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Drug Interaction Effects on Antitumor Drug (XIV) : Protection of Methimazole against Cisplatin-Induced Renal and Systemic Toxicity and Its Influence on the Therapeutic Activity of Antitumor Drug

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Summary

Methimazole, which has a sulfhydryl group and antioxidant properties, was examined for its ability to protect mice from the nephrotoxicity of cisplatin (CDDP) without compromising the therapeutic utility of the drug. Mice given CDDP (17.5 mg/kg, intraperitoneally) exhibited significant elevations in blood urea nitrogen concentrations, which correlated with the appearance of renal histopathological changes. In mice the subcutaneous administration of methimazole 1 hr after the intraperitoneal CDDP injection efficiently lowered not only the lethal toxicity, but also the renal toxicity (indicated by increased blood urea nitrogen values) which were usually observed in mice treated which CDDP in a dose dependent manner. Moreover, the administration of methimazole had no observeable effect on the antitumor activity of CDDP in mice inoculated subcutaneously with Sarcoma 180 cells. The present findings suggest the therapeutic benefit of used concomitantly with CDDP. The protective effect of methimazole on the CDDP-induced toxicity is discussed.

Introduction

Cisplatin {cis-diamminedichloroplatinum (II), CDDP} is a widely used anticancer agent that is effective against ovarian, testicular and other tumors[1~3]. The therapeutic value of CDDP is limited by its toxicity to several organs, especially kidenys[4~7]. The mechanism by which CDDP produces toxicity requires further study ; CDDP has been reported to inhibit the synthesis of DNA, RNA, and proteins as well as the transport of amino acids[8,9]. There is evidence that CDDP binds to thiols such as cystein and glutathione[10], and it has been reported to inhibit a number of sulfhydryl-containing enzymes including ATPase, thymidylates synthetase, glyceraldehyde-3-phosphate dehydrogenase, glucose-6-phpsphate dehydrogenase, gamma glutamylcysteine synthetase and ribonucleotide reductase[11~16]. Since glutathione functions in maintaining cellular thiol levels, a decrease in the cellular level of

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glutathione might increase the toxicity of CDDP. As expected, treatment with diethylmaleate, a nonspecific thiol-decreasing reagent, was found to increase CDDP toxicity[17,18]. Similar observations were made after treatment of mice with DL-buthionine-SR-sulfoximine (DL-BSO)[19,20], an inhibitor of glutathione synthesis[21~24]. On the other hand, another study revealed that DL-BSO inhibits nephrotoxicity induced by CDDP[25]. The administration of glutathione before treatment with CDDP has been reported to lower nephrotoxicity[26~29].

Furthermore, lipid peroxidation was suggested to play a role in CDDP-induced nephrotoxicity because increased renal damage was observed in glutathione-depleted animals, whereas *in vivo* pretreatment with glutathione reduced the renal toxicity. Recent in vivo and in vitro studies have shown that CDDP causes lipid peroxidation after the depletion of glutathione[30~34]. However, antioxidants which maintain the concentration of glutathione may restore the celluar defense mechanisms, block lipid peroxidation and thus protect against the toxicity of CDDP.

Methimazole, a drug commonly used to treat hyperthyroidism[35], was found to reduce free radical metabolites of prostaglandin H synthetase[36] and to inhibit hepatic and renal cystein conjugate S-oxidative activities[37]. Herein, we examined whether methimazole could function as a protective agent against CDDP nephrotoxicity without compromising its useful therapeutic activity.

Materials and Methods

Animals Male ddY mice (5 weeks old) were obtained from Japan SLC (Hamamatsu, Japan) and were used when they weighed about 25 g. Animals were maintained on a 12-h lilght/ 12-h dark cycle in a humidity- and temperature-controlled facility and allowed free access to food and water during the experiments. All animals studied were performed in compliance with guidelines established in "Guide for the Care and Use of Laboratory Animals" published by the Japan Association of Laboratory Animals Care. Animals were housed in facilities accredited by the Japan Association of Laboratory Animal Care, and research protocols were approved by the Institutional Animal Care and Use Committee of the Tohoku College of Pharmacy. Treatmet groups ranged from 6 to 12 mice.

