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# Interactions of procainamide, verapamil, guanethidine and hydralazine with adsorbent antacids and antidiarrhoeal mixtures

Hasan I. Al-Shora, Mamdouh A. Moustafa, Esmail M. Niazy, Mohamed Gaber and M. Wafik Gouda

*College of Pharmacy, King Saud University, Riyadh (Saudi Arabia)*

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## Summary

The in vitro interactions of procainamide, verapamil, guanethidine and hydralazine with some commercial adsorbent antacids and anti-diarrhoeal preparations were studied. Kaopectate was found to adsorb procainamide, verapamil, guanethidine and hydralazine with a limiting adsorptive capacity of 16.67, 15.15, 9.62 and 20.12 mg/g, respectively, while magnesium trisilicate was found to adsorb the same drugs with a limiting adsorptive capacity of 20.08, 25.13, 33.9 and 100 mg/g respectively. The limiting adsorptive capacity of hydralazine and guanethidine on Pepto-Bismol were 84.03 and 12.5 mg/g while Simeco adsorbed hydralazine with a limited capacity of 26.2 mg/g. Peak salivary procainamide concentration in humans were decreased by about 31% and the AUC was decreased by about (32%) on concurrent administration of kaopectate with the drug. These interactions could lead to important differences in bioavailability of the above drugs.

## Introduction

Drug interactions could result in less than optimum therapeutic outcome. Drug interactions involving adsorbent antacids and antidiarrhoeal mixtures, which are used for self-medication, have been recently reviewed and classified according to their actual clinical importance (D'Arcy and McElnay, 1987).

Antiarrythmics like procainamide and verapamil, and antihypertensives like guanethidine and hydralazine, are drugs that may be used for prolonged periods of time. The common adverse effects of these drugs are gastrointestinal disturbances, including nausea, vomiting and diarrhoea. The concomitant administration of antacids or antidiarrhoeals, in an attempt to relieve the gastrointestinal side effects, present a potential source of interaction for these potent drugs.

Interactions of some antiarrythmics with antacids and antidiarrhoeals were previously studied (Moustafa et al., 1987; Moustafa et al., 1986; Remon et al., 1983; Remon et al., 1979; Romankiewicz et al., 1978). The adsorption of procainamide and propranolol on common antacids and antidiarrhoeals was reported (Moustafa et al., 1986; Remon et al., 1981). The influence of aluminium phosphate on the bioavailability of procainamide was also studied (Albin et al., 1981). The effect of aluminium hydroxide and magnesium oxide on the bioavailability of procainamide in dogs was reported (Remon et al., 1983).

*Correspondence*: M. Wafik Gouda, College of Pharmacy, King Saud University, P.O.B. 2457, Riyadh-11451 (Saudi Arabia).

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The aim of the present investigation was to study the in-vitro interactions of the antihypertensive drugs, guanethidine and hydralazine, and the antiarrythmic drugs, procainamide and verapamil, with commercially available Kaopectate (kaolin-pectin suspension), Pepto-Bismol (bismuth subsalicylate tablets). Simeco (co-dried aluminium hydroxide and magnesium carbonate with magnesium hydroxide and simethicone tablets) and magnesium trisilicate. The effect of the interaction between procainamide and Kaopectate on oral absorption of procainamide was assessed in vivo in a limited bioavailability study, using salivary secretion data, in humans.

## Materials and Methods

*Materials*

Procainamide hydrochloride (Lederle Laboratories Division American Cyanamid Company, Pearl River, N.Y., U.S.A.), verapamil hydrochloride (Knoll AG, D 6700 Ludwigshafen, F.R.G.), guanethidine monosulphate (Ciba Geigy AG, Basel, Switzerland), hydralazine hydrochloride (Ciba Laboratories, Horsham, West Sussex, Switzerland), Kaopectate (kaolin-pectin suspension, SF 168, Upjohn, Puurs, Belgium), Pepto-Bismol (bismuth subsalicylate tablets, control No. 134925, Norwich Eaton Pharmaceuticals, Norwich, U.S.A.), Simeco (co-dried aluminium hydroxide and magnesium carbonate with magnesium hydroxide and simethicone tablets lot E 4591, Wyeth Havant, U.K.) and magnesium trisilicate (BDH Chemicals, Poole, U.K.) were used. All other chemicals were reagent grade.

