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Effects of sodium thiosulfate on the pharmacokinetics of total platinum after intravenous administration of cisplatin to rabbits

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Summary

The pharmacokinetic parameters of cisplatin measured as total platinum were compared after intravenous administration of cisplatin with and without coadministration of sodium thiosulfate (STS) in rabbits. The mean values of $t_{1/2}$ (47.7 vs 27.4 h) and MRT (65.1 vs 37.1 h) decreased significantly on pretreatment with STS. The mean values of AUC (1010 vs 714 μg min ml^{-1}) and V_{ss} (12.7 vs 8.89 l kg^{-1}) tended to decrease, and those of the amounts of total platinum excreted in 24 h urine (X_u, 3110 vs 4150 μg per 24 h) and CL (3.30 vs 4.46 ml min^{-1} kg^{-1}) tended to increase on pretreatment with STS. The tissue to plasma ratios of total platinum decreased on pretreatment with STS except fat, and indicated that the affinity of total platinum to tissues was reduced by pretreatment with STS. In vitro plasma protein binding of total platinum decreased with increasing concentrations of STS. The above data indicate that total platinum resides less and is eliminated rapidly from rabbits on pretreatment with STS.

Cisplatin (*cis*-diamminedichloroplatinum(II)) has been widely used in the treatment of a number of adult and pediatric tumors (Crom et al., 1987). Its primary dose-limiting toxicity has been nephrotoxicity (Balis, 1986; Crom et al., 1987). Several other agents have been administered with cisplatin in an attempt to protect the kidney from such damage and, therefore, to increase the therapeutic index of the drug (Balis, 1986). These agents include furosemide, mannitol, probenecid, sodium thiosulfate (STS) and acetazolamide (Balis, 1986). Hydration and forced diuresis are commonly employed to reduce nephrotoxicity induced by cisplatin (Balis, 1986).

The toxicity of cisplatin was reported to be reduced by treatment with STS; the life-span increased significantly in STS-treated mice (Iwamoto et al., 1984), and patients tolerated 2-fold higher doses of cisplatin when STS was administered simultaneously with cisplatin (Pfeifle et al., 1985). This could be due to the formation of a platinum-thiosulfate complex (Uozumi et al., 1984). However, the effects of STS on the pharmacokinetics of cisplatin have not been thoroughly studied (Campbell et al., 1983; Uozumi et al., 1984; Pfeifle et al., 1985). The most effective timing of subcutaneous (s.c.) administration of

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STS for protection against cisplatin-induced lethal toxicity was reported to be 1 min before intraperitoneal (i.p.) administration of cisplatin (Taniguchi and Baba, 1982), and the intravenous (i.v.) route of STS administration appeared to be superior to the s.c. route for the protection of mice against cisplatin-induced lethal toxicity (Iwamoto et al., 1984). In a preliminary study, cisplatin-induced nephrotoxicity decreased and the cisplatin-induced reduction in life-span was lowered on pretreatment with STS in Wistar rats as reported earlier by other investigators. The results led us to perform the present experiments in an attempt to explain the reasons pharmacokinetically using rabbits as an animal model.

The purpose of this paper is to report the effects of STS on the pharmacokinetics and tissue distribution of total platinum after i.v. administration of cisplatin to rabbits.

20 healthy, male, New Zealand White rabbits (A–T, 1.70–2.10 kg) were anesthetized with 50–100 mg of ketamine (50 mg ml^{-1}, kindly supplied by the Yu-Han Research Center, Kunpo, Korea) via an ear vein. The carotid artery and jugular vein were catheterized with silastic tubing (Dow Coring Inc., Midland, MI) for blood sampling and drug administration, respectively. The cannulas were exteriorized on the dorsal side of the neck where each cannula terminated in a three-way stopcock. The animals were allowed to recover from anesthesia for 4–5 h and fasted during the experiment before the study. Urine samples were collected via a pediatric Foley catheter (Dover Searle Medical Products, U.S.A. Inc., Dallas, TX) which was introduced into the urinary bladder.

Cisplatin (10 mg 20 ml^{-1}, kindly donated by Dong-A Pharmaceutical Co., Seoul, Korea), 5 mg kg^{-1} was administered as an i.v. bolus in 10 s via the jugular vein to rabbits A–E (treatment I). STS, 200 mg kg^{-1} (dissolved in approx. 25 ml of normal saline injectable solution and filtered through a 0.45 μm filter) was infused during a 30 min period using an infusion pump (Microfeeder, Furue Science Co., Japan), and after 1 min, cisplatin, 5 mg kg^{-1} was administered as an i.v. bolus via the jugular vein of rabbits F–J (treatment II). Blood and urine samples were collected for up to 24 h and 0.5 ml of plasma and urine samples were stored in a freezer prior to analysis of total platinum. Blood and urine collection methods were similar to those reported previously (Yoon et al., 1991).

