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Effects of sodium thiosulfate in combination therapy of *cis*-dichlorodiammineplatinum and vindesine

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Summary. The effects of sodium thiosulfate (STS) were studied in patients who received a combination therapy of *cis*-dichlorodiammineplatinum (CDDP) and vindesine. In this study, 61 patients with non-small-cell lung carcinoma were randomized to receive either CDDP and vindesine (both given i.v.) with i.v. STS [30 patients, STS(+) group] or CDDP and vindesine without STS [31 patients, STS(−) group]. In the STS(+) group, 16 patients who showed an improvement (reduction in tumor size or relief of symptoms) after the first course received the second STS(+) treatment, and 15 patients in the STS(−) group who showed an improvement after the first course received the second STS(−) treatment. Urinary levels of β_2-microglobulin (BMG) and *N*-acetyl-β-D-glucosaminidase (NAG) were measured as an index of proximal tubular function. Analysis of both levels indicated that STS suppressed CDDP nephrotoxicity to a minimal level. Serum BMG, blood urea nitrogen (BUN), and total as well as 24-h creatinine clearance levels were measured as an index of glomerular function. There were no significant differences in these levels between the STS(+) and STS(−) groups. The urinary recoveries of total platinum 24 h after CDDP administration were 29% and 21% in the STS(+) and STS(−) groups, respectively. The mean plasma concentrations of total platinum at 24 h after CDDP administration were 2.24 and 2.70 μg/ml in the STS(+) and STS(−) groups, respectively. There were no significant differences in the response rates of the STS(+) and STS(−) groups at a fixed dose of 100 mg/m^2 CDDP. Therefore, the present study clearly demonstrates that systemic administration of STS reduces the side effects of CDDP to a minimal level without impairing its antitumor activity and that STS treatment is applicable in a repeated chemotherapy using CDDP alone or in combination with other antitumor agents.

Introduction

A number of studies have revealed the excellent antitumor effects of *cis*-dichlorodiammineplatinum (CDDP) on various tumors. However, nephrotoxicity is the dose-limiting toxicity in the clinical use of this agent either alone or in combination with other antitumor drugs. A number of antidotes such as sodium thiosulfate (STS) [4], WR-2721 [9], thiourea, diethyldithiocarbamate [2], and bismuth subnitrate have been tested to reduce the nephrotoxicity of CDDP. One notable method previously reported by Baba et al. [1] and Pfeifle et al. [7] involves the i.v. administration of STS to prevent the nephrotoxicity of CDDP given locally. Since STS has been proven clinically effective in reducing such side effects, we initiated a study of STS in patients with advanced non-small-cell lung carcinoma who were given a combination of CDDP and vindesine systemically. The usual doses and dosing schedule for vindesine were used, which ensured that the renal side effects of vindesine would be minimized [3].

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Materials and methods

Patients. From December 1985 to December 1987, 61 patients with histologically confirmed non-small-cell lung carcinoma (adenocarcinoma, 38 cases; squamous cell carcinoma, 20 cases; large-cell carcinoma, 3 cases) were enrolled in the study (Table 1). These patients fulfilled the following eligibility requirements: age <80 years, creatinine clearance of >60 ml/min, serum creatinine level of <1.5 μg/dl, and an Eastern Cooperative Oncology Group (ECOG) performance status of $\leqq 3$. Entry in the study also required that patients have either bidimensionally measurable indicator lesions or visible, evaluable lesions on physical examination by chest X-ray or computerized axial tomography (CAT) scans. None of the patients had previously received chemotherapy.

Clinical protocols. The patients were randomly allocated into two groups by block randomization using sealed cards: 30 patients received STS in combination chemotherapy with CDDP and vindesine [STS(+) group], and 31 patients received only chemotherapy [STS(−) group]. In the STS(−) group, 1500 ml saline was infused over 4.5 h, and 100 mg/m^2 CDDP (Nippon Kayaku Co. Ltd., Tokyo, Japan) was then given as a 0.5 mg/ml solution in 0.9% sodium chloride over 1 h, followed by 300 ml mannitol (200 mg/ml solution in distilled water) plus 1500 ml saline by infusion over 4.5 h. In the STS(+) group, a total dose of STS (100 mg/ml solution in distilled water) at 400-fold that of CDDP on a molar basis was given i.v. in three separate doses at 5, 35, and 65 min after the completion of CDDP administration. The chemotherapy protocol in both groups were as follows: 100 mg/m^2 CDDP on day 1 along with vindesine (1 mg/ml in distilled water) at a dose of