*Adsorption studies*

Kaopectate (15 ml), Pepto-Bismol (2.23 g equivalent to two tablets ground and screened through no. 170 sieve), Simeco (1.2 g equivalent to 3 tablets ground and screened through no. 170 sieve) and magnesium trisilicate (1 g previously heated at 120 °C for 3 h and screened through no. 170 sieve), were placed in separate 100 ml bottles. The drugs solutions in 0.05 M KCl-HCl buffer (pH 2.2) were added to the adsorbents and the volumes were adjusted to 50 ml using the same buffer. Drug concentrations were 5–100 mg/50 ml for procainamide hydrochloride, 10–82 mg/50 ml for verapamil hydrochloride, 5–52 mg/50 ml for guanethidine monosulfate and 7–136 mg/50 ml for hydralazine hydrochloride. The bottles were shaken in a constant temperature water bath at $37 \pm 0.5$ °C for 3 h. Equilibrium was established at that time. Aliquots were filtered (Millipore 0.45 $\mu$m) and the drug concentration was determined. Procainamide was assayed spectrophotometrically (Koch-Weser and Klein, 1971), verapamil spectrofluorometrically (McAllister and Howell, 1976), guanethidine according to the British Pharmacopoeia (1980), and hydralazine according to the United States Pharmacopeia (1975).

*Bioavailability study*

Salivary concentrations of procainamide were determined following the protocol previously reported (Moustafa et al., 1987). Four healthy informed adult volunteers with no evidence of cardiac, renal, liver or gastrointestinal abnormalities participated in the study, in a cross-over design. The study was carried out under medical supervision. All subjects did not receive any medication for 7 days or any enzyme inducing agent for 30 days before the study. During the study, subjects received only the medication prescribed with 14 days separating each of the treatment design. All subjects abstained from food from 22:00 h the night before their allocated treatment, until 4 h after taking the medication. Smoking was not permitted during the study. The subjects were administered 250 mg of procainamide orally in the control experiments, and in the second treatment 30 ml of Kaopectate were coadministered with the same amount of drug. Subjects were required to expectorate into 10 ml stoppered test tube until 3 ml of mixed saliva has been collected. Samples were obtained at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 10 h after administration, and all samples were refrigerated until analysis. Aliquots (2 ml) of saliva (centrifuged to remove sputum) were analyzed for procainamide spectrophotometrically (Koch-Weser and Klein, 1971). Blank specimens of saliva were assayed in the same manner as the samples, and the appropriate blank corrections were applied.

## Results and Discussion

All 4 drugs, hydralazine, guanethidine, verapamil and procainamide were adsorbed on Kaopectate and magnesium trisilicate. The adsorption was found to follow the Langmuir isotherm (Figs. 1, 2, and Table 1). The adsorption of hydralazine and guanethidine on Pepto-Bismol was found to have a similar pattern (Fig. 3 and Table 1).

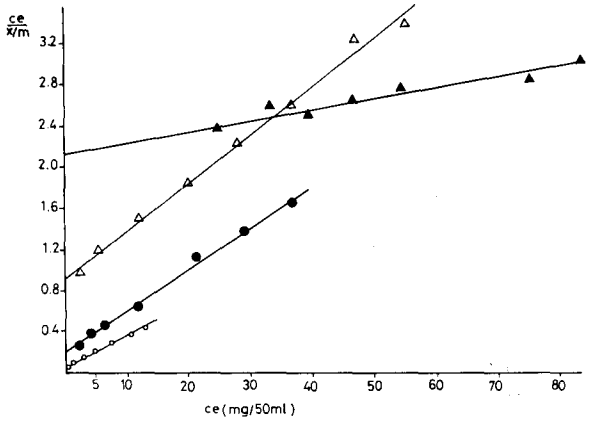


Fig. 1. Langmuir adsorption isotherm of ▲, hydralazine; △, procainamide; ●, verapamil; ○, guanethidine on magnesium trisilicate.

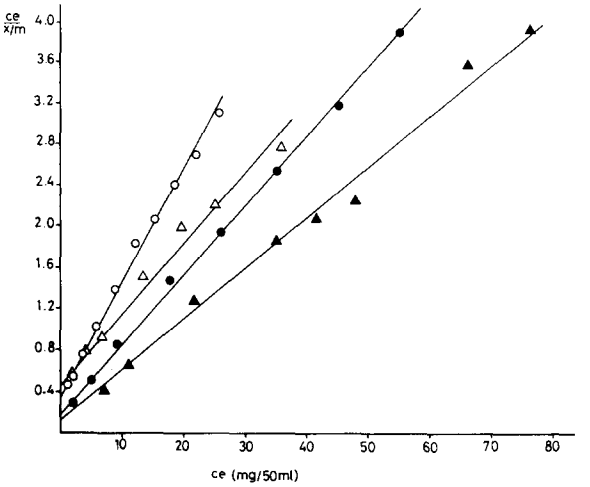


Fig. 2. Langmuir adsorption isotherm of ○, guanethidine; △, procainamide; ●, verapamil; ▲, Hydralazine on kaolin–pectin.

