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Decreased bioavailability of some antipsychotic phenothiazines due to interactions with adsorbent antacid and antidiarrhoeal mixtures

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Summary

The interactions of the antipsychotic phenothiazines; trifluperazine, fluphenazine, perphenazine and thioridazine on milk and on adsorbent antacid and antidiarrhoeal mixtures including magnesium trisilicate, bismuth subnitrate, kaolin-pectin mixture and aluminium hydroxide–magnesium carbonate mixture were studied. Adsorption was essentially complete (> 90%) when a fraction to several times the dose of each of the phenothiazines was allowed to interact with approximately 1 g of each of the adsorbents. The effect of the interaction of thioridazine with kaolin-pectin mixture and with magnesium trisilicate on the bioavailability of thioridazine was also studied. Peak phenothiazine plasma concentration in rats was decreased to 49% and 23% of control values (drug without adsorbent) in both cases respectively. Area under the plasma concentration time curves, but not absorption rate, was also decreased to 49% and 21% of control values for the same combinations. These interactions suggest possible clinical failure when a phenothiazine and an adsorbent are taken concurrently.

Introduction

Antipsychotic phenothiazines are usually used in the treatment of psychiatric patients for prolonged time periods and often for a lifetime. Adsorbent antacid and antidiarrhoeal mixtures are mostly over-the-counter preparations available for self-medication. The interaction of these two classes of drugs, when taken concurrently, is of both physicochemical as well as therapeutic interest. The action of phenothiazines is commensurate with certain plasma concentration levels which may be reduced by drug interactions. Antacid and antidiarrhoeal preparations are known to interfere with the gastrointestinal absorption of many drugs (Brown and Juhl, 1976; Naggar et al., 1977; Hurwitz, 1977; Bucci et al., 1981; Ericsson et al., 1982; Chen et al., 1983; Feldman and Hedrick, 1983; Gouda et al., 1984; Takahashi et al., 1985; Moustafa et al., 1986, 1987). Interactions of some phenothiazines, in particular, with adsorbent and antacid preparations were also reported (Sorby, 1965; Sorby and Liu, 1966; Sorby et al., 1966; Fann et al., 1973). In this respect, the effect of

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activated attapulgite and activated charcoal on promazine bioavailability in humans was studied by Sorby (1965). Activated attapulgite was found to slow absorption rate (as measured from urinary excretion data) whereas activated charcoal decreased both the rate and extent of promazine absorption. Sorby and Liu (1966), using human urinary excretion data, also reported a decrease in rate and extent of promazine absorption when administered concurrently with an antidiarrhoeal mixture containing attapulgite and citrus pectin. Another study by Sorby et al. (1966), on the adsorption of phenothiazine derivatives by Kaolin, talc and activated charcoal revealed that adsorption of phenothiazines was affected by the pH and electrolyte concentration of the medium. Fann et al. (1973) reported a significant lowering in chlorpromazine plasma levels in man, 2 h post administration, by the concomitant administration of a gel-type antacid containing magnesium trisilicate and aluminium hydroxide. They attributed this effect to adsorption and not to a rise in pH of the intestinal tract. Takahashi et al. (1981) studied the binding properties of phenothiazine derivatives to pectin in aqueous solution and reported a good positive correlation between the binding parameters and adsorption parameters of the phenothiazines.

The object of this report is to study the in-vitro interactions of four commonly used antipsychotic phenothiazine derivatives (trifluoperazine, fluphenazine, perphenazine and thioridazine) with commercially available Simeco (codried aluminium hydroxide and magnesium carbonate with magnesium oxide tablets), Kaopectate (kaolin–pectin suspension), magnesium trisilicate, bismuth subnitrate and with milk powder in one case. The effect of an interaction between a selected phenothiazine (thioridazine) and an antidiarrhoeal adsorbent (Kaopectate) and an antacid (magnesium trisilicate) on drug bioavailability in rats is also to be studied.