Table 1. Patient characteristics

	STS (+)	STS (−)
Number of patients	30	31
Sex: male/female	24/6	24/7
Age: Mean	62	60
(range)	(39–74)	(39–79)
Histology		
Adenocarcinoma	18	20
Squamous cell carcinoma	11	9
Large-cell carcinoma	1	2
Performance status		
0	2	3
1	19	19
2	9	8
3	0	1
CDDP + vindesine therapy		
1 course	14	16
2 courses	16	15
Evaluable cases	30	31
Response		
CR	0	0
PR	6	7
MR	6	3
NC	15	19
PD	3	2

CR, complete response; PR, partial response; MR, minor response; NC, no charge; PD, progressive disease

3 mg/m^2 on days 1, 8, and 15. The patients who underwent a reduction in tumor size more than a minor response (defined as ≧25% reduction of all indicator lesions according to WHO criteria) and/or an improvement in symptoms after the first course of chemotherapy received the second course at 4 or 5 weeks after the initial administration of CDDP. Of 30 patients in the STS(+) group, 14 patients received 1 course and 16 underwent 2 courses of chemotherapy, whereas 16 patients in the STS(−) group received 1 course and 15 underwent 2 courses of chemotherapy. In this study, antibiotics belonging to the aminoglycosides, which could have affected renal function, were not used.

Determination of plasma and urinary platinum levels. Blood samples were collected into ice-cold heparinized tubes at 0, 5, and 30 min and at 1, 2, 4, 8, and 24 h after the completion of CDDP administration and centrifuged immediately at 4° C. The plasma samples were stored at −20° C. The total platinum concentrations in plasma (free, protein-bound, and STS-bound) were determined by atomic absorption spectrometry at 265.9 nm (Hitachi-Zeaman, Model 170-70). Urine samples were collected at 1, 2, 4, 8, and 24 h after the completion of CDDP administration and stored at −20° C. The total platinum concentrations in urine were also measured by atomic absorption spectrometry.

Renal function tests. For tubular function, urinary levels of β_2-microglobulin (BMG) and *N*-acetyl-β-D-glucosaminidase (NAG) were measured on days 3, 7, 14, 21, and 28. Serum levels of magnesium were measured on days 7, 14, 21, and 28. For glomerular function, serum levels of BUN, creatinine, and BMG were measured on the same days as urinary BMG levels, and 24-h creatinine clearance levels were measured on the same days as magnesium levels.

Results

Plasma platinum level

Figure 1 indicates the plasma platinum elimination curve after i.v. administration of CDDP. The mean total platinum concentrations in plasma measured 8 h after CDDP administration were 2.83 μg/ml (SD = 0.45) in the STS(+) group and 3.13 μg/ml (SD = 0.50) in the STS(−) group; those measured after 24 h were 2.24 μg/ml (SD = 0.40) and 2.70 μg/ml (SD = 0.41), respectively. The difference in total platinum levels between the STS(+) and STS(−) groups was significant ($P < 0.05$; Student's *t*-test), indicating that STS is effective in reducing total platinum levels.

Urinary recovery of platinum

Figure 2 indicates the urinary recovery of total platinum after i.v. administration of CDDP. The accumulated uri-

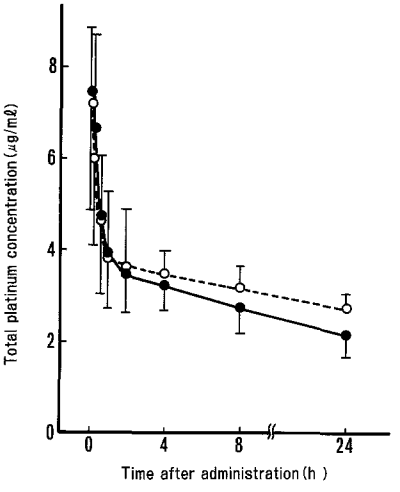

Fig. 1. Plasma concentration for total platinum in patients after administration of CDDP. ●, STS(+) group (n = 11); ○, STS(−) group (n = 10). Data represent the means ± SD. Time 0, end of infusion