Simeco showed poor affinity for all drugs except hydralazine which was adsorbed according to the Langmuir isotherm (Fig. 4 and Table 1). The lack of adsorption of procainamide on Simeco is in agreement with in-vitro results of Remon et al. (1981) showing no adsorption of procainamide on aluminium hydroxide and magnesium oxide, and

TABLE 1

*Adsorption parameters for procainamide, verapamil, guanethidine and hydralazine with various adsorbents*

| Adsorbent | Langmuir isotherm | Procainamide | Verapamil | Guanethidine | Hydralazine |
|---|---|---|---|---|---|
| Kaopectate | Slope $\times 10^2$ | 6.00 | 6.60 * | 10.40 | 4.97 |
| | Intercept $\times 10^2$ | 57.88 | 20.00 * | 38.00 | 6.24 |
| | Constant b. $\times 10^2$ | 10.37 | 33.00 * | 27.37 | 79.65 |
| | 1/Slope, mg/g | 16.67 | 15.15 * | 9.62 | 20.12 |
| Magnesium trisilicate | Slope $\times 10^2$ | 4.98 | 3.98 | 2.95 | 1.00 |
| | Intercept $\times 10^2$ | 95.40 | 21.10 | 5.79 | 216.50 |
| | Constant b. $\times 10^2$ | 5.22 | 18.86 | 50.08 | 0.46 |
| | 1/Slope, mg/g | 20.08 | 25.13 | 33.90 | 100.00 |
| Pepto-Bismol | Slope $\times 10^2$ | – | – | 8.00 | 1.19 |
| | Intercept $\times 10^2$ | – | – | 13.62 | 109.00 |
| | Constant b. $\times 10^2$ | – | – | 58.74 | 1.09 |
| | 1/Slope, mg/g | – | – | 12.50 | 84.03 |
| Simeco | Slope $\times 10^2$ | – | – | – | 3.82 |
| | Intercept $\times 10^2$ | – | – | – | 25.41 |
| | Constant b. $\times 10^2$ | – | – | – | 15.03 |
| | 1/Slope, mg/g | – | – | – | 26.20 |

* Kaolin–pectin suspension of similar concentration was used instead of Kaopectate due to interference in the assay method.

TABLE 2

Procainamide bioavailability from salivary concentration data

| Subject | $C_{max}$ (μg/ml) | | (Expt./control) ×100 | $t_{max}$ (h) | | AUC (μg · h/ml) | | (Expt./Control) ×100 |
|---|---|---|---|---|---|---|---|---|
| | Expt. | Control | | Expt. | Control | Expt. | Control | |
| 1 | 1.90 | 3.30 | 57.58 | 1.00 | 1.10 | 5.99 | 9.08 | 65.98 |
| 2 | 3.25 | 4.50 | 72.22 | 1.25 | 1.15 | 8.39 | 12.23 | 68.61 |
| 3 | 1.41 | 2.35 | 60.00 | 1.10 | 0.95 | 4.03 | 6.66 | 60.44 |
| 4 | 2.20 | 2.50 | 88.00 | 2.05 | 2.10 | 9.14 | 12.03 | 75.97 |
| Mean | 2.19 | 3.16 | 69.45 | 1.35 | 1.33 | 6.89 | 10 | 67.75 |
| C.V., % | 35.53 | 31.14 | 20.05 | 35.39 | 39.37 | 33.83 | 26.52 | 9.52 |

Expt. = 30 ml of Kaopectate coadministered with 250 mg of procainamide hydrochloride. Control = a dose of 250 mg of procainamide hydrochloride.

