kaolin and activated dimethicone over the 100 min experimental time period. The cumulative absorption profile of warfarin while alone and while in combination with magnesium trisilicate is shown in the figure. This graph shows clearly the extent of the interaction.

*Comment.* The results indicate that neither kaolin nor activated dimethicone will effect the absorption of concomitantly administered warfarin sodium. Bismuth carbonate gave a slight absorption reduction (7%); however, this is unlikely to be clinically significant. The magnesium trisilicate gave rise to a 19% reduction in absorption and such a decrease in vivo may give rise to instability problems in warfarin treated patients. Concomitant administration of warfarin and magnesium trisilicate should perhaps be avoided as a precaution against possible changes in warfarin absorption kinetics.

Decreased warfarin absorption in the prescence of antacid constituents

| Antacid constituent | Amount of constituent used | Percentage decreased absorption |
|---|---|---|
| Kaolin (light) | 2 g | 0 |
| 35% aqueous emulsion of activated dimethicone | 1 ml | 0 |
| Bismuth carbonate | 500 mg | 6.9 |
| Magnesium trisilicate | 500 mg | 19.3 |

The in vitro absorption of warfarin (20 mg of sodium salt) was compared while alone and while in combination with the given quantities of antacid constituents. The results are expressed as percentage decreased absorption of warfarin in the presence of antacid constituent with respect to control (warfarin alone) values.


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## Protective effect of selenite on nitrite toxicity


T. Masukawa and H. Iwata

*Department of Pharmacology, Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-kami, Suita-shi, Osaka (Japan), 25 January 1979*



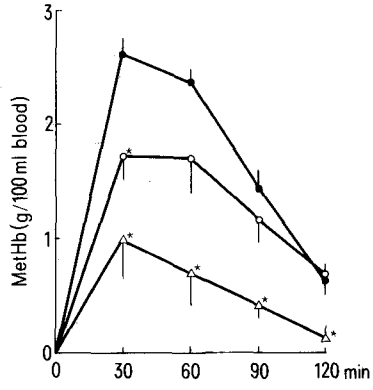
*Summary.* Selenite was found to decrease nitrite-induced mortality in a dose-dependent manner. Its effect seems to be due to its action in reducing methemoglobin formed by nitrite.


Previously we reported that selenite stimulates reduction of methemoglobin (metHb) in nitrite-treated erythrocytes[1]. Its action is due to catalysis of metHb-reduction by reduced glutathione (GSH)[2,3]. Recently we found that druginduced methemoglobinemia is markedly suppressed by administration of selenite in rats[4]. In the present work we tested the effect of selenite on the lethality of sodium nitrite, a direct oxidant of hemoglobin (Hb).

*Methods and materials.* Male dd strain mice weighing 20–25 g were used for experiments of the acute toxicity of sodium nitrite. $LD_{50}$-values were calculated from the lethality within 24 h after nitrite injection by the method of Litchfield and Wilcoxon[5]. Experiments on nitrite-induced methemoglobinemia in rats were carried out as reported previously[4]. MetHb was determined by the method of Evelyn and Malloy[6], and Hb by the cyanmethemoglobin technique. All chemicals used were of reagent grade.

*Results and discussion.* As shown in the table, the acute i.p. $LD_{50}$-value of sodium nitrite was 178 mg/kg in mice. The $LD_{50}$-value of nitrite was significantly increased to 209 mg/kg and 224 mg/kg by concomitant s.c. administration of selenite at doses of 1.0 mg/kg and 3.0 mg/kg, respectively. After these doses of sodium nitrite in mice, cyanosis developed within 15–30 min, and in the most cases death occurred within 2 h. The survival time after injection of sodium nitrite alone (260 mg/kg, i.p.) was $29.5 \pm 6.3$ min ($N = 6$), whereas it was prolonged significantly to $70.6 \pm 13.8$ min ($N = 5$) by simultaneous injection of selenite (3.0 mg/kg, s.c.).

The toxicity of sodium nitrite is thought to be mainly due to its oxidation of Hb to metHb, since formation of large amounts of metHb seriously impairs the oxygen-carrying capacity of the blood, causing anemic hypoxia[7]. We examined the effect of selenite on nitrite-induced methemoglobinemia in rats. As shown in the figure, s.c. injection of 0.1 mg/kg to 0.5 mg/kg with sodium selenite suppressed methemoglobinemia in a dose-dependent manner.




Effect of selenite on methemoglobinemia induced by nitrite in rats. ●—● $NaNO_2$ 40 mg/kg, i.p.; ○—○ $NaNO_2 + Na_2SeO_3$ 0.1 mg/kg, s.c.; △—△ $NaNO_2 + Na_2SeO_3$ 0.5 mg/kg, s.c. Selenite was injected immediately after treatment with nitrite. Points are means ± SE for 4 rats. * $p < 0.01$.

In a preliminary experiment in vitro, we found that selenite did not influence the oxidation of Hb produced by incubation of erythrocytes with nitrite. Therefore, the suppressive effect of selenite on methemoglobinemia may be due to increased reduction of metHb. Similar results have been obtained on the effect of selenite on methemoglobinemia produced by aniline or phenylhydrazine[4]. Nitrite is also known to cause marked hypotension by vasodilation[7]. However, we found that 3.0 mg/kg of sodium selenite, when given i.v. to rats 1 min before nitrite (20 mg/kg, i.v.), had no effect on the hypotension caused by sodium nitrite. Therefore, the protective effect of selenite against the lethal effect of nitrite seems to be due to its action on nitrite-induced methemoglobinemia.

