International Journal of Pharmaceutics, 34 (1987) 207–211
Elsevier

IJP 01158

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

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

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

(Received 19 June 1986)
(Accepted 30 July 1986)

Key words: Quinidine; Interaction; Magnesium trisilicate; Kaopectate; Simeco tablet; Bismuth subnitrate; Antacid; Adsorbent; Antidiarrhoeal

Summary

The in vitro adsorption of quinidine sulphate on some commercial antacid and antidiarrhoeal preparations was assessed; the effect of some of these admixtures on drug absorption in human bioavailability studies was also measured using salivary secretion data. The adsorption of quinidine on Kaopectate (kaolin–pectin suspension) (25.8 mg/g) and magnesium-trisilicate (23.6 mg/g) was greater than that on Simeco tablets (aluminium hydroxide, magnesium carbonate and hydroxide, simethicone) (5.8 mg/g) or bismuth subnitrate (3.3 mg/g). Salivary quinidine concentrations decreased by 54% and the AUT by 58%, compared with control data, during the quinidine–Kaopectate interaction in vivo. This latter finding suggests a need for clinical monitoring of patients taking quinidine concomitantly with this type of adsorbent–antacid–antidiarrhoeal formulation.

Introduction

Literature is full of reports of drug interactions with adsorbents, antacids and antidiarrhoeal preparations (Gibaldi, 1984; Thoma and Lieb, 1983; Remon et al., 1979; Huruwitz, 1977). These preparations are usually available for self-medication and are often used when the side-effects of a drug include gastrointestinal disturbances such as diarrhoea. The interactions were shown in many cases to decrease the bioavailability of drugs (Moustafa et al., 1986; Takahashi et al., 1985; Gouda et al., 1984; Bucci et al., 1981; Albert et al., 1978).

Correspondence: M.A. Moustafa, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Quinidine is an antiarrhythmic drug, the therapeutic effectiveness of which is associated with a rather narrow plasma concentration level (Reynolds, 1982). The bioavailability of quinidine is variable and incomplete owing to first-pass metabolism (Guentert et al., 1979; Ueda et al., 1976). Considerable inter- and intra-subject variability was noted in its biological half-life (Reynolds, 1982). Further variation in bioavailability may be anticipated when the drug is taken concurrently with antidiarrhoeal preparations because of possible interactions. A study in 4 healthy subjects indicated that aluminium hydroxide mixture did not interfere with the absorption of quinidine sulphate (Romankiewicz et al., 1978). Remon et al. (1983) on the other hand, reported bioavailability changes of antiarrhythmic drugs, including quinidine, when given with aluminium hydroxide

and magnesium oxide to dogs. In vitro interaction studies involving quinidine salts with kaolin, pectin, montmorillonite and other antacids and adsorbents also suggest possible alteration of drug absorption from the gastrointestinal tract (Sanchez and Sanchez, 1982; Bucci et al., 1981; Remon et al., 1979; Hayden and Comstock, 1975). Relative bioavailability studies have been suggested (Bucci et al., 1981) to determine the significance of quinidine interactions with kaolin and pectin. Adsorption–desorption studies of quinidine salts (Bucci et al., 1981; Sanchez and Sanchez, 1982; Remon et al., 1979) have interpreted the extent of adsorption in terms of pH and ionic strength of the medium. The general pattern of the findings was that quinidine, being a weak base, was adsorbed to a greater extent when the pH was increased and/or the ionic strength decreased.

The object of this report is to study the in vitro adsorption of quinidine sulphate on commercially available Kaopectate (kaolin–pectin suspension), Simeco (codried aluminium hydroxide and magnesium carbonate with magnesium hydroxide and simethicone tablets) and on magnesium trisilicate and bismuth subnitrate. The effect of some of these interactions on drug absorption is also to be assessed in a limited bioavailability study using salivary secretion data in humans.

Materials and Methods

Quinidine sulphate (E. Merck, Darmstadt, F.R.G.), Kaopectate (Kaolin–pectin suspension, lot RD 119, Upjohn, Puurs, Belgium), Simeco (co-dried aluminium hydroxide and magnesium carbonate with magnesium hydroxide and simethicone tablets, lot (E) 4591, Wyeth, Havant, U.K.), bismuth subnitrate (Riedel-De Haen, Seelze-Hannover, F.R.G.) and magnesium trisilicate (BDH Chemicals, Poole, U.K.) were used. All other chemicals were reagent grade.