Cisplatin, 5 mg kg^{-1} (diluted with normal saline injectable solution to make 25 ml) was infused over 30 min through the jugular vein of rabbits K–O (treatment III). STS, 200 mg kg^{-1} (dissolved in normal saline injectable solution to make 25 ml) was infused over 30 min and after 1 min, cisplatin, 5 mg kg^{-1} was infused during a 30 min period through the jugular vein of rabbits P–T (treatment IV). At the end of cisplatin infusion, as much blood as possible was collected through the carotid artery and each rabbit was exsanguinated. Approx. 1 g of liver, kidney, heart, lung, small intestine, large intestine, mesentery, rectum, stomach, muscle, fat, brain, spleen or testis was quickly removed, rinsed, minced and homogenized with 4 volumes of normal saline solution using a tissue homogenizer (Tissuemizer, Tekman Co., Model SDT-1810 Cincinnati, OH), and centrifuged immediately. Plasma was also diluted with 4 volumes of normal saline solution. Two 0.5-ml aliquots of diluted plasma or supernatant of each tissue homogenate were stored in the freezer prior to analysis of total platinum.

The concentrations of total platinum in the above biological samples were determined at 214.42 nm with a detection limit of 0.03 ppm using Jobin Yvon 38 Plus Inductively Coupled Plasma Emission Spectroscopy (Jobin-Yvon, Longjumeau Cedex, France). Since total platinum concentrations were measured in this study, they do not represent concentrations of cytotoxic drug only, i.e., non-protein-bound platinum: they correspond to the sum of both the protein-bound and non-protein-bound platinum.

Pharmacokinetic parameters, such as the area under the plasma concentration-time curves from time zero to time infinity (AUC), time averaged total body clearance (CL), area under the first moment of plasma concentration-time curve (AUMC), mean residence time (MRT), terminal half-life ($t_{1/2}$), and apparent volume of distribution at steady-state (V_{ss}) were estimated (Yoon et al., 1991) by the standard method (Gibaldi and Perrier, 1982).

TABLE 1

Some pharmacokinetic parameters of cisplatin (measured as total platinum) after intravenous bolus administration of cisplatin, 5 mg kg^{-1} to rabbits A–E (treatment I) and sodium thiosulfate, 200 mg kg^{4} infusion in 30 min followed by intravenous bolus administration of cisplatin, 5 mg kg^{-1} to rabbits F–J (treatment II)

	Treatment I						Treatment II						p value
Rabbit	A	B	C	D	E	Mean (S.D.)	F	G	H	I	J	Mean (S.D.)	
AUC (μg min ml^{-1})	1470	1080	795	906	789	1010 (284)	1030	540	516	738	751	714 (206)	0.0992
MRT (h)	66.8	70.4	46.0	72.9	69.3	65.1 (10.9)	57.0	31.8	44.3	35.8	16.6	37.1 (15.0)	0.00967
$t_{1/2}$ (h)	49.6	51.6	35.8	54.3	53.0	47.7 (7.61)	45.8	27.2	38.5	29.8	15.5	27.4 (12.4)	0.0139
V_{ss} (l kg^{-1})	9.10	13.0	11.6	16.1	17.5	12.7 (3.48)	11.1	11.8	17.0	9.71	4.41	8.89 (5.08)	0.193
X_u^a (μg)	1740	2680	2990	4410	3740	3110 (1030)	5130	3210	4350	4370	3690	4150 (732)	0.102
CL (ml min^{-1} kg^{-1})	2.27	3.07	4.19	3.68	4.22	3.30 (0.850)	3.24	6.17	6.46	4.52	4.43	4.46 (1.38)	0.0975

[a] Amounts of total platinum excreted in 24 h urine.

The mean values of CL, V_{ss}, and $t_{1/2}$ were calculated by the harmonic mean method (Chiou, 1979). The data were analyzed for statistical significance ($p < 0.05$) using the t-test between two means for unpaired data.