Materials and Methods

Materials

Trifluoperazine hydrochloride (Stelazine, SK and F, Hertfordshire, U.K.), fluphenazine hydrochloride (Moditen, E.R. Squibb and Sons Ltd., Hounslow, Middlesex, U.K.), perphenazine (Trilafon, Schering Corporation, Kenilworth, New Jersey, U.S.A.), thioridazine hydrochloride (Melleril, Sandoz Ltd., Basle, Switzerland), Simeco (dried aluminium hydroxide and magnesium carbonate with magnesium hydroxide and simethicone tablets, lot E 4598, Wyeth Ltd., Havant, U.K.), Kaopectate (kaolin-pectin suspension, lot PE 128, Upjohn, Puurs, Belgium), magnesium trisilicate (BDH Chemicals, Poole, U.K.), bismuth subnitrate (Riedel-Dehaen AG, Seelze-Hannover, F.R.G.) and milk powder (Nido, Nestle, lot CW 7AC prepared by Allgauer Alpenmilch AG, Munich, F.R.G.) were used in the present study. All other chemicals were reagent grade.

Adsorption studies

Solutions containing varying amounts (a fraction to several times the average dose) of trifluoperazine hydrochloride (1–30 mg), fluphenazine hydrochloride (0.5–4.5 mg), perphenazine (2–15 mg), thioridazine hydrochloride (10–100 mg), in 0.1 M glycine-NaCl-HCl buffer (pH 2) were added, in separate experiments, to Simeco (1 g), kaopectate (5 ml), magnesium trisilicate (1 g), bismuth subnitrate (1 g) or milk powder (7.22 g). Bismuth subnitrate and magnesium trisilicate were previously heated at 120 °C for 3 h and screened through a number-170 sieve. Simeco tablets were previously powdered and screened through the same sieve. The volumes were adjusted to 50 ml using the same buffer, in 100 ml bottles. The bottles were shaken in a constant temperature water bath at 37 ± 0.5 °C for 3 h. Equilibrium was established at that time. An aliquot was filtered (Millipore, 0.45 μm) and the concentration of each of the phenothiazines was determined spectrophotometrically (Sorby et al., 1966). Because of interfering materials in case of Kaopectate and milk, the assays were carried out spectrofluorometrically (West et al., 1974).

Absorption studies

Adult male rats weighing about 200 g each, divided in 3 groups, were fasted for 12 h prior to drug administration. Thioridazine hydrochloride

was given orally in an aqueous solution at a dose of 10 mg/kg b.wt. to all groups. Kaopectate or magnesium trisilicate suspension (1 g/5 ml) were given to two separate groups at a dose of 5 ml/kg body weight immediately before drug administration. The third (control) group received thioridazine hydrochloride solution only. The animals were allowed free access to water all the time and were allowed food only 3 h after drug administration. Eight animals from each group were sacrificed at intervals of 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h. Total phenothiazine concentration in the plasma of rats was determined spectrofluorometrically (Mahju and Maickel, 1969; West et al., 1974).

Results and Discussion

Trifluoperazine, fluphenazine, perphenazine and thioridazine were adsorbed on all adsorbents and thioridazine was adsorbed on milk following a Freundlich-type isotherm. Fig. 1 shows a Freundlich-type plot for the adsorption of the phenothiazines on magnesium trisilicate and on milk. Similar plots were obtained for other adsorbents. Adsorption was essentially complete in all cases; however, in the case of milk the amount adsorbed per unit mass was less. Plotting of the Langmuir adsorption isotherm was only possible when equilibrium concentration (C_e) values were measurable (Fig. 2). In most cases, because more than 90% of the drug was adsorbed, C_e values were found to be too low to allow for a meaningful Langmuir plot. In those cases, where the plot was possible, limiting adsorptive capacities for trifluoperazine, fluphenazine, perphenazine and thioridazine on bismuth subnitrate were 21.4, 8, 12 and 76.9 mg/g, respectively. Magnesium trisilicate was found to adsorb fluphenazine and perphenazine with limiting adsorptive capacities of 4.5 and 19.2 mg/g respectively. The adsorbent-adsorbate affinity was high so that desorption attempts, collecting repeated washings of the combination with the same buffer used in adsorption studies (0.1 M glycine-NaCl-HCl, pH 2) produced less than 10% of the adsorbed phenothiazine in the eluate in most cases.