Adsorption study

Quinidine solutions (4–42 mg/50 ml) in 0.05 M KCl–HCl buffer pH 2.2 were added, in separate bottles to the adsorbents; namely, Kaopectate (5 ml), magnesium trisilicate (1 g, previously heated at 120°C and screened through No. 170 sieve), Simeco (1 g equivalent to 2.5 tablets ground and screened through No. 170 sieve) and bismuth subnitrate (1 g previously heated at 120°C and screened through No. 170 sieve). The volume in each bottle was adjusted to 50 ml using the same buffer. The bottles were shaken in a constant temperature water-bath at 37 ± 0.5°C for 3 h. Equilibrium was established at that time. Aliquots were filtered (Millipore, 0.45 μm) and quinidine was determined spectrofluorometrically (Bucci et al., 1981); maximum excitation at 350 nm and maximum emission at 443 nm.

Bioavailability study

Four healthy adult informed volunteers with no evidence of cardiac, renal, 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 treatments design. Subjects were required to fast from 22.00 h the night before their allocated treatment until 4 h after taking the medication. Smoking was not permitted during the experiment. One treatment consisted of administering 100 mg of quinidine sulphate; the other treatment required administering of 30 ml of Kaopectate prior to 100 mg of quinidine sulphate. Subjects were required to expectorate into 10 ml test tubes until 3 ml of mixed saliva have been collected. Samples were obtained at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h after administration. Aliquots (2 ml) of saliva (centrifuged to remove sputum) were analysed for quinidine (Jaffe et al., 1975). Blank specimens of saliva were assayed in the same manner as the samples, and the appropriate blank corrections were applied.

Results and Discussion

The adsorption of quinidine sulphate on antacid and antidiarrhoeal preparations was found to follow both the Freundlich and Langmuir adsorp-

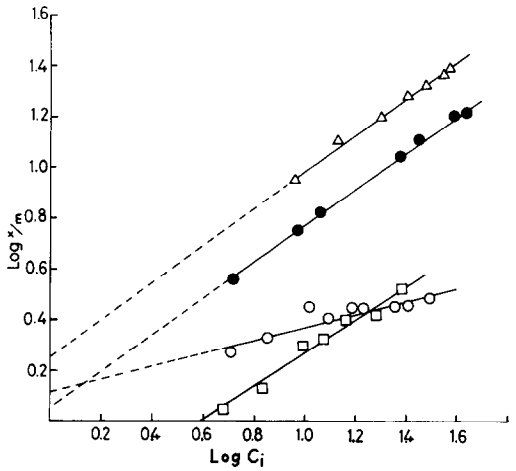

Fig. 1. Freundlich adsorption isotherms of quinidine on △, kaolin–pectin; ●, magnesium trisilicate; ○, bismuth subnitrate; □, Simeco.

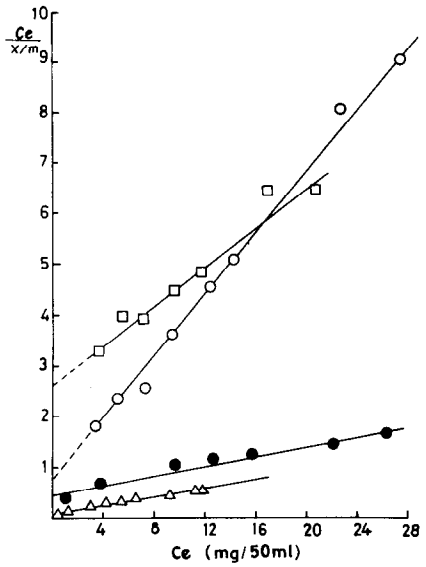

Fig. 2. Langmuir adsorption isotherms of quinidine on: ○, bismuth subnitrate; □, Simeco; ●, magnesium trisilicate; △, kaolin–pectin.

tion isotherms (Figs. 1 and 2). Adsorption parameters evaluated from the plots are shown in Table 1. It can be seen that Kaopectate and magnesium trisilicate adsorbed quinidine to a much greater extent than Simeco and bismuth subnitrate. Comparison of results of the present study with those of previous reports (Remon et al., 1983; Bucci et al., 1981; Romankiewicz et al., 1978) shows that agreement was only qualitative. The relatively poor adsorption of quinidine on aluminium hydroxide preparations, as found with Simeco tablets in the present study, might be the reason why such an interaction was reported, not to interfere with the extent of drug absorption in humans (Romankiewicz et al., 1978) while, in another study in dogs, it was found to decrease the maximum drug plasma concentration, shift the time required to reach that concentration but does not decrease the area under the plasma concentration–time curve (Remon et al., 1983). Poor adsorption was also found for quinidine on bismuth subnitrate and other adsorbent antacids studied (bismuth subnitrate, bismuth subsalicylate suspension, calcium carbonate) which adsorbed less than 5% of the drug.