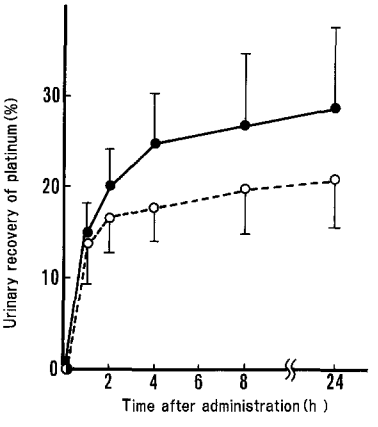

Fig. 2. Accumulated urinary recovery of total platinum after administration of CDDP. ●, STS(+) group (n = 10); ○, STS(−) group (n = 9). Data represent the means ± SD. Time 0, end of infusion

nary recoveries in the STS(+) group at 0–8 and 0–24 h were 27% (SD = 11.0) and 29% (SD = 12.0), respectively, whereas those for the STS(−) group were 20% (SD = 5.6) and 21% (SD = 5.8), respectively. The difference in urinary recovery rates between the two groups was significant ($P < 0.05$; Student's *t*-test). The mean 24-h urinary volume on the day of CDDP administration was 4,740 ml (SD = 680) in the STS(+) group, which was significantly higher than the 4020 ml (SD = 460) determined in the STS(−) group ($P < 0.05$; Student's *t*-test). The mean total platinum levels in urine calculated as a 24-h average were 10.4 μg/ml (SD = 2.1) and 8.9 μg/ml (SD = 2.2) in the STS(+) and STS(−) groups, respectively.

Renal function test

Urinary BMG. During the first course, the mean urinary BMG levels remained approximately within the normal range in the STS(+) group, with a peak of 104 μg/l (SD = 42) on day 3 after CDDP administration (normal range, 0–254 μg/l) (Fig. 3), whereas those in the STS(−) group were significantly higher: 495 μg/l (SD = 110) on day 3 and 111 μg/l (SD = 71) on day 28 ($P < 0.05$; Student's *t*-test). During the second course, the mean urinary BMG levels increased on day 3 to 380 μg/l (SD = 209) and 1317 μg/l (SD = 700) in the STS(+) and STS(−) groups, respectively. However, the levels in the STS(+) group declined on day 7 to a normal level.

Urinary NAG index (urinary NAG/urinary creatinine = IU/g). Figure 4 shows the changes in the urinary NAG index after CDDP administration. In the STS(+) group, the mean NAG index remained within a normal range during both the first and second courses of chemotherapy (normal range, 1.6–15.0 IU/g), whereas in the STS(−) group, the mean NAG index increased rapidly to an abnormally high level and did not decline to a normal level for up to 14 days into the first and second courses of chemotherapy. The difference in NAG indexes between the STS(+) and STS(−) groups was significant ($P < 0.05$; Student's *t*-test), indicating that STS is effective in protecting against CDDP toxicity.

Serum Mg. No significant change in mean serum magnesium levels were observed between the STS(+) and STS(−) groups.

24-h creatinine clearance. During the first course, the mean 24-h creatinine clearance were reduced on day 7 by a maximum of 26% (SD = 20) in the STS(+) group and by a maximum of 36% (SD = 30) in the STS(−) group. There was no significant difference observed between the two groups at any time during or after the second course of chemotherapy.

Serum creatinine. No remarkable changes in serum creatinine levels were observed in the STS(+) group during the first and second courses. In the STS(−) group, the mean serum creatinine levels increased slightly on day 7 to 1.4 mg/dl (SD = 0.4) and 1.5 mg/dl (SD = 0.4) in the first and second courses, respectively.

Serum BUN. The serum BUN levels in both groups increased to a transient peak on day 7 and declined to normal thereafter.

