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The interaction of warfarin with antacid constituents in the gut

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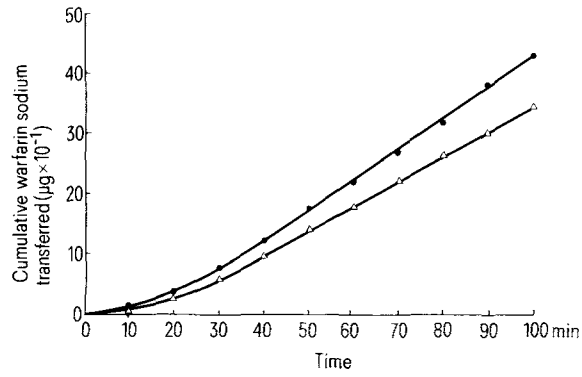
Summary. A study was made of the effect of 4 constituents of antacid preparations on the absorption of the coumarin derivate warfarin sodium using an in vitro experimental model. The constituents tested were activated dimethicone (a silicone) magnesium trisilicate, bismuth carbonate and the adsorbant, kaolin. Slight decreased intestinal absorption was shown by magnesium trisilicate (19%) and bismuth carbonate (7%), the other 2 components showing no effects.

Drug interactions between apparently inert substances and certain groups of drugs giving rise to decreased drug absorption have been well documented[1]. The best known interactions of this type are the tetracycline interaction with divalent and trivalent metal ions[2,3] and digoxin's interaction with antacid constituents[4,5]. It has been suggested that antacids may also effect the absorption of the anticoagulant warfarin from the gastro-intestinal tract[6]. Studies in human volunteers have since shown no change in the intestinal absorption of warfarin when administered together with both magnesium and aluminium hydroxides[7,8]. A report by Tolbot and Meade[9], however, suggested that the decreased absorption of warfarin seen in several patients could be attributed to dimethicone, a constituent in certain cooking oils.

Activated dimethicone is increasingly being used as a constituent in antacid preparations and it was, therefore, important to determine if, and to what extent, an interaction between warfarin and activated dimethicone may occur. The present study also examined the effects of magnesium trisilicate, bismuth carbonate and kaolin on the absorption of warfarin using an in vitro model.

Materials and methods. The study employed an in vitro model of drug interaction in the gut which has already been used in evaluating the tetracycline/metal ion[10] and the digoxin/antacid[11] interactions, the results reflecting clinical findings. The technique involved the collection of warfarin absorbed across control and test everted rat intestinal segments by infusion of buffer through the segments. During each experimental run consecutive segments from the same rat were used as the control and test. The segments were bathed in a buffer solution (pH 7.4); the control chamber contained warfarin sodium (20 mg in 120 ml) while the test segment buffer contained the same amount of warfarin plus a clinically equivalent dose of antacid constituent (table). Infused samples (10 ml) were collected each 10 min for 100 min; the samples were assayed for warfarin content using a fluorimetric technique[12]. Each antacid constituent was tested in triplicate and the averaged cumulative absorption values of warfarin in the presence of the antacid constituents were then compared with control absorption values found for warfarin alone (taken as 100%).

Results. The results show that there were small percentage decreases in the cumulative absorption of warfarin when in the presence of magnesium trisilicate (19%) and bismuth carbonate (7%). No such decreases were seen in the cases of



Cumulative absorption profiles of warfarin sodium alone and while in combination with magnesium trisilicate across everted rat intestine. Each point is the average of 3 individual determinations in segments from individual rats. In both cases, as is normal with the technique, a lag period is followed by a period of linear absorption. ●——● warfarin sodium alone (control); △——△ warfarin sodium + magnesium trisilicate (test).

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

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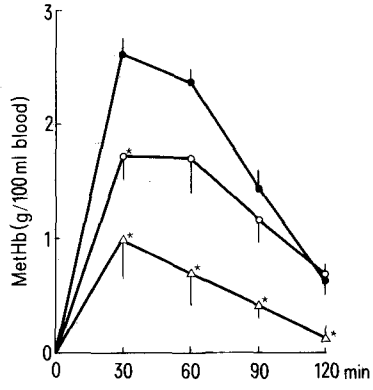
Summary. Selenite was found to decrease nitrite-induced mortality in a dose-dependent manner. Its effect seems to be due to its action in reducing methemoglobin formed by nitrite.

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 ± 6.3 min ($N = 6$), whereas it was prolonged significantly to 70.6 ± 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. * $p < 0.01$.