The extent of adsorption of quinidine on kaolin in Kaopectate was found to be more than 25 mg/g, whereas a value of less than 4 mg/g was reported by Bucci et al. (1981). The discrepancy is probably due to the hypothesis, previously re-

TABLE 1

ADSORPTION PARAMETERS FOR QUINIDINE SULPHATE INTERACTION WITH VARIOUS ADSORBENTS

	Magnesium trisilicate	Kaopectate	Simeco	Bismuth subnitrate
Freundlich isotherm, slope $\times 10^2$	71.4	73.6	65.6	25.0
Freundlich isotherm, intercept $\times 10^2$	7	25	−40	12
Langmuir isotherm, slope $\times 10^2$	4.237	3.882	17.326	30.200
Langmuir isotherm, intercept $\times 10^2$	55.0	7.0	265.0	80.0
Langmuir isotherm, constant b. $\times 10^2$	7.70	55.50	6.50	37.80
Limiting adsorptive capacity, (1/Langmuir slope, mg/g)	23.60	25.76	5.77	3.31

ported (Moustafa et al., 1986), that kaolin in Kaopectate exists in a fine state of subdivision together with other formulation ingredients which make the preparation a much more effective adsorbent than kaolin alone. The high adsorption capacity of magnesium trisilicate is probably due to a high specific surface as a result of the formation of colloidal silicic acid in the low pH buffer. A pH 2.2 buffer was used, in the present study, to simulate conditions in the stomach when the drug is ingested.

A good correlation between plasma and saliva quinidine concentration was observed after a single dose of the drug (Narang, 1983). Various reports have given salivary concentration data for quinidine, and most of these suggest the possible use of saliva in bioavailability studies rather than for clinical monitoring (Narang, 1983; Danhof and Breimer, 1978; Jaffe et al., 1975). In the present study, salivary quinidine concentrations were used to find out the effect of one important interaction, namely, quinidine–Kaopectate, on the bioavailability of quinidine. A decrease in peak saliva quinidine concentration of 54% and a decrease of AUC of 58% were observed; absorption rate, however, was not significantly affected ($P > 0.05$). Results are shown in Fig. 3 and Table 2.

It can be seen that in spite of the limited number of subjects receiving the drug alone or in combination with Kaopectate and inter-subject variability in maximum saliva concentration levels, time to reach this maximum and area under the saliva concentration–time curves, the ratio of these

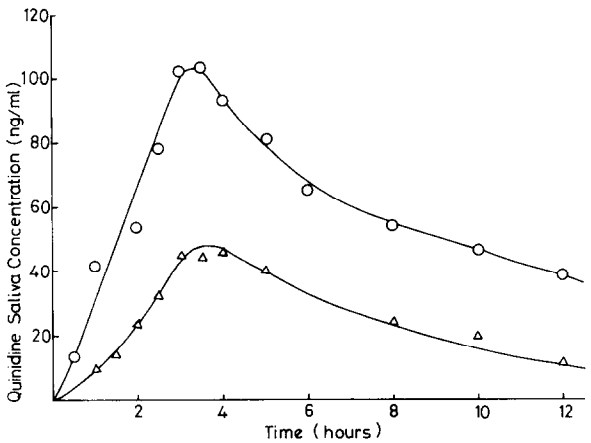

Fig. 3. Effect of adsorption on the mean salivary quinidine concentration–time curve. ○, control; △, kaolin–pectin.

values (treatment to control) was essentially the same for each individual. Saliva concentrations as measured in this report reflected more of the free rather than total quinidine concentrations in saliva (Jaffe et al., 1975). Saliva pH was also variable and might, consequently, account for intrasubject variability (Levy and Lampman, 1975). The highly significant decrease ($P < 0.05$) in maximum salivary concentrations and area under the saliva concentration–time curve, a bioavailability decrease of more than 55%, with the quinidine–Kaopectate interaction would suggest a need for clinical monitoring of patients taking quinidine regularly when adsorbent–antacid or antidiarrhoeal therapy of this type is concomitantly instituted.

TABLE 2

QUINIDINE BIOAVAILABILITY FROM SALIVARY CONCENTRATION DATA

Subject	C_{max} (ng/ml)		(Expt./Control) ×100	t_{max} (h)		AUC (ng · h/ml)		
	Expt.	Control		Expt.	Control	Expt.	Control	(Expt./Control) ×100
A	53	107	49.53	4.25	4.00	346	816	42.40
B	39	88	44.32	2.50	2.25	172	410	42.00
C	55	122	45.08	3.50	3.25	383	924	41.30
D	45	99	45.45	3.75	3.50	295	714	41.45
Mean	48	104	46.10	3.50	3.25	299	716	41.75
C.V., %	15.40	13.76	5.08	21.02	22.65	30.78	30.91	1.21

Expt. = 30 ml of Kaopectate preceded administration of 100 mg quinidine sulphate. Control = a dose of 100 mg of quinidine sulphate.