The mean arterial plasma concentration-time profiles of total platinum in treatments I and II are shown in Fig. 1 and the relevant pharmacokinetic parameters are listed in Table 1. The plasma concentrations of total platinum decayed polyexponentially with mean terminal half-lives of 47.7 and 27.4 h for treatments I and II, respectively. Longer terminal half-lives of total platinum, such as 58–73 h (DeConti et al., 1973), and longer than 24 h (Himmelstein et al., 1981) have been reported in human studies without STS treatment. In contrast to total platinum, non-protein-bound platinum (48 min, Belt et al., 1979; 18 min, Himmelstein et al., 1981; 38 min, Pfeifle et al., 1985) or cisplatin itself (70 min, Himmelstein et al., 1981) were reported to have shorter half-lives without STS treatment in humans. Significantly reduced values of $t_{1/2}$ ($p < 0.0139$) and MRT ($p < 0.00967$) in treatment II when compared

TABLE 2

Mean (±S.D.) amounts of cisplatin (measured as total platinum, μg per g tissue) remaining after 30 min infusion of cisplatin, 5 mg kg^{-1} to rabbits K–O (treatment III) and sodium thiosulfate, 200 mg kg^{-1} infusion in 30 min followed by intravenous bolus administration of cisplatin, 5 mg kg^{-1} to rabbits P–T (treatment IV)

	Amounts (μg per g tissue)		Tissue/plasma ratio (T/P)	
	Treatment III	Treatment IV	Treatment III	Treatment IV
Kidney	5.41	7.40 [c]	2.21	1.75 [a]
	(0.589)	(0.988)	(0.751)	(0.253)
Liver	2.29	2.44	0.938	0.575 [b]
	(0.270)	(0.243)	(0.349)	(0.0563)
Large intestine	1.21	1.55	0.497	0.364
	(0.481)	(0.318)	(0.239)	(0.0762)
Small intestine	1.08	0.871	0.442	0.206 [b]
	(0.230)	(0.132)	(0.184)	(0.0379)
Testis	1.02	1.31	0.417	0.310
	(0.205)	(0.211)	(0.2000)	(0.0650)
Lung	1.01	1.37	0.413	0.319
	(0.181)	(0.480)	(0.170)	(0.105)
Rectum	0.995	1.18	0.407	0.273
	(0.375)	(0.342)	(0.263)	(0.0631)
Stomach	0.797	0.890	0.326	0.207 [a]
	(0.264)	(0.285)	(0.104)	(0.0526)
Spleen	0.774	1.03 [c]	0.317	0.243 [a]
	(0.149)	(0.0799)	(0.104)	(0.0196)
Heart	0.642	1.08	0.263	0.254
	(0.0852)	(0.157)	(0.112)	(0.142)
Brain	0.593	0.828	0.243	0.194
	(0.110)	(0.098)	(0.164)	(0.103)
Muscle	0.499	0.629 [c]	0.204	0.148 [a]
	(0.0567)	(0.0487)	(0.0618)	(0.0176)
Mesentery	0.428	0.697 [b]	0.175	0.164
	(0.146)	(0.136)	(0.0732)	(0.354)
Fat	0.0496	0.142 [c]	0.0207	0.0337
	(0.0318)	(0.0160)	(0.0112)	(0.00541)
Plasma	2.44	4.26 [c]	1.000	1.000
	(1.05)	(0.343)		

[a] $p < 0.1$.
[b] $p < 0.05$.
[c] $p < 0.01$.

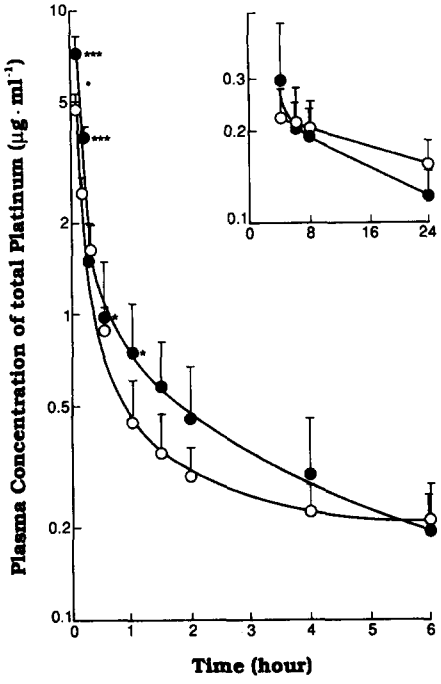

Fig. 1. Mean plasma concentration-time profiles of total platinum after intravenous bolus administration of cisplatin, 5 mg kg^{-1} to rabbits A–E (○), and 30 min infusion of sodium thiosulfate, 200 mg kg^{-1} followed by the intravenous bolus administration of cisplatin, 5 mg kg^{-1} to rabbits F–J (●). The bars represent standard deviations. (Inset) Plasma profiles from 4 to 24 h. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

