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Decreased bioavailability of propranolol due to interactions with adsorbent antacids and antidiarrhoeal mixtures

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Summary

The interaction of propranolol (50–160 mg/100 ml) with recommended doses of magnesium trisilicate, kaolin–pectin and bismuth subsalicylate suspensions was studied. Magnesium trisilicate and bismuth subsalicylate were found to adsorb propranolol with a limiting adsorptive capacity of 112 and 97 mg/g, respectively. Kaolin–pectin suspension adsorbed practically all of the drug. The effect of these interactions on the bioavailability of propranolol in rats was determined. The extent, but not the rate, of propranolol absorption was decreased on concomitant administration of the adsorbents. Peak propranolol plasma concentrations decreased by 29–45% and a parallel decrease of 35–44% in AUC values was observed. These interactions suggest possible clinically important differences in propranolol bioavailability.

Introduction

Drug interactions within the gastrointestinal tract have been implicated in the decreased bioavailability of many drugs (Gibaldi, 1984; Hurwitz, 1977). Antacids and antidiarrhoeal mixtures, which are usually available for self-medication, received attention for their potential effect on drug absorption. These products were found to interact and consequently reduce the bioavailability of certain drugs (Brown and Juhl, 1976; Bucci et al., 1981; Ericsson et al., 1982; Gouda et al., 1984; Takahashi et al., 1985).

Propranolol, a β-adrenergic blocking agent, is prescribed in doses which are adjusted for the individual patient. Common side-effects of this drug include nausea, vomiting and diarrhoea. Patients on propranolol therapy are, therefore, likely to self-medicate with antacids and/or antidiarrhoeal mixtures. Dobbs et al. (1977) reported a decrease in the bioavailability of propranolol on concomitant administration of aluminium hydroxide gel. Using the rat everted-intestine technique, McElnay et al. (1982) reported a slight decrease in propranolol absorption due to interaction with kaolin.

The object of this report is to evaluate the in vitro adsorption of propranolol on commercially available Kaopectate (kaolin–pectin suspension), Pepto-Bismol (bismuth subsalicylate suspension) and on magnesium trisilicate, as well as to study the effects of adsorption on bioavailability in rats.

Materials and Methods

Materials

Propranolol (Ayerst Laboratories, NY, U.S.A.),

Kaopectate (Kaolin–pectin suspension, lot B309R, Upjohn, Puurs, Belgium), Pepto-Bismol (bismuth subsalicylate suspension, control no. 133095, Norwich-Eaton Pharmaceuticals, Norwich, U.S.A.) and magnesium trisilicate (BDH Chemicals, Poole, U.K.) were used. All other chemicals were reagent grade.

Adsorption studies

Recommended doses of kaolin–pectin suspension (45 ml), bismuth subsalicylate suspension (30 ml) and magnesium trisilicate (1 g, previously heated at 120°C and screened through no. 170 sieve) were placed in 200 ml bottles. Propranolol solutions in 0.05 M KCl–HCl buffer (pH 2.2) were added to the adsorbents and the volume adjusted to 100 ml using the same buffer. The concentration of propranolol ranged from 50–160 mg/100 ml. The bottles were shaken in a constant temperature water bath at 30 ± 0.5°C for 3 h. Equilibrium was established at that time. An aliquot was filtered (Millipore, 0.45 μm) and propranolol was determined spectrofluorometrically (Hussain et al., 1980); maximum excitation at 288 nm and maximum emission at 340 nm.

Absorption studies

Adult rats of either sex ($\simeq$ 200 g) were divided into four groups. Each animal in one group received, orally, 200 mg of magnesium trisilicate suspended in 1 ml of water; animals in two other groups received 1 ml of kaolin–pectin suspension (200 mg kaolin + 4 mg pectin) or 1 ml of bismuth subsalicylate suspension (17.5 mg). A control group received 1 ml of water. All animals were given oral propranolol concurrently in a dose of 8 mg/kg body weight. The animals (an average of six) were killed after 15, 30, 45, 60, 90, 120 and 240 min intervals following propranolol administration. Propranolol plasma levels were estimated spectrofluorometrically (Hussain et al., 1980).

