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DECREASED BIOAVAILABILITY OF INDENOLOL DUE TO COADMINISTRATION OF SOME GASTROINTESTINAL DRUGS

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ABSTRACT

Gastrointestinal drugs like kaopectate, magnesium trisilicate and bismuth subnitrate are known to absorb B-blockers with different adsorbing capacity and thereby affect their bioavailability. The adsorbing capacity of those drugs and their effect on the bioavailability of a recently introduced B-blocker, indenolol have been studied in rats. Concomitant administration of sucralfate and kaolin-pectin with indenolol significantly decreased the extent but not the rate of absorption of indenolol. Those findings indicate towards a possible clinically significant interaction between these drugs and indenolol.

INTRODUCTION

Decreased bioavailability of many drugs has been attributed to drug interactions within the gastrointestinal tract (1,2). Available self-medication antacids have been found responsible for such interactions with a number of drugs including B-adrenergic blocking agents (3-7). Patients on B-blockers therapy are liable to self medication with antacids and/or antidiarrhoeal drugs due to gastrointestinal complaints of nausea, vomiting and diarrhoea associated with most of the drugs in this class. This work describes a possible drug interaction between the commonly used antacids and antidiarrhoeal drugs and a recently introduced B-blockers, indenolol.

MATERIALS AND METHODS

Indenolol (Yamanouchi Pharmaceuticals Co. Ltd., Japan). Magnesium trisilicate (BDH Chemicals, Poole, U.K.), Bismuth subnitrate (Ricedel AC, Germany), Sucralfate (Marion Lab., Kansas), Kaopectate (Kaolin-pectin suspension, Upjohn, Belgium).

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Adsorption Studies

Recommended doses of kaolin-pectin suspension (15 ml), magnesium trisilicate (1 g.) previously heated at 120°C and screened through No. 170 sieve were placed in 100 ml. bottles. Indenolol solution in 0.05 M KCL-HCL buffer (ph. 2.2) was added to the adsorbents and the volume adjusted to 50 ml. using the same buffer, the concentration of indenolol ranged from 5-60 mg/50 ml. The bottles were shaken in a constant temperature water bath at 37 ± 0.5°C for 3 hours, where equilibrium was established by that time. An aliquot was filtered (millipore 0.22 mm.) and indenolol was determined spectrophotometrically (at 250 nm) in case of magnesium trisilicate and other adsorbents or spectrofluorometrically, (maximum excitation at 260 nm and maximum emission at 320 nm) in case of kaolin-pectin.

Absorption Studies

Healthy Wistar Albino rats (150-200 g.) were divided into 3 groups and fasted for 12 hours prior to experiments. The first group (control) received indenolol solution (10 mg./kg. p.o) only whereas the animals in groups 2 and 3 received 1 ml. of 10% solution of sucralfate, and 1 ml. of kaolin-pectin respectively immediately before drug administration. The animals were allowed free access to water all the time. Food was allowed only 3 hours after drug administration. Five animals from each group were sacrificed at intervals of 0, 15, 30, 45, 60, 120, 240 and 360 minutes after administration, and plasma indenolol was determined spectrofluorometrically (8). Bioavailability of indenolol was assessed based on AUC calculated by trapezoidal method and statistical analysis was carried out using student t-test.

RESULTS AND DISCUSSION

The adsorption of indenolol on the adsorbents tested followed a Freundlich-type isotherm (Fig. 1). The adsorptive capacity of magnesium trisilicate and bismuth subnitrate were found to be 18.18 mg./g. and 21.55 mg./g. respectively (Fig. 2 Table 1). Kaolin-pectin, however, adsorb practically all of the drug. Sucralfate did not adsorb any appreciable amount of the drug.

The results of in-vivo absorption studied was indicated by the plasma levels of indenolol have been depicted in Fig.3. The graph suggests that both kaolin-pectin and sucralfate decrease the extent but not the rate of absorption of indenolol. There was an initial steep rise in plasma concentration of indenolol. The peak concentration (2.46 ± 0.15 ug/ml) was achieved within 45 min. in the control group. However, peak concentrations in the sucralfate (1.21 ± 0.12 ug/ml) and kaolin-pectin (0.85 ± 0.03 ug/ml) treated groups were obtained at 45 min. and 60 min. after the administration of indenolol. There levels were significantly lower as compared to the control group (50% and 65.45% respectively). Similarly the area under the curve over the same period of time (6 hrs.) was also lower than the control group (15.1% and 30.4% respectively). Those limited findings show a positive correlation between the in-vitro adsorption and in-vivo plasma levels of indenolol with sucralfate and kaolin-pectin. Kaolin-pectin is a strong adsorbent as com-

