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Increased therapeutic effect on metastatic liver tumors in rats of two-route chemotherapy using *cis*-diamminedichloroplatinum (II) and its antidote, sodium thiosulfate, with temporary clamping of the abdominal aorta*

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Summary. To improve the therapeutic effects of conventional "two-route chemotherapy" (TRC) comprising *cis*-diamminedichloroplatinum(II) (CDDP) given via the hepatic artery plus simultaneous i.v. sodium thiosulfate (STS) on metastatic liver tumors in rats, we combined TRC with aortic clamping at the supraceliac level. Treatments were evaluated in Wistar-King-Aptekman (WKA) rats bearing metastatic liver tumors 7 days after the inoculation of 10^6 syngenic RBT-1 (transitional-cell carcinoma) cells via the mesenteric vein. When 15 mg/kg CDDP was injected i.a. over 5 min, immediately followed by STS 1,580 mg/kg (200-fold the molar equivalent of 15 mg/kg CDDP) given i.v. over a further 5 min, the antitumor activity, evaluated by the number of tumor nodules present 12 days after treatment, was superior to that of conventional TRC (15 mg/kg i.a. CDDP plus simultaneous administration of 1,580 mg/kg i.v. STS), but the blood urea nitrogen (BUN) level was highly elevated (63.6 mg/dl). With aortic clamping for 7.5 min during CDDP administration and the first half of STS treatment, the TRC consisting of CDDP plus delayed STS (modified TRC) exhibited a further improvement in antitumor activity, with no nephrotoxicity (BUN, 17.1 mg/dl). Although the antitumor activity of 3 or 5 mg/kg i.a. CDDP was also increased by aortic clamping, in animals with normal BUN levels the survival of those treated with modified TRC was greater than that of rodents given 3 mg/kg i.a. CDDP with aortic clamping; however, the former was the same as that of animals given 5 mg/kg i.a. CDDP with aortic clamping whose BUN levels were elevated (31.2 mg/dl). Loss of body weight, the decrease in WBC counts, and changes in the serum transaminase levels in rats given modified TRC were tolerable. The improved therapeutic effect of modified TRC can be explained as follows: during aortic clamping, (a) CDDP delivery to the kidney decreased by 96% and made feasible the delay in STS administration after CDDP without nephrotoxicity, and (b) CDDP retention in the liver was increased by 366%, as aortic clamping decreased the portal blood flow, thereby inhibiting the washout of CDDP from the liver.

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Abbreviations used: TRC, two-route chemotherapy; CDDP, *cis*-diamminedichloroplatinum(II); STS, sodium thiosulfate; i.a., intra-arterial; BUN, blood urea nitrogen; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; WBC, white blood cell

Introduction

Intra-arterial infusions of anticancer drug have been widely used for the treatment of regionally confined malignant tumors ever since Klopp et al. [18] reported their efficacy in human head and neck cancer. However, the dose of drug to be given locally is limited because of the related general toxicity. We designed a "two-route chemotherapy" (TRC) in which a large amount of an anticancer drug is given locally at the tumor site in combination with the systemic administration of its antidote, the objective being to diminish the related side effects [3, 26].

CDDP [*cis*-diamminedichloroplatinum(II)] is a potent anticancer drug in a variety of human cancers, but side effects such as nausea, vomiting, and, particularly, nephrotoxicity limit the dose that can be given [20, 39]. Attempts have been made to reduce its toxicity [2, 5, 24, 29], and sodium thiosulfate (STS) has proved to be an effective antidote [11, 13]. We previously reported that the effectiveness of TRC using CDDP plus STS in metastatic liver tumors [37, 38], urinary bladder tumors [32], i.p. disseminated tumors [15, 35], metastatic lung tumors [14], and limb tumors [16] was evident in laboratory animals. In most cases, however, STS had to be given simultaneously with CDDP to afford such protection.

In the conventional TRC for metastatic liver tumors in rats, consisting of CDDP given via the hepatic artery plus simultaneous i.v. STS [38], we found that the antitumor

activity of CDDP in both small tumor nodules (diameter, <0.8 mm) and the peripheral portions of larger tumor nodules (diameter, >0.8 mm), in which the blood supply via the hepatic artery was not necessarily predominant, was reduced by the influx of STS through the portal vein. In addition to this inactivation of CDDP by STS, the washout of CDDP from the tumor site via the portal blood flow may be another factor linked to the observed reduction in the antitumor activity of CDDP.