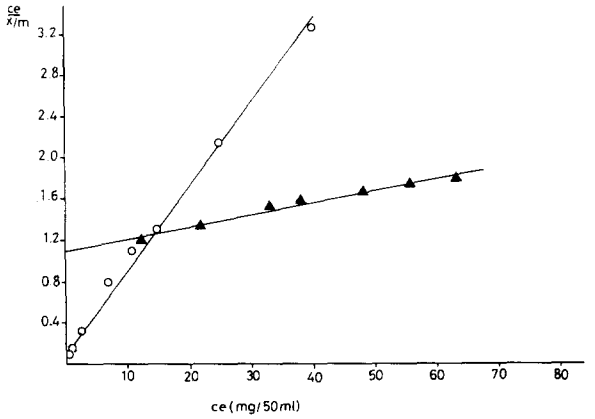


Fig. 3. Langmuir adsorption isotherm of ▲, Hydralazine; ○, guanethidine on Pepto-Bismol.

the in-vivo results (Remon et al., 1983), indicating no significant decrease in the AUC when procainamide was administered with these two antacids to dogs.

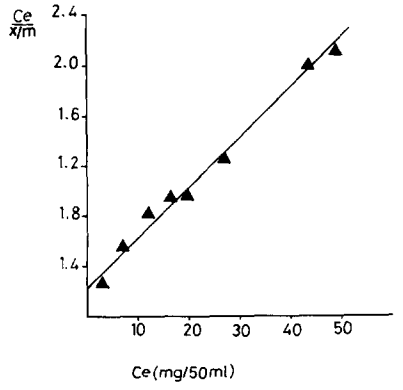


Fig. 4. Langmuir adsorption isotherm of hydralazine on Simeco.

It can be seen (Table 1) that the limiting adsorptive capacity for hydralazine, guanethidine, verapamil and procainamide on Kaopectate were 20.12, 9.62, 15.15, and 16.67 mg/g respectively, while magnesium trisilicate was found to adsorb hydralazine, guanethidine, verapamil and procainamide with limiting adsorptive capacity of 100, 33.9, 25.13 and 20.08 mg/g respectively. The high adsorptive capacity of magnesium trisilicate is probably due to a high-specific surface resulting from the formation of colloidal silicic acid in the low pH buffer. The limiting adsorptive capacity of hydralazine and guanethidine on Pepto-Bismol were 84.03 and 12.5 mg/g respectively while Simeco adsorbed hydralazine with a limited capacity of 26.2 mg/g.

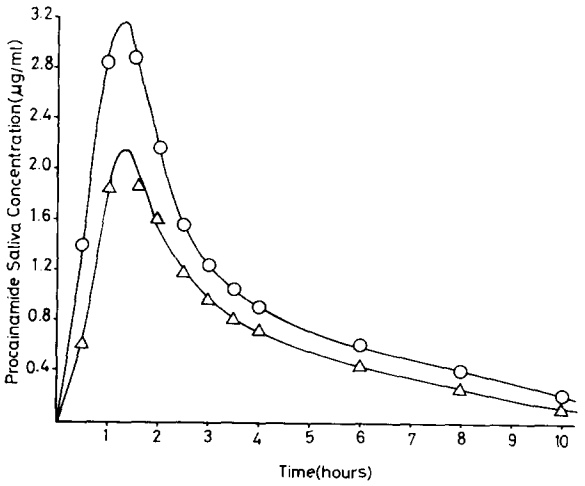


Fig. 5. Effect of adsorption on the mean salivary procainamide concentration-time curve, ○, control; △, Kaolin–pectin.

In the present study salivary procainamide concentrations were used to find out the effect of one of the interactions, namely procainamide-Kaopectate, on the bioavailability of procainamide. A decrease in peak saliva procainamide concentration of about 31% and a parallel decrease of AUC of about 32% of control values were observed (Table 2 and Fig. 5). Absorption rate, however, was not significantly affected. Intersubject variability in salivary procainamide concentrations was observed in this study and was also previously reported (Galeazzi et al., 1976). Koup et al. (1975) reported that serum protein binding is not likely to be a factor causing the variability in salivary concentration, and, intersubject variations may be attributed to differences in salivary pH or salivary flow rate. Although no correlation between saliva concentration and plasma concentration of procainamide was observed (Galeazzi et al., 1976), saliva drug concentrations seem to reflect, more precisely, the drug concentration at the cardiac site. The pharmacological effects of procainamide and its saliva concentration follow the same kinetics. Therefore, the salivary concentration of procainamide may be clinically more relevant than the corresponding plasma concentration (Danhof and Briemer, 1978).

The present results indicate that adsorption of procainamide on Kaopectate, following concomitant administration, reduce the bioavailability of the drug as measured by salivary concentration. Because of the narrow therapeutic index of procainamide, it is recommended that this drug should not be given concurrently with adsorbents. Although the effect of adsorption on the bioavailability of the other drugs in this study was not investigated, a similar reduction in bioavailability is expected to take place upon their concomitant administration with adsorbents.

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