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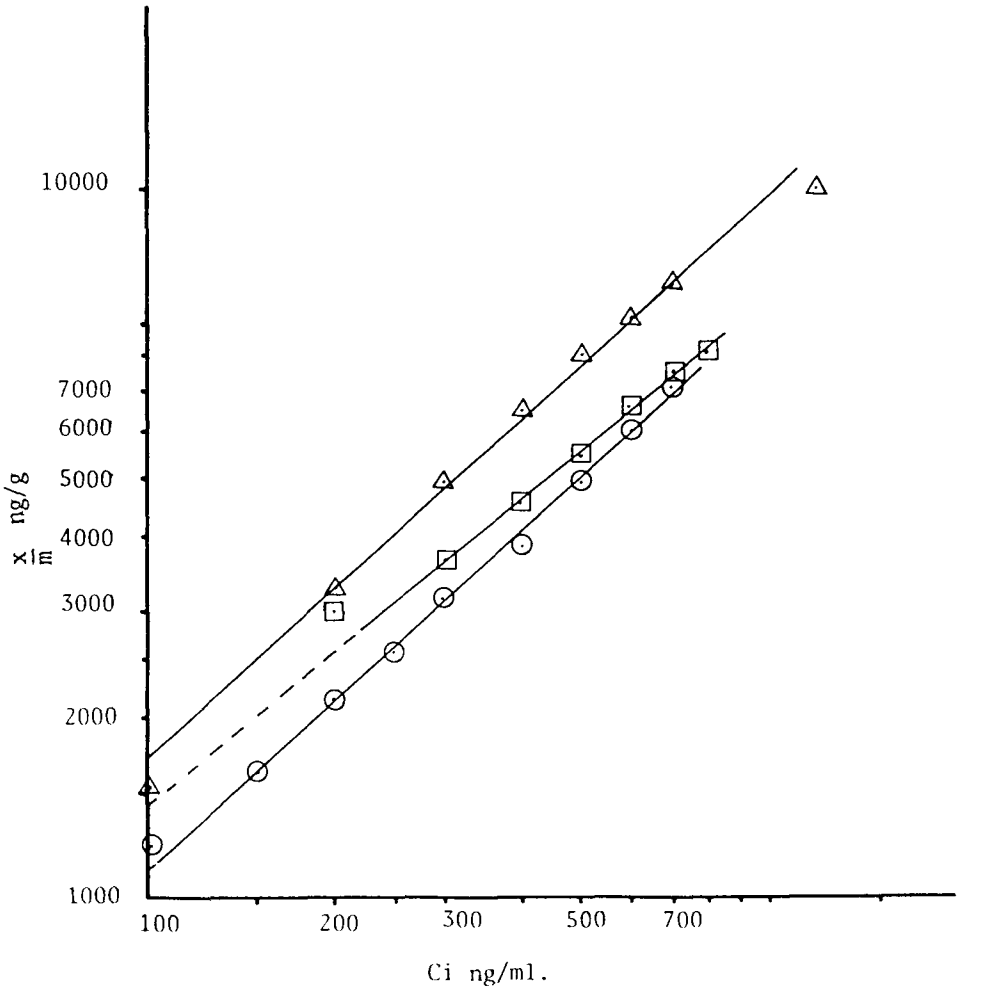

Fig.1: Frenndlich Adsorption isotherm of indenolol on:-
○; Magnesium trisilicate, □ ; Bismuth subnitrate;
△; and Kaolin-pectin.

pared to sucralfate and hence produces greater effect on the bioavailability of indenolol. Sucralfate, on the other hand is a non-absorbable anti-ulcer drug which forms a protective coat on the gastric mucosa and change the gastric potential difference thereby interferring with the absorption process (9,10). These observations are in accord with the earlier reports on the decreased bioavailability of propranolol following aluminium hydroxide administration (11). However, a decreased gastric emptying rate and reduced gastro-intestinal motility caused by aluminium hydroxide were considered responsible for this effect rather than its capacity to adsorb the drug (5).

