EFFECT OF SELENITE ON RENAL TOXICITY AND ANTITUMOR ACTIVITY OF *CIS*-DIAMMINEDICHLOROPLATINUM IN MICE INOCULATED WITH EHRlich ASCITES TUMOR CELL

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Effect of sodium selenite on renal toxicity and antitumor activity of *cis*-diamminedichloroplatinum (Cisplatin; CDDP) repeatedly administered to mice inoculated with Ehrlich ascites tumor cells were examined. Simultaneous repeated administration of selenite with CDDP markedly improved the growth depression, the renal toxicity indicated by blood urea nitrogen value and the diarrhea caused by CDDP, and inhibited the growth of Ehrlich ascites tumor cells cooperatively with CDDP. This results suggest that selenium compounds are useful for prevention of the toxic side effects of CDDP.

Keywords — *cis*-diamminedichloroplatinum; selenium; mouse; renal toxicity; diarrhea; antitumor activity

INTRODUCTION

cis-Diamminedichloroplatinum (Cisplatin; CDDP)¹⁾ is an anticancer drug extensively used for the treatment of various human tumors.^{2–5)} Several toxic side effects of CDDP are also well known.⁴⁾ The most common dose-limiting factor is dose-related and cumulative renal toxicity.^{7–9)} Recently, selenite, a selenium compound, has been shown to prevent the lethal toxicity and acute nephrotoxicity of CDDP in mice receiving a single dose of this anticancer drug.¹⁰⁾ The selenium compound did not mask the antitumor activity of repeatedly administered CDDP in a separate experiment¹⁰⁾ using lower doses of either compounds than those used in the toxicity experiment as above. However, it has not been clarified whether the antitumor activity of CDDP is modified by the dose of selenite which depresses the renal toxicity of CDDP.

In the present study, therefore, the effects of selenite on the renal toxicity and antitumor ac-

tivity of CDDP repeatedly administered to mice inoculated with Ehrlich ascites tumor cells were examined.

MATERIALS AND METHODS

CDDP was kindly supplied by Nippon Kayaku Co., Ltd., Tokyo and sodium selenite was obtained from Nakarai Co., Ltd., Tokyo. These chemicals were dissolved in saline prior to use. Male ICR mice (weighing about 22–26 g) were obtained from Charles River Japan, Inc.

Mice ($n=5$) inoculated with Ehrlich ascites tumor cells or those without inoculation ($n=15$) were administered [CDDP (*i.p.*; 10 $\mu\text{mol/kg}$), sodium selenite (*s.c.*; 10 $\mu\text{mol/kg}$), CDDP (*i.p.*; 10 $\mu\text{mol/kg}$) and sodium selenite (*s.c.*; 10 $\mu\text{mol/kg}$), or saline (*i.p.*)] once a day for 5 d. Ehrlich ascites tumor cells (10^6 cells/mouse) were inoculated *i.p.* to mice 2 h before the first administration of the drugs. The body weight of these mice was measured every day. From each the group, five mice were employed for determi-

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nation of blood urea nitrogen (BUN) value and number of living tumor cells at 10 d after the first administration of CDDP. BUN value was measured using Urea NB-Test reagent (Wako Pure Chemical Ind. Ltd., Tokyo). Number of living tumor cells in the ascites was estimated by trypan blue dye exclusion test.

RESULTS AND DISCUSSION

Figure 1A shows changes in the body weight of mice (tumor cell was not inoculated) administered with CDDP alone, sodium selenite alone, or CDDP and selenite simultaneously once a day for 5 d. CDDP caused marked growth depression. Although selenite itself slightly suppressed body weight gain of mice, the growth depression of mice caused by CDDP was markedly modified by simultaneous administration of selenite.

FIG. 1. Effect of Simultaneous Administration of Selenite with CDDP on Growth (A) and BUN Values (B) of Mice

Mice were administered CDDP ($10 \mu\text{mol/kg}$; i.p.) alone, selenite ($10 \mu\text{mol/kg}$; s.c.) alone, or CDDP ($10 \mu\text{mol/kg}$; i.p.) and selenite ($10 \mu\text{mol/kg}$; s.c.) simultaneously once a day for 5 d ($\square$; administration period). BUN value was determined at 10 d after the first administration. a) Significant difference between "CDDP" and "CDDP + Se" ($p < 0.001$).

Increase of BUN which has been known as a suitable index for early renal lesions produced by CDDP¹¹⁾ was also prevented by simultaneous administration of selenite (Fig. 1B). These results indicated that selenite has a protective effect on the growth depression and renal lesions produced not only by single administration of CDDP,¹⁰⁾ but also by the repeated administration of relatively low doses (Figs. 1A and B). In the present experiment diarrhea which has occasionally been encountered in CDDP treated patient^{12,13)} was observed in all the mice treated with CDDP alone, but not in the mice injected selenite with CDDP.

Figure 2 shows the effect of selenite on anti-tumor activity and nephrotoxicity of CDDP in the tumor cell inoculated mice. CDDP diminished the number of the living tumor cells in the ascites (Fig. 2A) and increased BUN value (Fig. 2B). Simultaneous administration of selenite with CDDP prevented increase in BUN value (Fig. 2B) as in the case using non-inoculated mice (Fig. 1) and rather strongly depressed tumor cell growth than CDDP administered alone (Fig. 2A). These results proved that selenite efficiently depressed renal toxicity of CDDP without masking its antitumor activity against Ehrlich ascites tumor cell.

Greeder and Milner¹⁴⁾ reported that sodium selenite inhibited growth of Ehrlich ascites tumor cells in mice. Such an effect of selenite as above was also observed in the present study (Fig. 2A). CDDP and selenite may depress the tumor cell growth cooperatively when both the compounds were administered simultaneously.

The present new findings, selenite markedly prevents not only renal lesions¹⁰⁾ but also diarrhea induced by CDDP and inhibits tumor cell growth cooperatively with CDDP, strongly suggest that the selenium compound such as selenite is a specific antidote against CDDP toxicity and clinically useful for prevention of the toxic side effects of CDDP.

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FIG. 2. Effect of Simultaneous Administration of Selenite with CDDP on Number of Tumor Cells in Ascites (A) and BUN Values (B) of Mice Inoculated with Ehrlich Ascites Tumor Cells

Mice were administered CDDP ($10 \mu\text{mol/kg}$; i.p.) alone, selenite ($10 \mu\text{mol/kg}$; s.c.) alone, or CDDP ($10 \mu\text{mol/kg}$; i.p.) and selenite ($10 \mu\text{mol/kg}$; s.c.) simultaneously once a day for 5 d from 2 h after inoculation of Ehrlich ascites tumor cells. Number of tumor cells and BUN values were measured at 10 d after the first administration.

a) Significant difference between "control" and "CDDP" or "Se" (in Fig. 2A) ($p < 0.001$).

b) Significant difference between "CDDP" and "CDDP + Se" (in Figs. 2A and B) ($p < 0.001$).

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