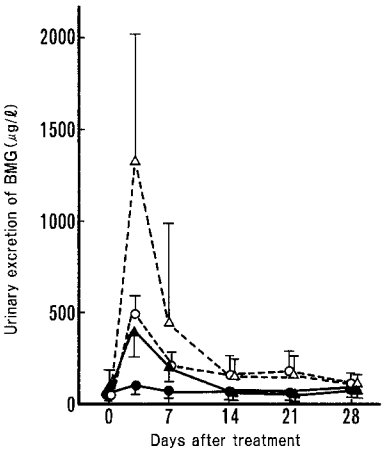

Fig. 3. Effect of STS on urinary excretion of BMG. ●, STS(+) group, 1st course ($n = 30$); ▲, STS(+) group, 2nd course ($n = 16$); ○, STS(−) group, 1st course ($n = 31$); △, STS(−) group, 2nd course ($n = 15$). Data represent the means ± SD

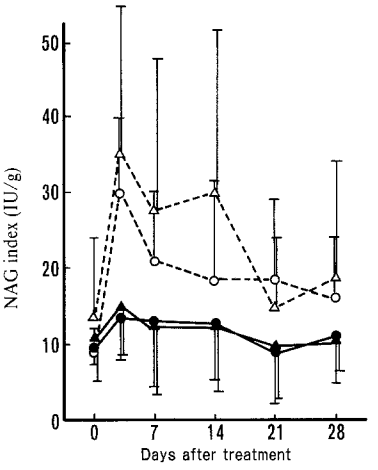

Fig. 4. Effect of STS on urinary NAG index. ●, STS(+) group, 1st course ($n = 30$); ▲, STS(+) group, 2nd course ($n = 16$); ○, STS(−) group, 1st course ($n = 31$); △, STS(−) group, 2nd course ($n = 15$). Data represent the means ± SD

Antitumor effects. There was essentially no difference in the response rates between the two groups. Of 30 evaluable patients in the STS(+) group, there were 6 partial responses (PR) (20%), 6 minor responses (MR), 15 cases of no change (NC), and 3 of progressive disease (PD). Of 31 patients in the STS(−) group, there were 7 PR (22%), 3 MR, 9 NC, and 2 PD.

Discussion

The concomitant use of STS has been reported to reduce the renal toxicity of CDDP given locally by either the i.a., i.p., or intrathoracic route [1, 7]. The prophylactic use of STS to reduce the toxicity of CDDP given systemically has been reported by Pfeifle et al. [8] as part of a phase I trial. In the present study STS was given after the systemic administration of CDDP.

The detailed mechanism by which renal functions are altered after CDDP administration has not been fully elucidated, nor does it seem that the mechanism by which STS reduces the renal toxicity of CDDP is understood.

Therefore, we studied the effect of STS by measuring the plasma levels and urinary recovery rates of platinum, the urinary levels of BMG, BUN, and creatinine, and the volume of urine.

The results of the present pharmacokinetic study demonstrate that STS is effective both in reducing plasma concentrations of CDDP and in increasing the urinary recovery of this drug. This could partly be explained by the diuretic action of STS [5]; although diuretics such as furosemide and mannitol have not been reported to alter the urinary recovery of CDDP [6], STS increased both the total volume of urine and the urinary recovery of platinum. STS has been reported to react with non-protein-bound CDDP in the general circulation to form a nontoxic complex [4]. Our data suggest that such a complex might be more efficiently eliminated than non-protein-bound CDDP. Monitoring the urinary levels of BMG and NAG appears to be useful as an index of nephrotoxicity at the dose of CDDP used; they were more sensitive than serum BMG, BUN, total creatinine, or 24-h creatinine clearance levels. The differences in the urinary levels of BMG and NAG between the STS(+) and STS(−) groups clearly indicate that the proximal tubule is protected by the administration of STS. Since no differences in the response rate between the STS(+) and STS(−) groups were observed, the administration of STS is effective in reducing the side effects of CDDP without impairing its antitumor activity.

Conclusions

CDDP is an attractive antitumor agent alone and in combination with other antitumor agents; however, its nephrotoxicity has long been the subject of clinical concern. The prophylactic use of STS has been reported to be effective in reducing such toxicity. The present study demonstrates that the administration of STS after the systemic administration of CDDP is effective as a supportive treatment without altering the response rate. It is also apparent that such supportive treatment is applicable for repeated CDDP chemotherapy to improve its antitumor effects.

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