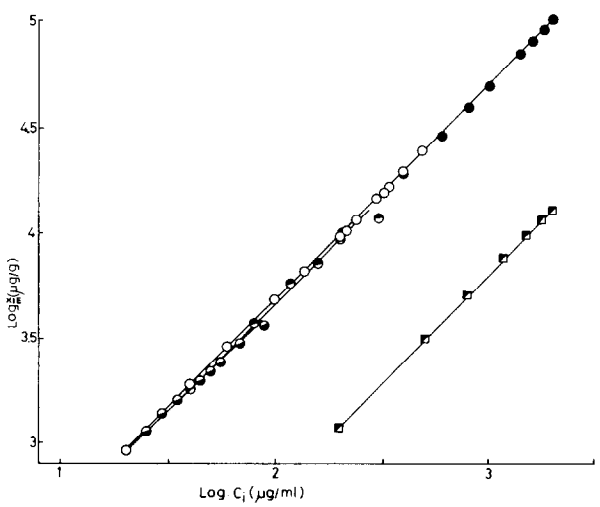

Fig. 1. Freundlich adsorption isotherms of; ○, trifluoperazine; ◒, fluphenazine; ◓, perphenazine; ●, thioridazine on magnesium trisilicate and ◩, thioridazine on milk.

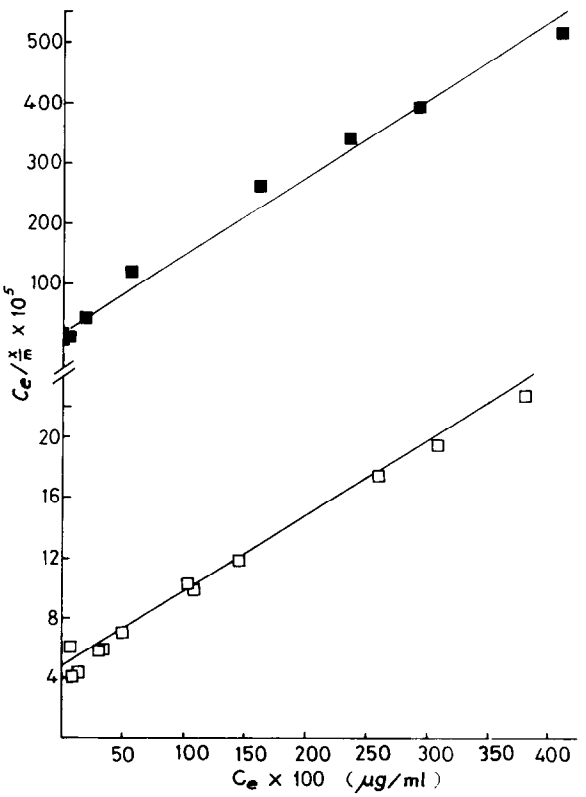

Fig. 2. Langmuir adsorption isotherms of: ■, thioridazine (upper scale, higher C_e values); □, trifluoperazine (lower scale, lower C_e values) on bismuth subnitrate.

In vivo studies in rats showed a decrease in the extent, but not the rate, of absorption of thioridazine when coadministered with Kaopectate and with magnesium trisilicate (Table 1 and Fig. 3). A decrease of maximum plasma concentration to 49% and 23% of control values (drug without adsorbent) was observed in both cases respectively. A parallel decrease of the area under the plasma concentration–time curves (AUC values) to 49% and 21% of control values was also observed. Time of peak plasma concentration was, however, unchanged (60 min). Although adsorption of thioridazine in vitro was essentially complete on both antacid and antidiarrhoeal preparations, in vivo drug bioavailability was still measurable, even though significantly compromised. In vitro–in vivo extrapolations did not work out quantitatively, understandably because of varying physiological as well as physicochemical factors. In spite of this, in vitro findings were still valuable in relating to the decreased bioavailability of the phenothiazine because the extent of the interaction was considerable.