Using systemic administration of both CDDP and STS for treatment of metastatic lung tumors in rats, we noted that the delayed administration of STS after CDDP with no nephrotoxicity was made feasible by clamping of the aorta, a procedure that led to a decrease in CDDP delivery to the kidney [14]. To improve the therapeutic effect of TRC for metastatic liver tumors, we combined it with clamping of the abdominal aorta for 7.5 min at the supraceliac level and assessed whether or not (a) STS administration could be delayed after i.a. CDDP without nephrotoxicity; (b) the antitumor activity of CDDP with STS against metastatic liver tumors would be increased with delayed administration of STS; and (c) aortic clamping at the supraceliac level would lead to a decrease in blood flow through the celiac and superior and inferior mesenteric arteries and, consequently, to a decrease in the portal blood flow. In the latter case, the antitumor effect produced by CDDP is further improved because the washout of CDDP from the tumor site by the portal blood flow is prevented.

We report the superior therapeutic efficacy of modified TRC for metastatic liver tumors in rats, comprising CDDP plus delayed STS given in combination with 7.5-min clamping of the abdominal aorta, as compared with the efficacy of both conventional TRC and treatment with i.a. CDDP alone, with or without aortic clamping.

Materials and methods

Animals. Female Wistar-King-Aptekman (WKA) rats were obtained from the Animal Center of Kyushu University and fed a standard diet and tap water ad libitum. Rats weighing 160–220 g at 9–11 weeks of age were used for experiments.

Tumor. A syngeneic transitional-cell carcinoma of the bladder (RBT-1) induced in WKA rats with *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine [8] was maintained by serial transplantation into the hind limb of WKA rats every 7–14 days. The tumor was excised, minced, suspended in Hanks' balanced salt solution (Nissui Seiyaku Co., Tokyo, Japan), and passed through a metal sieve to yield a single-cell suspension. After a trypan blue dye-exclusion test, 10^6 viable tumor cells were inoculated via the mesenteric vein into the liver.

Chemicals. All drugs were dissolved in 0.9% NaCl solution. CDDP (Nippon Kayaku Co. Ltd., Tokyo, Japan) was used after dilution to desired concentrations. STS (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was dissolved to a concentration of 79 mg/ml. Each solution was prepared just before use.

Chemotherapy experiments. Chemotherapy experiments were carried out 7 days after the tumor inoculation, when visible metastatic tumor nodules 0.5–1.0 mm in diameter appeared on the surface of the liver. All rats were anesthetized with 15 mg/kg i.p. sodium pentobarbital and laparotomized through a midline incision. Intrahepatic injections of CDDP were given through a fine, tapered polyethylene catheter inserted into the hepatic artery under an operation microscope (Konan Camera, R&I, K-280: Nishinomiya, Japan).

In the modified TRC group, the abdominal aorta was occluded by a noncrushing clamp at a point between the diaphragma and the celiac artery. Immediately after the occlusion, 15 mg/kg CDDP solution (2 × LD_{50} in rats) was injected i.a. in a volume of 3 ml/200-g rat over 5 min through the catheter. After CDDP injection, the catheter was removed and the hepatic artery was ligated to avoid bleeding. In all, 1,580 mg/kg STS solution (200-fold the molar equivalent of 15 mg/kg CDDP) was given in a volume of 4 ml/200-g rat over 5 min via the left femoral vein immediately after termination of the CDDP injection. After half of the volume of the STS solution had been injected, the aortic clamp was released such that the drugs would circulate systemically. As controls for modified TRC, rats were injected with 15 mg/kg CDDP via the hepatic artery over 5 min without aortic clamping and 1,580 mg/kg STS was given i.v. over 5 min simultaneously with (conventional TRC) or immediately after CDDP injection.

To compare the therapeutic effects of modified TRC with those of i.a. CDDP alone, 3 or 5 mg/kg CDDP was injected i.a., with or without aortic clamping, in a volume of 3 ml/200-g rat over 5 min; 0.9% NaCl solution was given i.v. in a volume of 4 ml/200-g rat over 5 min immediately after termination of the CDDP injection. The clamp was released after half of the volume of 0.9% NaCl solution had been injected. In addition to the above-mentioned groups, an untreated control group and a group with a ligated hepatic artery were added.