Results and Discussion

The in vitro adsorption of propranolol on all three adsorbents followed a Freundlich-type isotherm (Fig. 1). Adsorption constants evaluated from the plot are shown in Table 1. When the data were plotted according to the Langmuir isotherm (Fig. 2), magnesium trisilicate and bismuth subsalicylate were found to adsorb propranolol with a limiting adsorptive capacity of 112 and 97 mg/g, respectively (Table 1). Kaolin–pectin suspension, however, adsorbed practically all of the drug. Other antacid ingredients tested as to their affinity for propranolol included an aluminium hydroxide–magnesium hydroxide mixture, calcium carbonate and bismuth subcarbonate. They were found to adsorb 10% or less of the drug and were not subsequently tested in vivo.

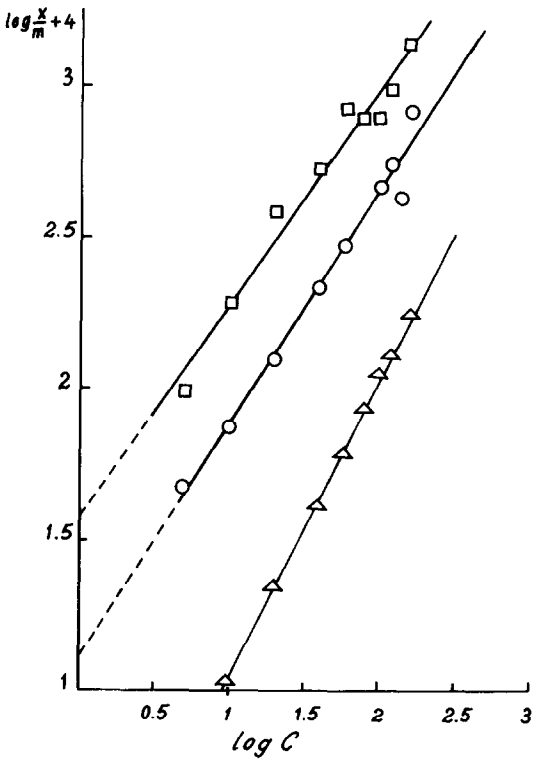

Fig. 1. Freundlich adsorption isotherms of propranolol on □, bismuth subsalicylate; ○, magnesium trisilicate; △, kaolin–pectin.

In vivo absorption studies in rats showed a decrease in the extent, but not the rate, of drug absorption on concomitant administration of the adsorbents (Fig. 3). A 29–45% decrease in peak propranolol plasma concentration was observed. A parallel decrease of 35–44% was observed in AUC values. Results are summarized in Table 1.

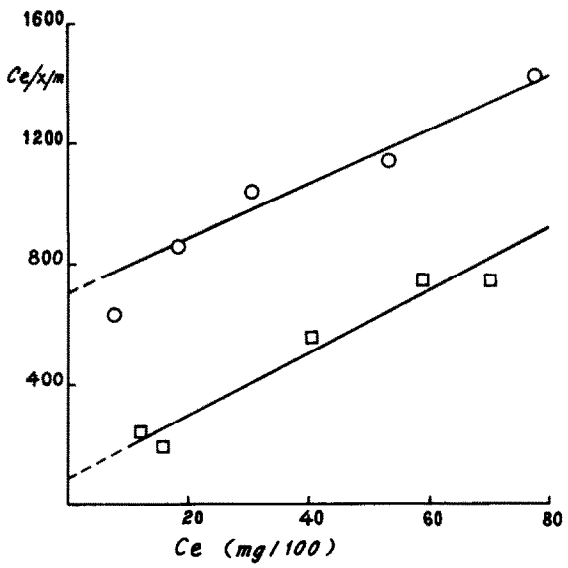

Fig. 2. Langmuir adsorption isotherms of propranolol on ○, magnesium trisilicate; □, bismuth subsalicylate.