References

Albert, K.S., Ayres, J.W., Disanto, A.R. Weidler, D.J., Sakmar, E., Hallmark, M.R., Stoll, R.G. DeSante, K.A. and Wagner, J.G., Influence of kaolin–pectin suspension on digoxin. *J. Pharm. Sci.*, 67 (1978) 1582–1586.

Bucci, A.J., Myre, S.A., Tan, H.S.I. and Shenouda, L.S., In vitro interaction of quinidine with kaolin and pectin. *J. Pharm. Sci.*, 70 (1981) 999–1002.

Danhof, M. and Breimer, D.D., Therapeutic drug monitoring in saliva. *Clin. Pharmacokin.*, 3 (1978) 39–57.

Gibaldi, M., *Biopharmaceutics and Clinical Pharmacokinetics*, Lea and Febiger, Philadelphia, 1984, pp. 257–285.

Gouda, M.W., Hikal, A.H., Babhair, S.A., El-Hofy, S.A. and Mahrous, G.M., Effect of sucralfate and antacids on the bioavailability of sulpiride in humans. *Int. J. Pharm.*, 22 (1984) 257–263.

Guentert, T.W., Halford, N.H.G., Coates, P.E., Upton, R.A. and Riegelman, S., Quinidine pharmacokinetics in man: choice of a disposition model and absolute bioavailability studies. *J. Pharmacokin. Biopharm.*, 7 (1979) 315–330.

Hayden, J.W. and Comstock, E.G., Use of activated charcoal in acute poisoning. Clin. Toxicol., 8 (1975) 515–533.

Huruwitz, A., Antacid therapy and drug kinetics. *Clin. Pharmacokin.*, 2 (1977) 269–280.

Jaffe, J.M., Strum, J.D., Martineau, P.C. and Colaizzi, J.L., Relationship between quinidine plasma and saliva levels in humans. *J. Pharm. Sci.*, 64 (1975) 2028–2029.

Levy, G. and Lampman, T., Relationship between pH of saliva and pH of urine. J. Pharm. Sci., 64 (1975) 890–891.

Moustafa, M.A., Gouda, M.W. and Tariq, M., Decreased bioavailability of propranolol due to interactions with adsorbent antacids and antidiarrhoeal mixtures. *Int. J. Pharm.*, 30 (1986) 225–228.

Narang, P.K., Carliner, N.H., Fisher, M.L. and Crouthamel, W.G., Quinidine saliva concentrations; Absence of correlation with serum concentrations at steady state. *Clin Pharmacol. Ther.*, 34 (1983) 695–702.

Remon, J.P., Van Severen, R. and Braeckman, P., Interaction between antiarrhythmics, antacids and antidiarrheals. Part 3. Effect of antacids and antidiarrheals on the resorption in-vitro of quinidine salts. *Pharm. Acta Helv.*, 54 (1979) 19–22.

Remon, J.P., Belpaire, F., Van Severen, R. and Braeckman, P., Interaction of antacids with antiarrhythmics, V. Effect of aluminium hydroxide and magnesium oxide on the bioavailability of quinidine, procainamide and propranol in dogs. *Arzneim. Forsch.*, 33 (1983) 117–120.

Reynolds, J.E.F., (Ed.), *Martindale, The Extra Pharmacopoeia*, The Pharmaceutical Press, London, 1982, pp. 1370–1373.

Romankiewicz, J.A., Reidenberg, M., Drayer, D. and Franklin, Jr., J.E., The noninterference of aluminium hydroxide gel with quinidine sulfate absorption: an approach to control quinidine-induced diarrhea. *Am. Heart J.*, 96 (1978) 518–520.

Sanchez, C.M. and Sanchez, M.M., Absorption of quinidine sulfate by montmorillonite. *J. Pharm. Belg.*, 37 (1982) 177–182.

Takahashi, H., Watanabe, Y., Shimamura, H. and Sugito, K., Effect of magnesium oxide on trichlormethiazide bioavailability. *J. Pharm. Sci.*, 74 (1985) 862–865.

Thoma, K. and Lieb, H., Adsorption of drug substances by antacids and adsorbents and their influence on bioavailability. *Dtch. Apoth. Ztg.*, 123 (1983) 2309–2316.

Ueda, C.T., Williamson, B.J. and Dzindzio, B.S., Absolute quinidine bioavailability. *Clin. Pharmacol. Ther.*, 20 (1976) 260–265.