Evaluation of antitumor effects and side effects. Antitumor effects were evaluated by the number of tumor nodules on the surface of the liver on day 12 after each treatment, when a few rats in the groups given conventional TRC or 3 mg/kg i.a. CDDP without aortic clamping died of tumors. Only rats given no treatment or those subjected to ligation of the hepatic artery alone were killed on day 7, because animals in these two groups died at about this time. In another experiment, the survival of rats in various groups was recorded.

Side effects were evaluated by changes in body weight, BUN level, WBC count, and serum GOT and GPT levels. Rats were weighed on days 4, 8, and 12 after treatment to assess general toxicity. BUN levels in blood samples taken from the tail vein were measured on day 4 using the urease technique [7] as an index of nephrotoxicity. To determine possible hematological disorders, leukocytes in the peripheral blood from the tail vein were counted on days 4 and 8 after treatment. Serum GOT and GPT levels in blood samples taken from the tail vein were measured on day 4 using the transaminase C II test (Wako Pure Chemical Industries Ltd., Osaka, Japan) as an index of hepatic dysfunction.

Monitoring changes in blood pressure and hepatic and renal blood flow during modified TRC. Blood pressure was monitored throughout the administration of modified TRC. Mean arterial blood pressure was recorded using a transducer (P23 ID; Gould Statham Instruments Inc., USA) through a polyethylene catheter inserted into the right carotid artery of non-tumor-bearing WKA rats. Changes in both hepatic and renal blood flow were monitored during modified TRC by a temperature-controlled thermoelectrical method [34] using a temperature-controlled thermoelectric flowmeter (UMW-101; Unique Medical Co. Ltd., Tokyo, Japan). The probe of the flowmeter was placed in the liver and kidney of non-tumor-bearing WKA rats, and changes in hepatic and renal blood flow were measured. As a control for modified TRC, changes in blood pressure and hepatic and renal blood flow were monitored in rats given 15 mg/kg i.a. CDDP over 5 min plus delayed administration of 1,580 mg/kg i.v. STS over 5 min without aortic clamping.

Platinum distribution in various organs. To assess the influence of aortic clamping on CDDP delivery to various organs during i.a. injection of the drug, 15 mg/kg CDDP was given via the hepatic artery of non-tumor-bearing rats in a volume of 3 ml/200-g rat over 5 min, with or without aortic clamping. Immediately after termination of the CDDP injection, the rats were killed and the livers, left kidneys, lungs, small intestines, and brains were excised. The platinum concentration in these tissues was estimated by flameless atomic absorption spectrophotometry [4].

Results

Antitumor activity and nephrotoxicity after TRC

Table 1 shows the number of tumor nodules and BUN levels after various TRC with or without aortic clamping. The number of nodules in rats given i.a. CDDP plus delayed i.v. STS (group D) was significantly smaller than that in rats given conventional TRC (group C), but the BUN level was highly elevated (63.6 mg/dl). The number of nodules seen in the group treated with i.a. CDDP plus delayed i.v. STS with aortic clamping (group E, modified TRC) was further decreased, with no incidence of nephrotoxicity. Ligation of the hepatic artery alone led to no increase in antitumor activity as compared with findings in the untreated control group. Figure 1 shows an illustration of the livers observed in groups C–E.

Table 2 shows the number of tumor nodules and BUN levels after i.a. CDDP alone, with or without aortic clamping, and after modified TRC. The antitumor activity of 3 or 5 mg/kg i.a. CDDP was significantly increased by a combination with aortic clamping. In rats with normal BUN levels, modified TRC showed greater antitumor activity than did 3 mg/kg i.a. CDDP plus aortic clamping. Although there were no significant differences in the number of tumor nodules between the group undergoing modified TRC and that receiving 5 mg/kg i.a. CDDP plus aortic clamping, the BUN level seen in the latter group was significantly higher than that in the former group.

As shown in Table 3, the survival of groups given modified TRC or 5 mg/kg i.a. CDDP plus aortic clamping lasted longer than that of groups given conventional TRC or 3 mg/kg i.a. CDDP plus aortic clamping. There were no significant differences in survival between the group undergoing modified TRC and that receiving 5 mg/kg i.a. CDDP plus aortic clamping. Ligation of the hepatic artery alone led to little increase in survival as compared with untreated control values.