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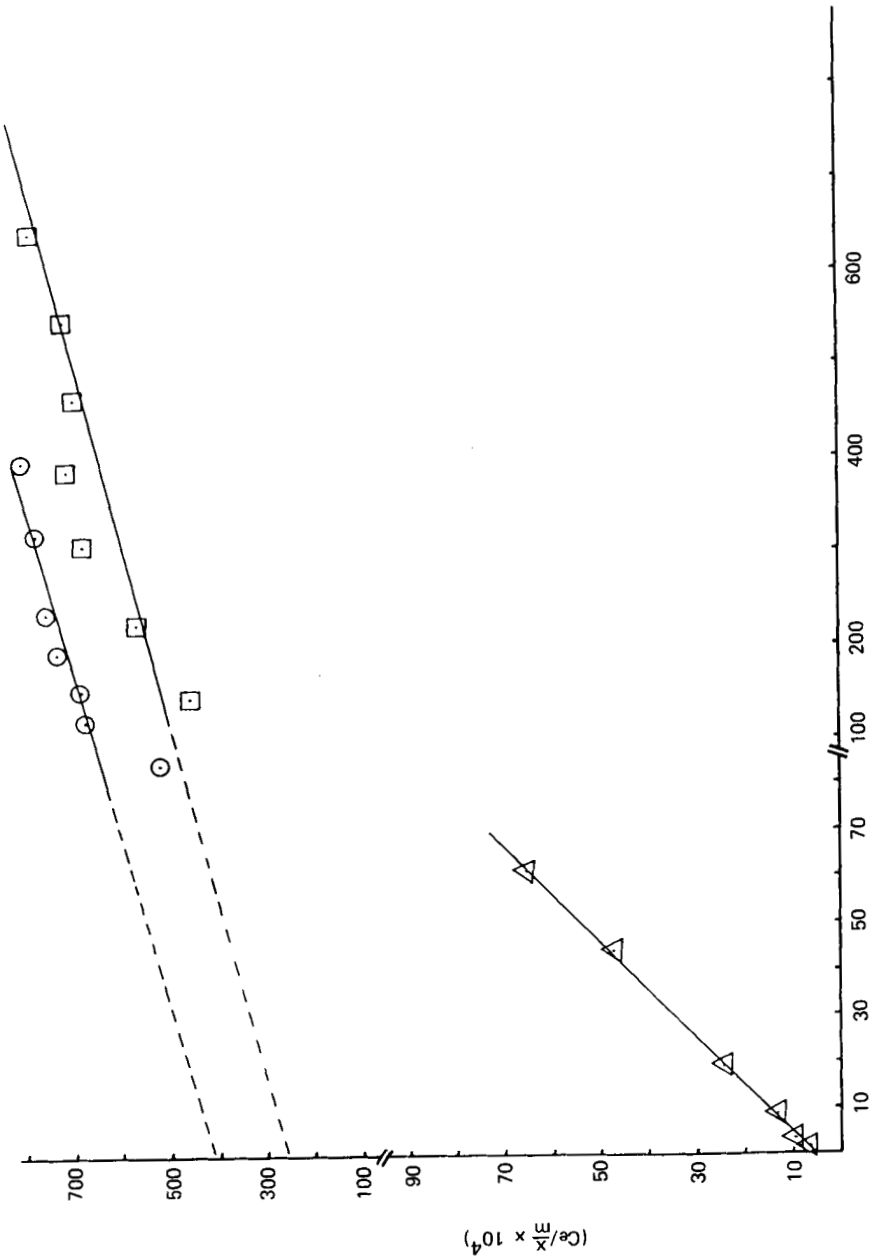

Fig. 2:Langmuir adsorption isotherm of indenolol on
○; Magnesium trisilicate □, Bismuth subnitrate
△; Kaolin-pectin.

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TABLE 1

	Magnesium Trisilicate	Bismuth Subnitrate	Kaolin-Pectin
n	0.852	0.747	0.93
b	18.18	21.55	15.63
a	0.0621	0.0487	0.006

n = slope of the Freundlich adsorption isotherm; b = reciprocal of slope of the Langmuir adsorption isotherm; a = adsorption constant of the Langmuir adsorption isotherm.

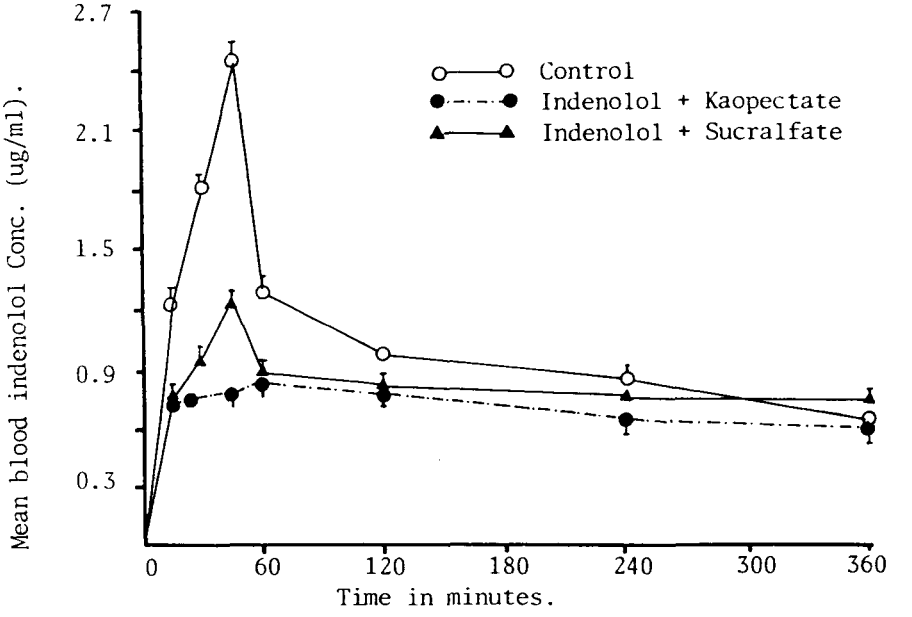

Fig. 3: Time course of plasma concentration after oral administration of 10 mg/kg of indenolol in control and gastrointestinal drug treated rats.

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In conclusion, the results of this study indicate towards clinically significant interactions between sucralfate and kaolin-pectin, and indenolol. It is suggested that spacing of two hours between the administration of indenolol and these drugs may be advisable. Further studies in a clinical setting are required to highlight this problem and find its proper solution.

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