with treatment I indicate that total platinum resides less and is eliminated rapidly from rabbits on pretreatment with STS. This hypothesis was supported by the approx. 30% decrease ($p < 0.0992$) in AUC, 35% increase ($p < 0.102$) in the amounts of total platinum excreted in 24 h urine (X_u), 43% increase ($p < 0.0975$) in CL and 30% decrease in V_{ss} ($p < 0.193$) on pretreatment with STS. The lack of significance between these values may reflect the limited number ($n = 5$) of rabbits used in the present study. It was also reported that the amounts of total platinum excreted in 24 h urine increased significantly ($p < 0.05$) in STS-treated patients (Hirosawa et al., 1987), and urinary excretion of cisplatin increased immediately after administration of STS to patients (Ikeda et al., 1986).

The amounts of total platinum remaining in each tissue, and tissue to plasma ratios (T/P) in treatments III and IV are listed in Table 2. In treatment III, total platinum was highly concentrated in the kidney as shown by the tissue to plasma (T/P) ratio which was 2.21, while other organs or tissues studied had values of less than unity. Similar results were also reported in rabbit, mouse and human (Lange et al., 1973), and beagle dog (LeRoy et al., 1979). This may explain the development of nephrotoxicity after administration of cisplatin (Balis, 1986; Crom et al., 1987). However, total platinum was less concentrated in brain as shown by the T/P ratio of 0.243 in treatment III. This indicated that the penetration of total platinum into the CNS system is poor, as reported previously (Gormley et al., 1981). It should be noted that the T/P ratios in treatment IV were less than those in treatment III in all the organs or tissues studied except fat. The above results suggested that the affinity of total platinum to the organs or tissues studied decreased on pretreatment with STS as shown by the 43% decrease ($p < 0.193$) in the mean V_{ss} in treatment II when compared with treatment I (Table 1). This could be due to the formation of a cisplatin-thiosulfate complex (Riabchikov, 1941) which is no longer capable of crossing the cell membranes (Loehrer and Einhorn, 1984). The entry of cisplatin into bacterial and cultured mouse tumor cells was also reported (Uozumi et al., 1984) to be prevented by STS due to the formation of a platinum-thiosulfate complex in the extracellular fluid. The complex between cisplatin and STS was reported to be $Pt(S_2O_3)_4^{-6}$ according to platinum coordination chemistry (Basole and Pearson, 1958) and the formation of this complex appeared to be the main cause of inactivation of cisplatin by STS (Howell et al., 1983).

The plasma protein binding of total platinum decreased with increasing concentrations of STS as determined using the equilibrium dialysis method (Table 3); the unbound fraction of total platinum at a fixed cisplatin concentration of 5 $\mu g\ ml^{-1}$ was 0.161 at STS concentrations of 0–10 $\mu g\ ml^{-1}$, however, it was 0.359 at an STS concentration of 100 $\mu g\ ml^{-1}$. The increased unbound fraction of total platinum with increasing concentrations of STS might result in increased amounts of total platinum excreted in 24 h urine (X_u) and

TABLE 3

Plasma protein binding of cisplatin (measured as total platinum) at cisplatin concentration of 5 $\mu g\ ml^{-1}$ with varying concentrations of sodium thiosulfate using the equilibrium dialysis method (n = 2) in rabbits

Concentrations of sodium thiosulfate ($\mu g\ ml^{-1}$)	Concentrations of total platinum in plasma ($\mu g\ ml^{-1}$)	Concentrations of total platinum in phosphate buffer of pH 7.4 ($\mu g\ ml^{-1}$)	Percentage of protein binding
0	2.0080	0.3226	83.9
10	1.9315	0.3104	83.9
20	1.8765	0.3109	83.3
50	1.5435	0.4092	73.4
100	1.5163	0.5435	64.1

the increased value of CL in treatment II (Table 1) when compared with treatment I. The protein binding of cisplatin was also reported to be inhibited by STS (Hayata et al., 1984; Elferink et al., 1986).

In conclusion, the pharmacokinetics of cisplatin measured as total platinum were affected by pretreatment with STS. For example, $t_{1/2}$ and MRT decreased significantly on pretreatment with STS. The values of AUC and V_{ss} tended to decrease, and the amounts of total platinum excreted in 24 h urine (X_u) and CL tended to increase on pretreatment with STS. The above pharmacokinetic data could, at least partly, explain the reduction of cisplatin-induced nephrotoxicity and the increase of life-span after i.v. administration of cisplatin induced by pretreatment with STS. Since the cytotoxic moiety of cisplatin is non-protein-bound platinum, further studies are required in order to measure non-protein-bound platinum concentrations in biological fluids.

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