Table 1. Number of tumor nodules and BUN levels in rats given various TRC with or without aortic clamping

Treatment[a]	Number of nodules[b] (mean ± SE)	BUN (mg/dl)[c] (mean ± SE)
A Untreated control	>200	19.4+1.0
B Ligation of the hepatic artery alone	>200	20.3 ± 2.3
C CDDP (15 mg/kg i.a.) + simultaneous STS (1,580 mg/kg i.v.)	127 ± 10	20.8 ± 0.6
D CDDP (15 mg/kg i.a.) + delayed STS (1,580 mg/kg i.v.)	71 ± 11	63.6 ± 11.2
E CDDP (15 mg/kg i.a.) + delayed STS (1,580 mg/kg i.v.) with aortic clamping	9 ± 3	17.1 ± 0.6

[a] Treatment was given 7 days after the inoculation of 10^6 viable RBT-1 tumor cells. CDDP (15 mg/kg) was injected via the hepatic artery over 5 min and STS (1,580 mg/kg) was given i.v. over 5 min simultaneously with or immediately after CDDP injection. Aortic clamping was combined in group E only. Each group comprised 8 rats

[b] The numbers of tumor nodules of rats in groups C–E were counted on day 12 after treatment and those in groups A and B, on day 7. Probability of the number of nodules was calculated by Student's *t*-test: C vs D, $P < 0.05$; E vs D, $P < 0.01$

[c] BUN levels were measured on day 4. Probability was calculated by Student's *t*-test: C vs D, $P < 0.01$; D vs E, $P < 0.01$

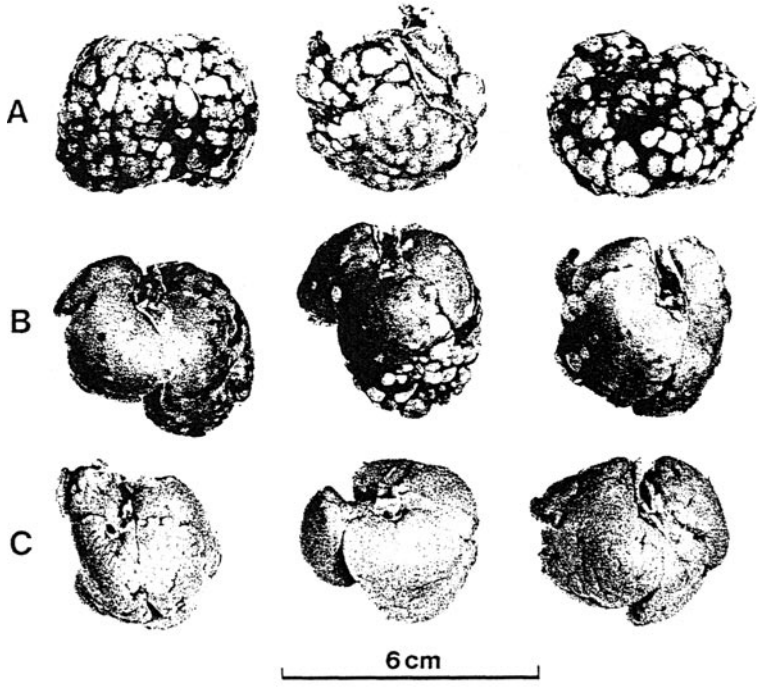

Fig. 1 A–C. Inhibition of tumor growth by various TRC given in Table 1. The livers were excised 12 days after each treatment. **A** Group C. **B** Group D. **C** Group E

Table 2. Number of tumor nodules and BUN levels in rats given various CDDP treatments with or without aortic clamping

Treatment[a]	Number of nodules[b] (mean ± SE)	BUN (mg/dl)[c] (mean ± SE)
A Untreated control	>200	21.2 ± 1.1
B CDDP (3 mg/kg i.a.) + 0.9% NaCl (i.v.)	>200	24.3 ± 1.4
C CDDP (3 mg/kg i.a.) + 0.9% NaCl (i.v.) with aortic clamping	87 ± 10	20.7 ± 1.0
D CDDP (5 mg/kg i.a.) + 0.9% NaCl (i.v.)	108 ± 13	47.1 ± 6.3
E CDDP (5 mg/kg i.a.) + 0.9% NaCl (i.v.) with aortic clamping	9 ± 4	31.2 ± 3.2
F CDDP (15 nmg/kg i.a.) + delayed STS (1,580 mg/kg i.v.) with aortic clamping	7 ± 3	19.7 ± 1.0

