International Journal of Pharmaceutics, 100 (1993) 249–252

IJP 03176

Notes

The effect of magnesium trisilicate on proguanil absorption

C.O. Onyeji and C.P. Babalola

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife (Nigeria)

(Received 23 September 1992)
(Modified version received 16 December 1992)
(Accepted 18 December 1992)

Key words: Magnesium trisilicate; Proguanil; Interaction; Bioavailability decrease

Summary

The in vitro adsorption of proguanil by some antacids was investigated. Results showed that magnesium trisilicate exhibited the highest adsorptive capacity, with the extent of adsorption being up to 88%. At 37.1°C only partial elution of the adsorbed drug on magnesium trisilicate could be achieved. The bioavailability of proguanil after a single oral administration of a 200 mg dose of the drug to eight volunteers was evaluated from saliva level data. The results were compared with the corresponding data obtained following concomitant administration of the same dose of the drug with magnesium trisilicate. The AUC^{∞}_{T} values of the drug were 3256 ± 990 and 1148 ± 619 (ng h ml^{-1}; ± S.D.) after administration of proguanil alone and proguanil-antacid combination, respectively. The results indicate that magnesium trisilicate markedly reduced the extent of absorption of proguanil. However, the rate of absorption was unaffected. The results of this study suggest that concomitant administration of proguanil with a non-systemic antacid like magnesium trisilicate should be discouraged.

Proguanil was introduced into clinical practice in 1945 and has since been used for the routine chemoprophylaxis of malaria, either alone or in combination therapy with other antimalarial drugs. Patients who are on malaria prophylaxis with proguanil could also be receiving treatment with an antacid for ulcer and non-ulcer dyspepsia. It appears necessary, therefore, to establish whether both drugs should be administered concurrently, since antacids have been reported to significantly affect the gastrointestinal absorption and/or renal excretion of a wide range of neutral, weakly basic and weakly acidic drugs (Garnett, 1986). There is no information in the literature on the effect of antacid on proguanil bioavailability. We therefore thought that it would be of interest and importance to determine, using an in vitro adsorption test, whether proguanil interacts with antacid preparations and also to evaluate the effect of the antacid on the bioavailability of the drug in man.

Adsorption and elution experiments were carried out at 37 ± 0.1°C, and the procedure adopted has been reported (Naggar et al., 1977). A duplicate series of 200 ml flasks containing 99.5 ml of 1% w/v of antacid suspended in water were prepared. 0.5 ml aliquots of different concentrations of proguanil solution were introduced into the antacid suspension such that the proguanil

Correspondence to: C.O. Onyeji, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria.

concentrations in the antacid ranged from 1 to 30 μg/ml. The flasks were equilibrated for 30 min in a water bath and the contents were centrifuged at 5000 rpm for 4 min. The supernatants were spectrophotometrically assayed for proguanil. By this procedure, the adsorption curve shown in Fig. 1 was obtained. Elution of proguanil adsorbed on magnesium trisilicate was performed by digesting the residue left after centrifugation in 100 ml of 0.01 N HCl. The flasks were shaken and at time intervals of 0.25, 0.5. 1, 1.5, 2 and 3 h, aliquots were centrifuged and concentrations of the extracted proguanil were determined. An average of three replicate runs was taken. The adsorption step before elution was carried out using 1% w/v magnesium trisilicate with an initial proguanil concentration of 15 μg/ml.

The gastrointestinal absorption characteristics of proguanil and proguanil-magnesium trisilicate combination were evaluated in eight adult male volunteers aged between 22 and 27 years and weighing 62–73 kg. The study was carried out with the approval of the Ethics Committee of the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria. A crossover design was followed and the subjects were instructed not to take other medication for at least 2 weeks prior to the study and through the entire test period; 200 mg of proguanil HCl (two tablets of Paludrine®) was given to each of the volunteers. The tablets were taken with 100 ml of water. A wash-out period of 2 weeks was allowed after which the same dose of the drug was administered with 100 ml of 1% w/v magnesium trisilicate in water. After each treatment, stimulated mixed saliva was collected at 0, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48 and 72 h following drug administration. All samples were stored at −20°C until analysis. The concentrations of proguanil in saliva samples were determined using a high-performance liquid chromatographic method developed earlier in our laboratory (Onyeji et al., 1989). This involved the use of a C_{18} reversed phase column (5 μm) through which is pumped at 1 ml/min a solvent system of methanol:0.5% ammonium acetate (1:1) containing 50 mM perchloric acid. The limit of detection of proguanil was 6 ng/ml. From the saliva proguanil concentration data, some pharmacokinetic parameters were evaluated. The elimination half-life ($t_{1/2}$) of the drug was calculated by linear regression analysis using at least three points in the terminal phase of the concentration-time profile. The area under the saliva concentration-time curve, AUC^s, was evaluated using the trapezoidal method, up to the last concentration determined. The extrapolated AUC was determined from the ratio of C_t to β, where C_t is the last saliva drug concentration measured. AUC^s_T was the sum of AUC^s and C_t/β. The results were subjected to statistical analysis using the Wilcoxon matched pairs signed rank test (two-tailed). Differences between pairs of data were taken to be significant when $p < 0.05$.