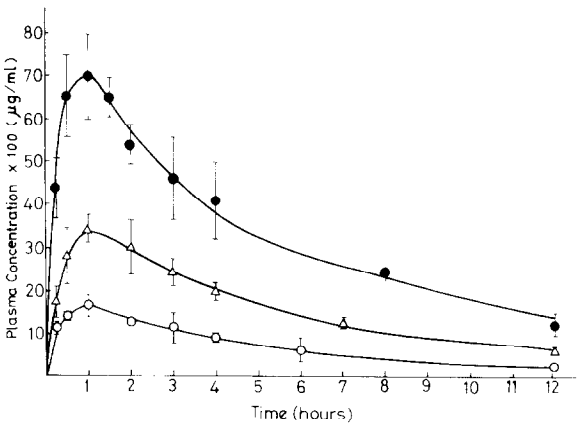

Fig. 3. Effect of adsorption on the mean plasma phenothiazine concentration-time curve. ●, control; △, kaolin–pectin; ○, magnesium trisilicate; ⊤ ⊥, limits of error.

Previous studies on the interactions of promazine and chlorpromazine with adsorbents (Sorby, 1965; Sorby and Liu, 1966; Forrest et al., 1970; Fann et al., 1973) refer to a decrease in plasma levels, rate and extent of drug absorption or to a decrease only in the rate of drug absorption. In the present study, the phenothiazine plasma levels resulting from administration of thioridazine to rats as well as AUC values, were considerably decreased by interaction with adsorbents. Rate of absorption, as measured by the time required to reach maximum drug plasma concentration, however, was not decreased. The decrease in bioavailability observed in the present study (50–75%) due to adsorption of thioridazine on antacid or antidiarrhoeal preparations was much higher than that observed in the previous reports (only about 25%). The difference is probably due to the relatively high doses of chlorpromazine compared to the smaller doses of antipsychotics used in the present study. A high concentration of the phenothiazine would presumably consume the adsorptive capacity of the adsorbent and consequently decreases bioavailability by only a smaller fraction. The decrease in bioavailability would, therefore, be expected to constitute a more important clinical problem in case of those phenothiazines which are administered in small doses.

In agreement with the interpretation of Fann et al. (1973), adsorption is thought to be responsible for the decrease in bioavailability of phenothiazines coadministered with adsorbents and antacids. Changes in pH of the gastrointestinal tract are unlikely to be responsible for the decrease. On the contrary, increase of pH would, based on pH partition theory, favour rather than decrease drug

TABLE 1

Bioavailability data of thioridazine with and without kaolin-pectin and magnesium trisilicate

	t_{max} (min)	C_{max} (ng/ml)	C_{max}/C_{max} (control)	AUC (ng · h/ml)	AUC/AUC (control)
Control	60	705	–	4061.25	–
Kaolin–pectin	60	346	49.1%	1980.0	48.75%
Magnesium trisilicate	60	163	23.12%	846.25	20.8%

absorption. pH was maintained relatively constant, during the present study, through the use of an acidic buffer thus simulating conditions in the stomach immediately following drug administration, even though this acidic medium may not be very favourable for absorption (Sorby and Liu, 1966). The mechanism of adsorption is not quite understood, however, cationic drugs, especially amine-type compounds were reported to interact with silicates and with other materials like pectin through hydrogen bonding or Van der Waal's forces (Sorby and Liu, 1966).

Important clinical implications pertain to results of the present study. Bioavailability of potent antipsychotic phenothiazine drugs can be decreased enough to lead to therapeutic failure. Spacing administration of the adsorbent and/or antacid preparations 1 h before or 2 h after administration of the phenothiazine as suggested by Fann et al. (1973), might be a good answer to the problem. Dose increase as suggested by the same authors cannot, however, be considered safe until the decrease of bioavailability can be metered for all possible combinations under standardised conditions, a rather uneasy task.

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