Drugs Methimazole (2-mercapto-1-methylimidazole) and cisplatin {cis-diamminedichloroplatinum (II), CDDP, 10 mg/vial, Briplatin} were purchased from Nacalai Tesque, Kyoto and Bristol Meyers Co., Tokyo, respectively. CDDP was dissolved in sterile saline to obtain a solution of 0.5 mg/ml. Various solutions of methimazole were administered subcutaneously in 0.1 ml of 0.9% of saline solution per 10 g of body weight. These solutions were prepared just before the administration of single injections to mice. BUN (blood urea nitrogen) reagent for determination of serum urea (Eiken Kit E-CN 11) was purchased from Eiken Chemical Co. Ltd., Tokyo, Japan. The protective effects of methimazole were assessed by observing the number of surviving mice, changes in body weight and total leukocytes, and determination of BUN value. All other chemicals used were of the highest grade commercially available.

Lethality Acute lethality was recorded for the 8 days following injection. The body

weight of mice was measured every day.

Blood analysis Blood samples were obtained from the orbital vein in heparinized microhematocrit capillary tubes[22, 23]; urea nitrogen levels in serum were determined using the kit-reagents of Eiken Chemical Co. Ltd., Tokyo.

Antitumor studies To assess the effect of methimazole on the antitumor activity of CDDP, 6 week-old ddY mice were inoculated subcutaneously with 3 x 10^6 Sarcoma 180 cells into the right thigh and 24 hr later treated with 0.9% saline solution, CDDP or methimazole 1 hr after CDDP. On the 16th day after Sarcoma 180 inoculation, mice were killed, and the tumors were removed and weighed.

Statistical analysis Student's t-test was used to test for statistical significance, taking $p=0.05$ as the limit of significance.

Results

Toxicity Mice were given various doses of CDDP intraperitoneally and acute toxicity were measured for 8 days. CDDP caused a marked and dose-dependent increase in acute toxicity. Since 17.5 mg/kg of CDDP consistently caused acute lethality, this dose was administered in the subsequent toxicity studies.

The protective effect of thiol compounds on the toxicity of the antitumor drug is dependent on the timing of the administration[38, 39]. Accordingly, mice were given methimazole at selected times preceding or following CDDP treatment to determine whether or not methimazole showed similar schedule dependency in its protective effect. When given simultaneously with CDDP, methimazole protected lethality of CDDP at doses higher lower than 30 mg/kg (data not shown); in the subsequent studies, 90 mg/kg of methimazole was used.

To determine the most effective schedule for protection against the CDDP-induced lethality, methimazole was administeredat various times before or after CDDP. Subcutaneous administration of methimazole was effective when it was perforemed simultaneously with CDDP or from 1 to 3 hr afterwards, but was ineffective when administered before CDDP (Fig.1).

Furthermore, two groups of 20 mice were subcutaneously treated with either methimazole (90 mg/kg) or saline 1 hr after the intraperitoneal CDDP (17.5 mg/kg) administration. This treatment regimen with methimazole caused : 1) a delay in the occur rence of death and 2) a decrease in 8-day cumulative lethality compared to injection with saline after CDDP.

Methimazole also ameliorated the nephrotoxicity of CDDP, and the treatment schedule for nephrotoxicity was quite similar to that for lethality (Figs.2, 3). An increase in BUN level, which is recognized as a suitable index for early renal lesions produced by CDDP, was prevented by methimazole administered 1 hr after CDDP administration. Initial studies in mice showed that CDDP produced a dose-dependent increase in BUN level at doses over 10 mg/kg. The maximal increase in BUN level occurred on day 4 ; these levels remained elevated for at least 10 days (data not shown). Methimazole treatment resulted in a dose-