Fig. 1 shows the adsorption of proguanil at 37 ± 0.1°C on three antacids. Magnesium trisilicate exhibited the highest adsorptive effect. For example, the percentages of proguanil adsorption, at an initial drug concentration of 15 μg/ml were 38, 48 and 88% by aluminium hydroxide,

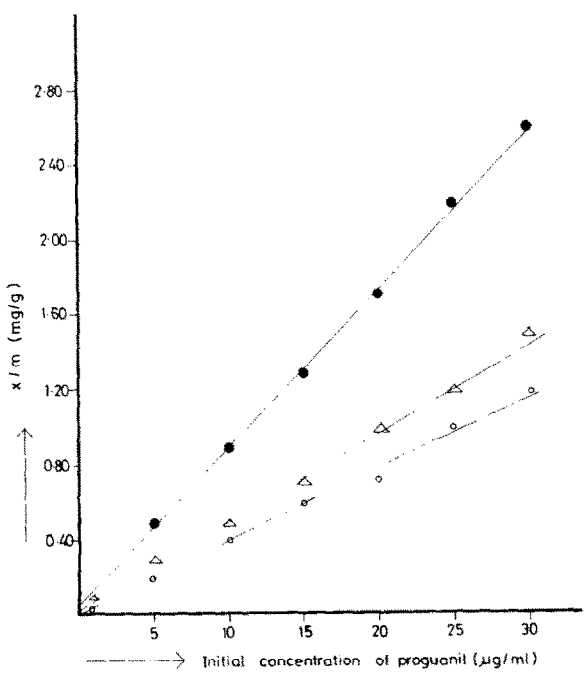

Fig. 1. Adsorption of proguanil by 1% w/v antacid preparations at 37 ± 0.1°C. (○) Aluminium hydroxide; (△) light magnesium carbonate; (●) magnesium trisilicate. Each point is an average of two determinations. X/m denotes mg of proguanil adsorbed per g of antacid.

magnesium carbonate and magnesium trisilicate, respectively. The elution experiment showed that only 20% of proguanil adsorbed by magnesium trisilicate was eluted within 3 h. That magnesium trisilicate exhibited the highest adsorptive effect on proguanil might not be surprising, since reports have shown this antacid to possess the greatest adsorptive capacity for other drugs (Khalil et al., 1976; Naggar and Khalil, 1979). It is pertinent to note that the in vitro adsorption of a drug by an antacid does not always signify that there would be a significant in vivo interaction. For example, magnesium trisilicate has been found to adsorb oestrogen and progesterone components of oral contraceptives in vitro (Khalil et al., 1976) but in vivo study revealed that the bioavailabilities of these steroids were not affected by concomitant administration with the antacid (Joshi et al., 1986). A similar phenomenon had been demonstrated for magnesium trisilicate and aminophylline interaction (Bhalla and Lloyd, 1984). Therefore, although magnesium trisilicate showed a high adsorptive capacity for proguanil, the effect of this antacid on the bioavailability of proguanil could only be established after in vivo testing.

It has been shown that there is a correlation between saliva and plasma levels of proguanil, and hence, saliva levels could be useful in the determination of pharmacokinetic parameters and therapeutic monitoring of the drug (Onyeji et al.,

TABLE 1

Absorption and disposition characteristics of proguanil following oral administration of 200 mg dose of the drug alone, and with 1 g of magnesium trisilicate, to each of eight volunteers

Drug	Volunteer	t_{max} (h)	C_{max} (ng ml^{-1})	$t_{1/2}$ (h)	AUC_T^s (ng h ml^{-1})
A	I	4	252.3	13.9	4913
	II	4	180.4	12.3	4326
	III	2	128.5	16.8	2089
	IV	4	180.3	18.7	3301
	V	4	190.3	14.5	3075
	VI	3	75.3	17.3	2100
	VII	4	133.6	11.3	2810
	VIII	5	170.5	14.3	3436
Mean ±		3.75	163.9	14.9	3256
S.D.		0.83	52.3	2.5	990
B	I	2	86.4	17.3	1534
	II	5	99.6	11.8	2527
	III	5	43.4	19.8	582
	IV	4	50.7	15.3	970
	V	3	43.8	15.4	830
	VI	2	38.9	13.6	853
	VII	4	56.3	12.8	1021
	VIII	5	48.4	13.4	870
Mean ±		3.75	58.4	14.9	1148
S.D.		1.19	22.2	2.6	619

A, 200 mg proguanil alone; B, 200 mg proguanil plus 1 g magnesium trisilicate.