The doses of 0.1 mg/kg and 0.5 mg/kg of selenite used in the experiments on methemoglobinemia corresponded to about 20 times and 100 times the daily requirement, respectively. The form of selenium in the diet is unknown, but it is possible that dietary selenium participates in a physiological process of reduction of metHb.

*Effect of selenite on sodium nitrite poisoning in mice*

| $NaNO_2$ (mg/kg, i.p.) | Mortality (dead/total) Saline | $Na_2SeO_3$ (1.0 mg/kg) | (3.0 mg/kg, s.c.) |
|---|---|---|---|
| 162 | 0/6 | | |
| 178 | 7/16 | 1/6 | 0/6 |
| 195 | 10/15 | 3/6 | 4/16 |
| 215 | 5/6 | 4/6 | 3/6 |
| 236 | 4/5 | 3/6 | 8/16 |
| 260 | 6/6 | 5/6 | 5/6 |
| $LD_{50}$ | 178.0 (159.1-199.2) | 208.9 (185.5-235.3) | 223.9 (183.7-272.9) |
| Potency ratio | | 1.17 (1.07-1.29*) | 1.26 (1.14-1.38*) |

Selenite was injected immediately after treatment with nitrite. Confidence limits ($p<0.05$) are shown in parentheses. *Significantly different from value for saline control ($p<0.05$).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## Reduction of acute toxicity of cyclophosphamide and X-rays by the new immunomodulating compound BM 12.531[1]


U. Bicker, K.D. Friedberg, G. Hebold and K. Mengel

*Department of Experimental Medicine, Boehringer Mannheim GmbH, Sandhofer Strasse 116, D-6800 Mannheim 31 (Federal Republic of Germany), and Institute of Pharmacology and Toxicology of the Chemical Department Mannheim, University Heidelberg, D-6900 Heidelberg (Federal Republic of Germany), 23 December 1978*



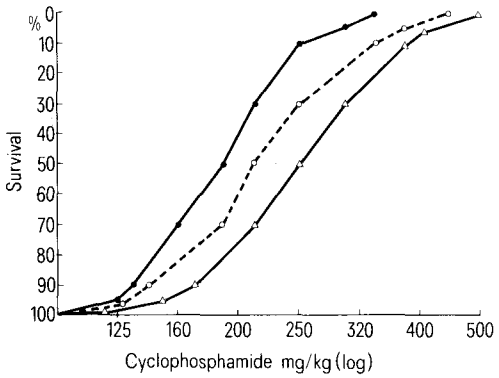
*Summary.* BM 12.531, the 2-[2-cyanaziridinyl-(1)]-2-[2-carbamoylaziridinyl-(1)]-propane, (prop. INN Azimexon), reduces significantly the acute toxicity of cyclophosphamide and X-rays in rats and mice, respectively. The leucopenia induced by X-rays was partially compensated by BM 12.531 in rats.


BM 12.531 (prop. INN Azimexon), 2-[2-cyanaziridinyl-(1)]-2-[2-carbamoylaziridinyl-(1)]-propane, derivative of the 2-cyanaziridine[2-6], has interesting therapeutic and immunomodulating effects[7-11]. This compound has therapeutic effects against various transplantation tumors[11] and increases resistance in bacterial, fungal and viral infections[12]. Therapeutic effects can be explained by stimulation of cellular immune functions for example T-lymphocytes[8] and macrophages[11]. The induction of leucocytosis in rats[13] by BM 12.531 and the increase of the colony-forming-units[11] in mice suggest a direct bone marrow stimulation. The aim of the present investigation was to demonstrate the influence of BM 12.531 on the acute toxicity of cyclophosphamide in rats and of X-rays in mice. Cyclophosphamide and X-rays especially damage the bone marrow and up to now no agent with a low molecular weight is known which can be used as a therapeutic drug after toxification by cyclophosphamide or X-rays.

*Materials and methods.* Substances. BM 12.531[5] was dissolved for administration in 0.5% methyl-cellulose or 0.9% NaCl-solution. Cyclophosphamide from the Asta Company, Chem. Werke Brackwede, Germany, was used.

For X-irradiation an X-ray apparatus set at 20 mA and 200 kV with a filter of 0.5 mm Cu was used. The dose was 70 r/min. The total dose used for rats were 175 and 350 r and for mice 650 r.

1. Influence of BM 12.531 on the leucopenia induced by X-irradiation. The experiments were carried out in mature female Sprague-Dawley rats from Wiga Company (Gassner, Sulzfeld, FRG), weighing 180-220 g. They were kept under constant temperature (23 ± 1 °C) and a constant relative humidity (55 ± 5%) over a 12-h day/night-rhythm. The animals were fed with Sniff pellet food from the




Influence of BM 12.531 on the acute toxicity of cyclophosphamide in rats (7 days after cyclophosphamide administration). ●——●, Cyclophosphamide. ○- -○, Cyclophosphamide + 3 × 10 mg/kg BM 12.531. △——△, Cyclophosphamide + 3 × 25 mg/kg BM 12.531. BM 12.531 was given 2, 24 and 48 h after cyclophosphamide administration.