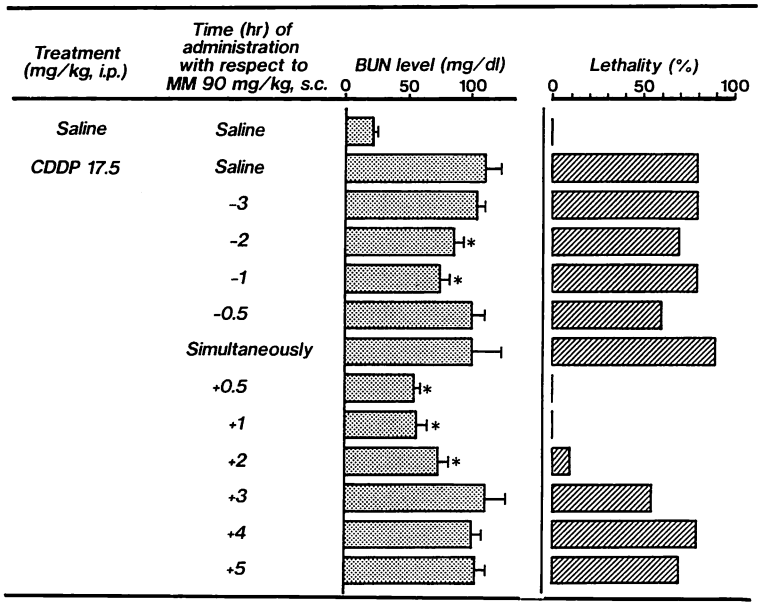

Fig. 1 Influence of treatment schedule on the protective effect of methimazole on the blood urea nitrogen values and lethality of mice

Mice were given cisplatin (CDDP, 17.5 mg/kg, *i.p.*) and methimazole (MM, 90 mg/kg, *s.c.*) at various times before or after cisplatin administration. (A) Blood urea nitrogen (BUN) values were determined 96 hr after CDDP adminis tration. Each value is the mean ± S.E. for 10 animals. * Significant difference from saline alone ($P<0.05$). (B) The mortality rate was observed for 8 days. Ten mice were used for each group.

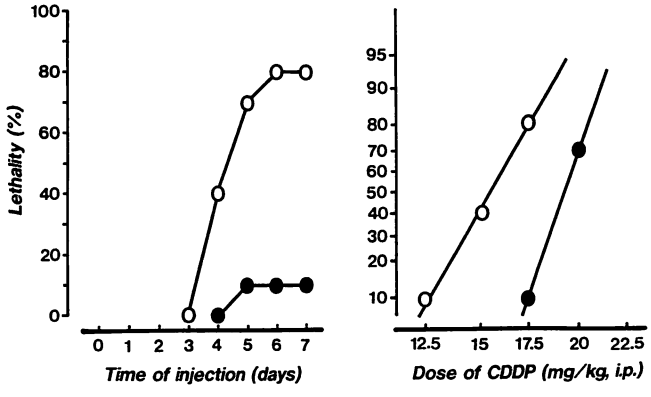

Fig. 2 Effect of methimazole on cisplatin-induced lethality in mice

Ten (left panel) or twenty (right panel) mice were used for each gruop. Mice received methimazole (90 mg/kg, *s.c.*) 1 hr after cisplatin (CDDP, *i.p.*) administration ; animal deaths were recorded over the succeeding 8 days. In left panel the dose of CDDP was 17.5 mg/kg. Open circle : CDDP alone, Closed circle : CDDP + Methimazole.

dependent decrease in the CDDP-induced elevation in the BUN level.

Also, we studied the changes in the body weight of mice administered CDDP alone, methimazole alone, or CDDP plus methimazole (by coadministration of methimazole according to the fixed schedule described above). CDDP (8 mg/kg, *i.p.*) caused marked body weight depression. Although methimazole caused some loss in the body weight of the mice, there were no other visible toxic signs during the experiment, the suppression of the growth of the mice caused by CDDP was slightly reduced by administration of methimazole (data not shown).

Antitumor studies Fig.4 shows the effect of methimazole on the antitumor activity of CDDP in mice inoculated subcutaneously with Sarcoma 180 tumor cells. The antitumor activity of CDDP indicated by inhibition of the tumor growth in mice inoculated subcutaneousl with Sarcoma 180 cells was not affected by the coadministration of methimazole.