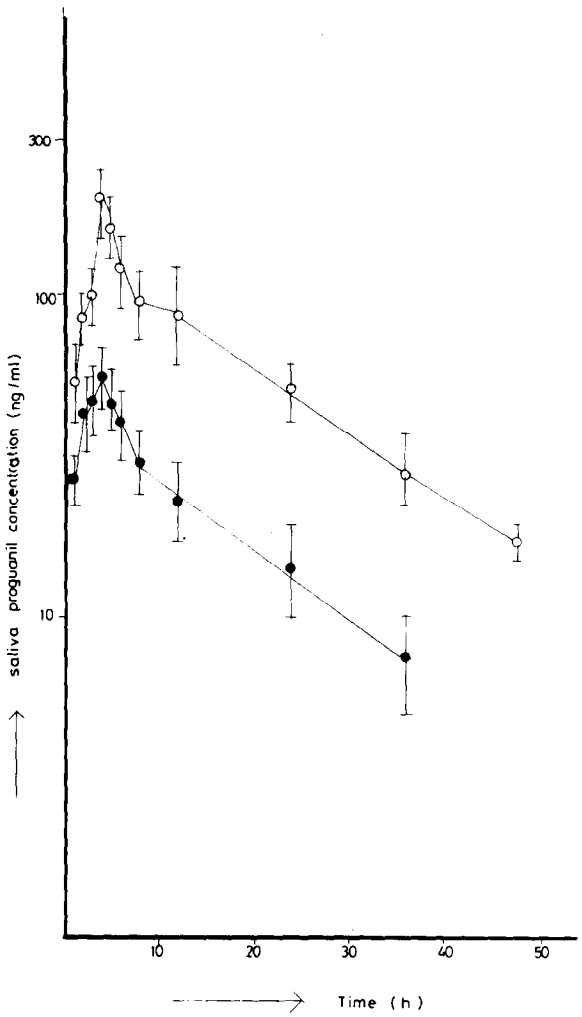

Fig. 2. A semi-logarithmic plot of average saliva proguanil levels as a function of time after oral administration of 200 mg of the drug alone (○) and when administered with 1 g of magnesium trisilicate (●). Each bar represents ± S.D.

1989). This report established the rationale, in this study, for evaluating proguanil bioavailability from its saliva concentration data. Furthermore, Svensson (1989) stressed that, in conducting pharmacokinetic studies, when alternative methods providing equally valid information are available, non-invasive methods should be used, for ethical considerations.

The antacid, magnesium trisilicate, did not affect the t_{max} of proguanil (Table 1) and the values obtained were in the range of the previously reported values derived from both plasma and saliva data (White, 1985; Onyeji et al., 1989). On the other hand, magnesium trisilicate caused about 65% decrease in both the C^s_{max} and AUC^s_T. Administration of magnesium trisilicate, therefore, resulted in a highly significant ($p < 0.01$) reduction in the extent for proguanil absorption and this is clearly indicated in Fig. 2. Also, the antacid did not affect the elimination kinetics of the drug as is evident in the elimination half-life ($t_{1/2}$) values which remained unaltered.

From the results of the adsorption study, and the elution test which showed only a partial elution (20%), it is apparent that the most probable basis for the significant reduction in bioavailability of proguanil was the adsorption of the dissolved drug on the surface of magnesium trisilicate or formation of insoluble complexes and the subsequent incomplete release of the drug from the antacid surface. In conclusion, magnesium trisilicate, a non-systemic antacid, reduces the bioavailability of proguanil. It is therefore, suggested that, when the indications arise, the concomitant administration of both drugs should be discouraged.

References

Bhalla, H.L. and Lloyd, S.J., Effect of magnesium trisilicate on the availability of aminophylline. *Ind. Drugs,* 22 (1984) 143–145.

Garnett, W.R., Antacid products. In *Handbook of Nonprescription Drugs,* 8th Edn, The American Pharmaceutical Association, Washington, DC, 1986, pp. 25–46.

Joshi, J.V., Sankolli, G.M., Shah, R.S. and Joshi, U.M., Antacid does not reduce the bioavailability of oral contraceptive. *Int. J. Clin. Pharmacol. Ther. Toxicol.,* 24 (1986) 192–195.

Khalil, S.A. and Iwuagu, M., The in vitro uptake of oral contraceptive steroids by magnesium trisilicate. *J. Pharm. Sci.,* 67 (1976) 287–289.

Naggar, V.F., Gouda, M.W. and Khalil, S.A., In vitro adsorption of some corticoseroids on antacids. *Pharmazie,* 32 (1977) 778–781.

Naggar, V.F. and Khalil, S.A., Effect of magnesium trisilicate on nitrofurantoin absorption. *Clin. Pharmacol. Ther.,* 25 (1979) 857–863.

Onyeji, C.O., Ogunbona, F.A. and Dixon, P.A.F., Excretion of proguanil in human saliva. *J. Pharm. Pharmacol.,* 41 (1989) 872–873.

Svensson, C.K., Ethical considerations in the conduct of clinical pharmacokinetic studies. *Clin. Pharmacokinet.,* 17 (1989) 217–222.

White, N.J., Clinical pharmacokinetics of antimalarial drugs. *Clin. Pharmacokinet.,* 10 (1985) 187–215.