[a] Treatment was given 7 days after the inoculation of 10^6 viable RBT-1 tumor cells. In groups B–E, CDDP at a dose of 3 or 5 mg/kg was injected via the hepatic artery over 5 min with or without aortic clamping, followed by 0.9% NaCl given i.v. over 5 min. The modified TRC (group F) was carried out as in Table 1. Each group comprised 8 rats

[b] The numbers of tumor nodules of rats in groups B–F were counted on day 12 after treatment and that in group A, on day 7. Probability was calculated by Student's *t*-test: C vs B, $P < 0.05$; E vs D, $P < 0.01$; F vs C, $P < 0.01$; F vs E, not significant

[c] BUN levels were measured on day 4. Probability was calculated by Student's *t*-test: F vs E, $P < 0.05$

Table 3. Survival of rats given various CDDP treatments

Treatment[a]	Survival days: Range	Median	% ILS[b]
A Untreated control	12–14	13.5	–
B Ligation of the hepatic artery alone	13–15	14.0	4
C CDDP (3 mg/kg i.a.) + 0.9% NaCl (i.v.) with aortic clamping	19–27	23.5	74
D CDDP (5 mg/kg i.a.) + 0.9% NaCl (i.v.) with aortic clamping	24–34	29.0	115
E CDDP (15 mg/kg i.a.) + simultaneous STS (1,580 mg/kg i.v.)	17–23	19.5	44
F CDDP (15 mg/kg i.a.) + delayed STS (1,580 mg/kg i.v.) with aortic clamping	25–39	28.5	111

[a] Treatment was carried out as in Tables 1 and 2. Each group comprised 8 rats

[b] % ILS = 100 (t/c-1), where t is the median survival day of the treatment group and c is the median survival day of the untreated control group. Probability was calculated by means of the generalized Wilcoxon test: A vs B, not significant; F vs C and E, $P < 0.05$; F vs D, not significant

Table 4. WBC counts and serum transaminase levels in rats given various CDDP treatments

Treatment[a]	Number of WBC[b] (mean ± SE)		Serum transaminases (Karmen unit)[c] (mean ± SE)	
	Day 4	Day 8	GOT	GPT
Untreated control	7,961 ± 697	–[d]	131 ± 14	16 ± 3
CDDP (3 mg/kg i.a.) + 0.9% NaCl (i.v.) with aortic clamping	7,490 ± 502	8,174 ± 877	71 ± 3	12 ± 1
CDDP (5 mg/kg i.a.) + 0.9% NaCl (i.v.) with aortic clamping	5,649 ± 639	7,548 ± 514	80 ± 6	13 ± 3
CDDP (15 mg/kg i.a.) + simultaneous STS (1,580 mg/kg i.v.)	6,900 ± 460	8,582 ± 384	91 ± 12	14 ± 2
CDDP (15 mg/kg i.a.) + delayed STS (1,580 mg/kg i.v.) with aortic clamping	5,617 ± 419	7,475 ± 239	88 ± 5	13 ± 2

[a] Treatment was carried out as in Tables 1 and 2. Each group comprised 8 rats

[b] WBC were counted on days 4 and 8 after treatment

[c] GOT and GPT levels were measured on day 4. GOT and GPT values in the serum of non-tumor-bearing WKA rats were 66 ± 2 and 10 ± 2 units, respectively

[d] All rats died within 7 days

Other side effects

Table 4 shows WBC counts and serum transaminase levels in rats given various CDDP treatments. On day 4, the number of WBC in rats given 5 mg/kg/i.a. CDDP plus aortic clamping or modified TRC was slightly decreased, but these values reverted to normal on day 8. There were slight elevations in serum transaminases in each group on day 4 as compared with findings in the non-tumor-bearing WKA rats; the elevations in the untreated control group were higher than in any other group, possibly as a result of progressive disease. Figure 2 shows changes in body weight after treatment. On day 4, weight loss amounted to <10% in all treated groups except the one (12%) receiving 5 mg/kg i.a. CDDP plus aortic clamping. On day 8, the body weight of rats in all groups was much the same as the initial values.