Discussion

The major problem in cancer chemotherapy is still the lack of selectivity of the available drugs. To increase the selective toxicity of anticancer agents against tumor cells pharmacological attempts have been made to reduce side effects (with particular reference to dose limiting) without interfering with the antitumor properties of the cytotoxic agents. Since this approach may require administration of antidote, the detoxifying of the protective agent on the cytotoxic drug could also produce a partial loss of antitumor activity. Thus, the manifestation of the toxic side effects can be prevented without lowering the therapeutic

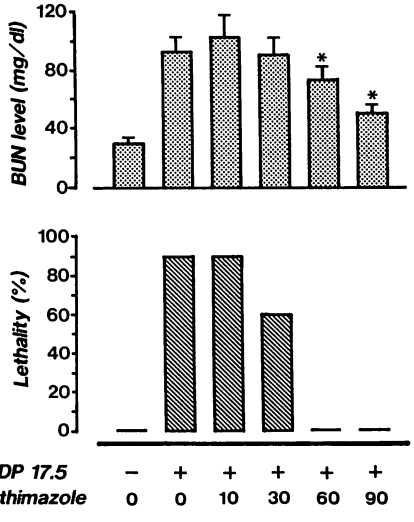

Fig. 3 Relationship of dose and protective effect of methimazole on cisplatin-induced blood urea nitrogen values and lethality of mice

Eight to ten mice were used for each gruop. Mice received methimazole (*s.c.*) 1 hr after cisplatin (17.5 mg/kg, *i.p.*) administration. Blood urea nitrogen (BUN) levels (upper panel) and lethality (lower panel) were determined. The experimental condition and analysis are the same as in Fig.1.

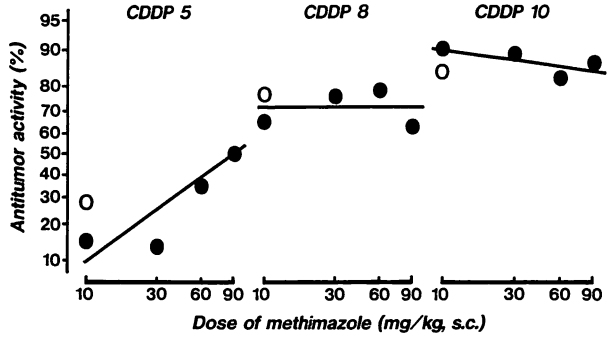

Fig. 4 Effect of methimazole on the antitumor activity of cisplatin against solid-type Sarcoma 180

Sarcoma 180 was inoculated by s.c. injection of 3 x 10^6 cells into the right thigh of ddY mice. On the 16th day after Sarcoma 180 inoculation, mice were killed, and the tumors were removed and weighed. Antitumor drug (5, 8 or 10 mg/kg) or saline was injected intraperitoneally 24 hr after the cell inoculation. Methimazole (10, 30, 60 or 90 mg/kg) or saline was administered subcutaneously 1 hr after cisplatin (CDDP) administration. Each value is expressed as the mean ± S.E. of inhibitory percentage compared with the control value (saline only) of 8-10 mice. Open circle : CDDP alone, Closed circle : CDDP + Methimazole.

effectiveness : (a) when the differences in the pharmacokinetic behavior of the antitumor drug and protective agent are expected to afford regional detoxification to prevent specific organotoxicity ; and (b) when different mechanisms are responsible for antitumor effect and some organspecific damage.