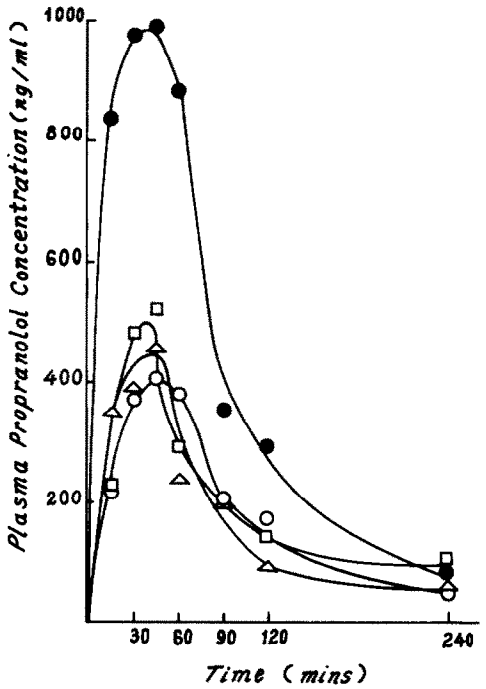

Fig. 3. Effect of adsorption on the mean plasma propranolol concentration–time curve. ●, control; □, bismuth subsalicylate; △, kaolin–pectin; ○, magnesium trisilicate.

Dobbs et al. (1977) have indicated a decrease in absorption due to concurrent administration of propranolol and aluminium hydroxide gel in humans. McElnay et al. (1982) reported that the decrease in propranolol absorption was not due to adsorption or complexation but was likely due to a decreased gastric emptying rate and decreased gastrointestinal motility caused by the antacid. In this report, results of the in vitro studies with aluminium hydroxide–magnesium hydroxide support the explanation of McElnay et al. (1982) regarding aluminium hydroxide–propranolol interaction. Also, the limited in vitro adsorption of propranolol on bismuth subcarbonate correlates

TABLE 1

ADSORPTION AND BIOAVAILABILITY PARAMETERS FOR PROPRANOLOL INTERACTIONS WITH VARIOUS ADSORBENTS

	Control	Magnesium trisilicate	Kaolin–pectin	Bismuth subsalicylate
n	–	0.774	1.038	0.700
b	–	112	CA	97
a	–	0.0125	CA	0.1184
t_{max} (min)	45	45	45	45
C_{max} (ng/ml)	735	406	455	521
$C_{max}/C_{max(control)}$	–	55%	62%	71%
AUC_{240min} (ng · min/ml)	90,075	50,319	53,393	58,853
$AUC_{240min}/AUC_{240min(control)}$	–	56%	59%	65%

n = slope of the Freundlich adsorption isotherm; b = reciprocal of slope of the Langmuir adsorption isotherm (limiting adsorptive capacity); a = adsorption constant of the Langmuir adsorption isotherm; CA = complete adsorption.

with a similar insignificant decrease in absorption of propranolol via the rat everted-intestine technique (McElnay et al., 1982).

Kaolin–pectin suspension strongly adsorbed propranolol in vitro and significantly reduced its bioavailability in rats (Table 1). A similar but less significant effect was observed by McElnay et al. (1982) with kaolin alone. The increased interaction of propranolol with the kaolin–pectin suspension is attributed to the finely divided state of kaolin in the mixture, as well as to other formulation variables. Magnesium trisilicate was also found to be a strong adsorbent and consequently decreased the bioavailability of propranolol. The effect reported by McElnay et al. (1982) for the same interaction was insignificant. The difference is probably due to the use, in the present study, of a pH 2.2 buffer which would lead to the formation of finely divided silicic acid with expectedly high adsorptive capacity. The parallel reduction in bioavailability observed in the present in vivo studies could be related to a similar effect on magnesium trisilicate by the stomach acid.

Bismuth subsalicylate suspension adsorbed propranolol in vitro and reduced its bioavailability. Bismuth subsalicylate was also reported to decrease the absorption of tetracyclines co-administered with it (Ericsson et al., 1982; Albert et al., 1979). Results of the present study support suggestions that adsorbents and antidiarrhoeals interact with various drugs through adsorption, complexation and change in gastrointestinal motility and/or pH (McElnay et al., 1982; Albert et al., 1979). These interactions may lead to clinically important differences in the bioavailability of drugs when taken with adsorbents and antidiarrhoeal preparations.

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