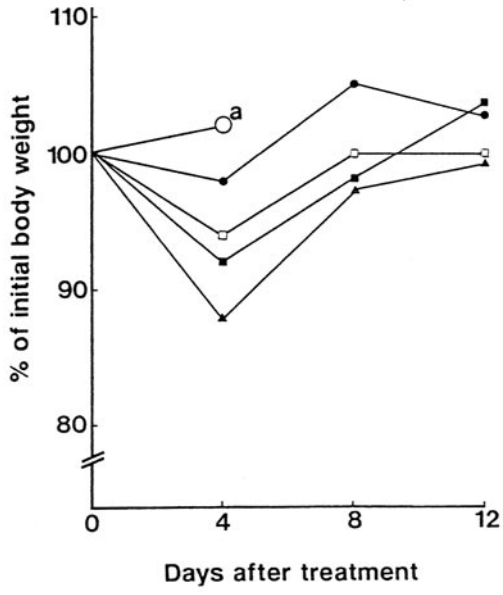

Fig. 2. Changes in the average body weight of rats after various CDDP treatments. ○, untreated control; ●, CDDP (15 mg/kg i.a.) plus simultaneous STS (1,580 mg/kg i.v.); □, CDDP (3 mg/kg i.a.) with aortic clamping; ■, CDDP (15 mg/kg i.a.) plus delayed STS (1,580 mg/kg i.v.) with aortic clamping; ▲, CDDP (5 mg/kg i.a.) with aortic clamping. Each group comprised 8 rats. *a*, All rats died within 7 days

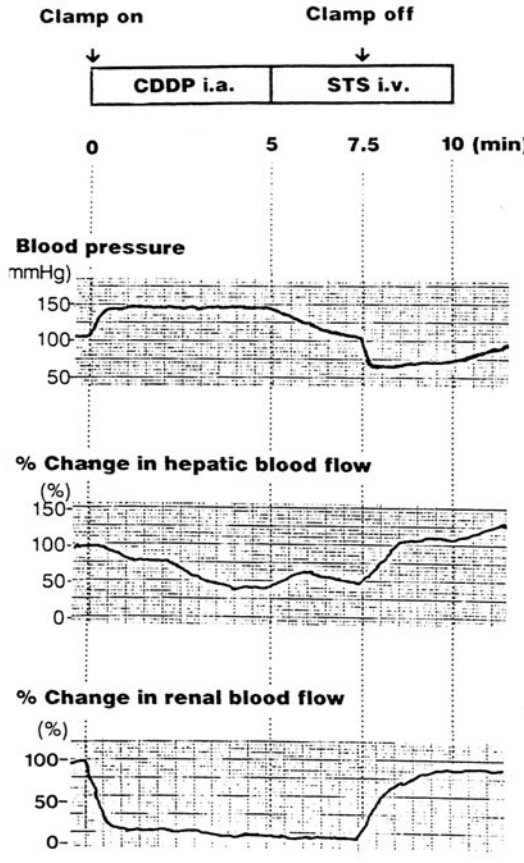

Fig. 3. Monitorings of changes in blood pressure and hepatic and renal blood flow during modified TRC

Table 5. Influence of aortic clamping on CDDP delivery to various organs immediately after intrahepatic CDDP injection

Treatment[a]	Platinum content (μg/g wet tissue) (mean ± SE):				
	Liver	Kidney	Small intestine	Lung	Brain
A CDDP (15 mg/kg i.a.)	16.2 ± 1.5	72.5 ± 5.4	16.5 ± 0.6	18.0 ± 0.6	1.5 ± 0.4
B CDDP (15 mg/kg i.a.) with aortic clamping	59.3 ± 9.1	3.1 ± 0.7	2.1 ± 0.4	31.7 ± 2.3	3.6 ± 0.9

[a] CDDP (15 mg/kg) was injected via the hepatic artery over 5 min with or without aortic clamping. Each group comprised 6 rats. Probability was calculated by Student's *t*-test. Liver: A vs B, $P < 0.01$. Kidney A vs B, $P < 0.01$

Changes in blood pressure and hepatic and renal blood flow during modified TRC

As shown in Fig. 3, blood pressure increased from 105 to 150 mm Hg immediately after the initiation of i.a. CDDP plus aortic clamping and remained at about 150 mm Hg for 5 min. With STS administration following CDDP, blood pressure gradually decreased to 105 mm Hg and immediately dropped to 70 mm Hg on release of the clamp; about 4 min after the release, blood pressure returned to the normal level. Fluctuations in blood pressure were never observed in rats given i.a. CDDP plus delayed i.v. STS without aortic clamping (data not shown). Hepatic blood flow gradually decreased to 40% of the initial level during i.a. CDDP plus aortic clamping; after release of the clamp, it reverted to the initial level within 1 min. Renal blood flow rapidly decreased by 93% after the initiation of i.a. CDDP plus aortic clamping and remained at that level until the clamp was released, at which point it reverted to the initial level within 2 min. Changes in hepatic and renal blood flow were not observed in rats given CDDP plus delayed STS without aortic clamping (data not shown).