Nephrotoxicity, which is induced by CDDP and related compound[4~7] is an example of the latter situation. The effect of methimazole treatment on CDDP-induced nephrotoxicity was studied using previously establieshed protocols to induce nephrotoxicity[4~7]. Methimazole protected mice against the in vivo nephrotoxicity elicited by CDDP without compromising its antitumor activity against transplantable tumors in mice. CDDP-induced nephrotoxicity was decreased when methimazole was given 1 hr after CDDP treatment. This may be due to the relatively slower excretion of CDDP by the kidneys and/or the slower development of the nephrotoxicity induced by CDDP compared to the other nephrotoxic chemicals[40]. The finding that methimazole blocked CDDP-induced nephrotoxicity when given 1 hr after CDDP suggests that the methimazole treatment is not likely to alter the therapeutic effects of CDDP, which has an initial half-life in plasma of 25 to 50 min[40], and would be distributed to its target organs before the administration of methimazole to reduce CDDP nephrotoxicity. It is of interest to note that diethyldithiocarbamate and selenium, which did not reduce the antitumor properties of CDDP, also protected experimental animals from CDDP-induced nephrotoxicity when given between 1 and 4 hr after CDDP[41,42].

The selective and severe nephrotoxicity associated with CDDP administration has led to the formulation of many hypotheses concerning its mechanism of toxicity. Many of these hypotheses focus on the binding of CDDP to extracellular sulfur-containing nucleophiles, glutathioneor metallothioneins. Equivocal data have been repoted concerning the role of these compounds in CDDP-induced nephrotoxicity. For example, platinum-containing species from rat plasma that coeluted on HPLC with the reaction product of CDDP and

distilled water were demonstrared to be more nephrotoxic, whereas species that coeluted with a CDDP-methionine reaction product were less nephrotoxic than that parent CDDP in rats[18]. By contrast, other investigators reported that methionine injection following CDDP administration enhances nephrotoxicity in rats[45]. Similarly, while the majority of reports do not support a direct intracellular reaction between glutathione and CDDP in renal tissue[18, 46], indirect interaction between the nephrotoxic mechanisms of CDDP and glutathione-dependent cellular processes has been suggested based upon increased lethality of nepthrotoxicity of CDDP in rodents following depletion glutathione with diethylmaleate or BSO[17, 18, 21~24]. The mechanism of this protection is not understood and there may be one or more possible explanations. The most likely is that methimazole, derived from hydrolysis, provides alternative nucleophilic centers to interact with reactive electrophiles so preventing the depletion of kindney glutathione below the critical threshold required for the induction of CDDP-induced nephrotoxicity. Data from a variety of studies suggest that depletion of kidney glutathione below approximately 80% of the control value is critical for the induction of the nephrotoxicity of a number of compounds including CDDP and cephaloridine[47]. When glutathione is depleted below this critical level, the reactive electrophiles may then bind covalently to critical cellular macromolecules possibly leading to toxicity[48]. Alternatively, methimazole by increasing intracellular sulfhydryl groups may alter CDDP toxicity by increasing sulphate conjugation either by maintaining the supply of both the cofactor adenosine 3'-phosphate 5'-sulphatophosphate and also inorganic sulphate. Thiol compounds have been shown to interact directly with the kidney and inhibit nephrotoxicity induced by compounds covalently binding to the kidneys[49]. In these studies methimazole protected against CDDP-induced toxicity equally as well as reduced glutathione, the compound most commonly used in the treatment of patients suffering from CDDP-induced nephrotoxicity.

The protective mechanism of methimazole is not known ; however, although it is tempting to speculate that the mechanism of methimazole protection against CDDP nephrotoxicity is similar to the mechanism of protection by glutathione, further studies are required to test this hypothesis.

Various attempts have been made in the past to antagonize the in vivo nephrotoxic effects of CDDP[50], but the problem of their own adverse side effects still remains. For example, phase 1 clinical trials with diethyldithiocarbamate and CDDP have been relatively unsuccessful due to the neurotoxic side effects caused by diethyldithiocarbamate[50]. Likewise, thiourea, methionine and selenium-containing chemicals have toxic side effects which make their therapeutic use questionable[51]. On the other hand, methimazole bas been used safely in the clinic since the 1940s to treat hyperthyroidism. Moreover, the dose of methimazole required to protect against nephrotoxicity did not cause any hepatotoxicity. Thus, methimazole treatment appears to be a promising method to prevent chemical nephrotoxicity in future clinical approaches.

In summary, the results presented findings provide evidence that methimazole treatment protected against CDDP-induced nephrotoxicity without compromising its antitumor activity against Sarcoma 180 tumor cells.

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