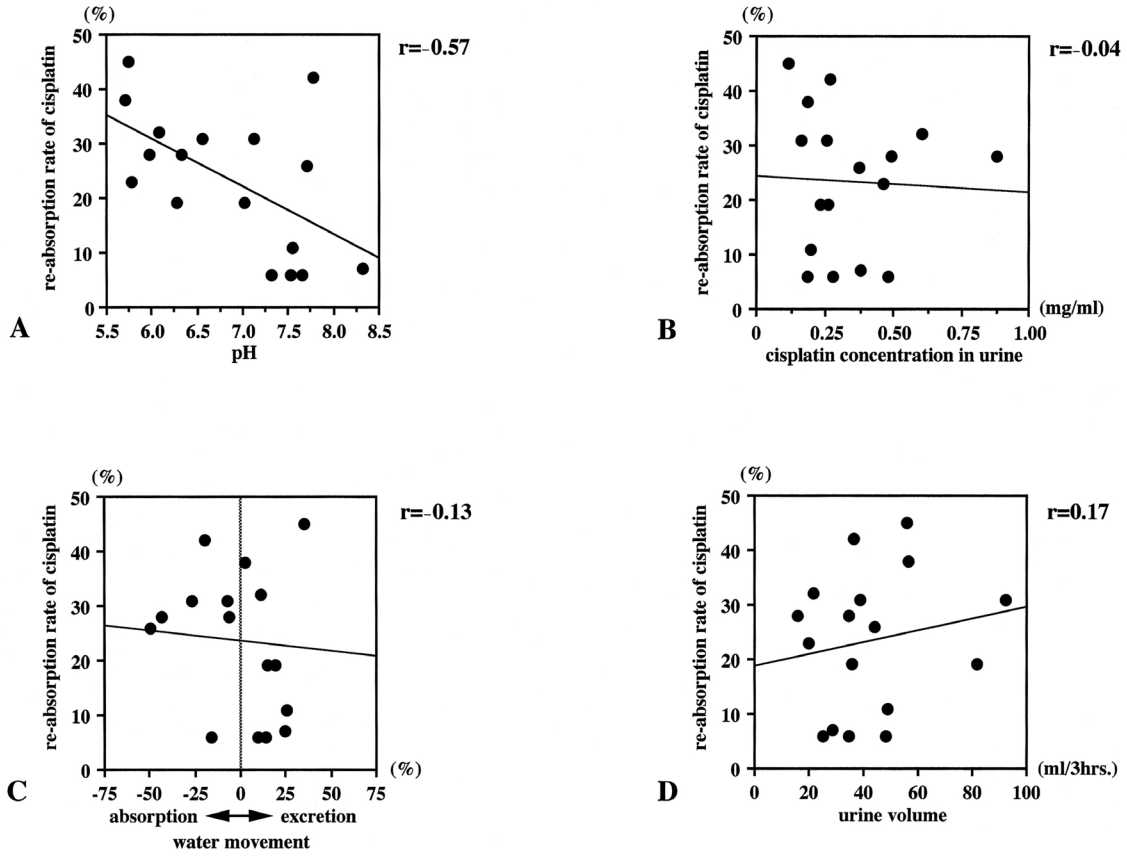

Fig. 3. Relationships between the re－absorption rate of cisplatin and urinary pH (A), the cisplatin concentration in urine (B), water movement (C), and urine volume (D).

from urine having a lower urinary pH (Fig. 3A : r＝－0.57). However, other factors such as the urinary volume, water movement, and urinary cisplatin concentration had no effect on the re-absorption of the drug from the urine(Fig. 3B : r＝－0.04, C : r＝－0.13, and D : r＝0.17).

Discussion

Cisplatin is one of the most effective anticancer drugs used as a single agent or in combination chemotherapy, and its usage has been limited solely to intravenous or intra-arterial administration. Therefore, most of the previous observations on the pharmacokinetics of cisplatin have been based on studies using intravascular administration, and only a few reports have appeared regarding the cisplatin metabolism in the digestive system. Houjou et al.[9] observed the gastrointestinal absorption of orally administered cisplatin, and Irie et al.[10] reported the biliary excretion of cisplatin in rats to be approximately 6.8% of the administered dose during the first 48 hours, which indicates that cisplatin and/or its metabolites was re-absorbed in the intestine. To our knowledge, no studies have described the re-absorption of urinary cisplatin from an ileal segment incorporated in the urinary tract. If re-absorption of urinary cisplatin from an ileal segment is significant enough to result in a higher level of plasma cisplatin, then the dose planning regarding chemotherapy should be modified in those patients with intestinal urinary diversion. Our original canine model with unilateral ileal conduit urinary diversion provides us with separate urine samples from each side of the upper urinary tract.

Ekman and Nyberg[11] investigated the absorption of drugs such as digoxin, theophilline, and terbutaline from a cecal urinary reservoir over a 24-hour period. The results differed among the drugs, and theophilline alone was absorbed from the reservoir. Our animal model was designed to ob-

tain separate urine through an ileal segment, which could then be compared with the urine from the contralateral side. In this model, the renal excretion of water, solutes, and cisplatin was theoretically identical on both sides when the equality of the bilateral renal function was confirmed by intravenous urography. However, the cisplatin excretion in the stomal urine was significantly less than that in the control urine. This difference can only be explained by the re-absorption of cisplatin through the ileal segment in the urinary tract.

In a pharmacological study by Gale et al.,[12] the intracellular accumulation of cisplatin was proportional to the cisplatin concentration in the experimental medium, and they postulated that cisplatin entered intracellularly only by passive diffusion. Concerning cisplatin absorption from the rat intestine, Binks and Dobrota[13] reported that cisplatin accumulation was influenced by the cisplatin concentration, contact time, and intraluminal pH. In our experiment, there was no correlation between the urinary volume and the cisplatin re-absorption rate. An increase in the urinary volume, however, would theoretically be beneficial since it would decrease the cisplatin re-absorption because of a dilution of the drug concentration and a decreased contact time due to a quicker urine flow. However, our results did not support of this hypothesis. Since this experiment was done *in vivo*, other factors that might influence re-absorption and the results could be different from those previously reported in Binks and Dobrota's experiment done *in vitro*. Taneda[14] reported on water and the solute metabolism in intestinal urinary diversion and he used the same experimental model that we used. He showed that both water and the solute metabolism were influenced by urine osmolality, and we therefore assumed that the re-absorption of cisplatin would also be similarly influenced too. Regarding the pH, they reported that cisplatin absorption from the intestinal tract was greater at a lower pH. In our observations as well, the lower the urinary pH, the more that cisplatin was re-absorbed from the ileal segment. The absorption of a drug by passive diffusion is conditioned by drug ionization. Cisplatin is less ionized in a lower pH solution and non-ionized cisplatin is more easily absorbed.

To our knowledge, no report has indicated any possible risk of toxicity due to a delayed elimination of cisplatin in patients with intestinal urinary diversion. However, various continent reservoirs such as the Indiana pouch,[15] Kock pouch[16] and Reddy's sigmoid neobladder[17] may pose a greater potential risk for the re-absorption of cisplatin than an ileal conduit because of the longer contact time and the wider surface area of contact. In our current experiment, we demonstrated that cisplatin was significantly re-absorbed from an ileal conduit and a lower urinary pH was thus considered to be an accelerating factor. We consider that further investigations of cisplatin kinetics, under both experimental and clinical conditions, should be conducted to provide additional information in order to eventually establish more effective and less harmful dosage schedules.

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