Platinum distribution in various organs

Table 5 shows the influence of aortic clamping on CDDP delivery to various organs during intrahepatic CDDP injections. Platinum concentrations in the livers and lungs of rats given i.a. CDDP with aortic clamping increased by 366% and 176%, respectively, as compared with findings in rats given i.a. CDDP alone. On the other hand, platinum concentrations in the kidneys and small intestines of rats in the former group decreased by 96% and 87%, respectively, as compared with findings in the latter group.

Discussion

The therapeutic effects of modified TRC combined with aortic clamping on rat metastatic liver tumors were superior to those of both conventional TRC and i.a. CDDP with aortic clamping, which can be explained as follows. First, i.a. CDDP delivery to the liver was increased by 366% when drug administration was combined with aortic clamping at the supraceliac level (Table 5). The clamping led to a decrease in blood flow through the celiac and superior and inferior mesenteric arteries and, consequently, to a decrease in blood flow to the liver, which is mainly supplied by the portal vein (Fig. 3). The retention of CDDP in the liver was elevated, probably because the washout of CDDP by the portal blood flow was prevented. Second, aortic clamping made feasible a delay in the administration of STS after i.a. CDDP without nephrotoxicity, because CDDP delivery to the kidney was decreased by 96% during the clamping (Table 5). Without aortic clamping, the BUN level was elevated (63.6 mg/dl) in rats given 15 mg/kg i.a. CDDP plus delayed administration of 1,580 mg/kg STS, whereas that (17.1 mg/dl) seen in rats given CDDP followed by STS in combination with aortic clamping was at a normal level (Table 1). Thus, aortic clamping can protect the kidney from CDDP-induced toxicity when STS administration is delayed after a high dose of the drug. Finally, the antitumor activity of CDDP plus STS against metastatic tumor nodules was enhanced by delayed STS administration (Table 1), which enabled the active CDDP to remain longer at the tumor site before being inactivated by STS.

We previously reported the efficacy of TRC combined with angiotensin II-induced hypertension, by which delayed STS administration was feasible and CDDP delivery to the tumors was increased [9, 19, 21]. Angiotensin II decreases renal blood flow [30, 36] and selectively increases tumor blood flow [33]. Using TRC with angiotensin II in metastatic liver tumors, we found a tendency toward an increase in antitumor activity as evaluated by the number of tumor nodules, with no incidence of nephrotoxicity. However, the survival obtained was not significantly longer than that of rats on conventional TRC (data not shown). In animals with normal BUN levels, those modified TRC with aortic clamping survived longer than did those treated with either conventional TRC or i.a. CDDP with aortic clamping.

The protective effect of STS against CDDP-induced nephrotoxicity is attributed to the direct reaction of STS with CDDP in the blood circulation [17]. The reaction forms an inactive complex, $Pt[(S_2O_3)_4]^{6-}$ [31], which is rapidly excreted through the urinary system. The diuretic action of STS may be also related to a reduction in nephrotoxicity [25].

In the present study, the hepatic artery was ligated to prevent inactivation of CDDP by the influx of STS at the tumor site and/or to prevent the flushout of CDDP by the arterial blood flow. However, ligation of the hepatic artery was done in all of the treated groups; thus differences in the antitumor activity seen in various treatment groups can be validly compared. Ligation of the hepatic artery alone afforded little antitumor efficacy as compared with untreated control values (Tables 1, 3).

Combination chemotherapy using CDDP plus STS is prescribed for patients with liver cancer [1, 27, 28] as well as for those with malignant lesions in other organs [12, 23, 40]. Clamping of the aorta for 10 min at the supraceliac level causes few complications in rats [22] or human [6]. Our modified TRC with aortic clamping for the treatment of metastatic liver tumors shows promise for clinical application.

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