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European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 299–303

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Altered pharmacokinetics of halofantrine by an antacid, magnesium carbonate

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Received 30 September 1997; accepted 3 March 1998

Abstract

This study investigated the in vitro adsorption of halofantrine (Hf) by some antacids. Magnesium carbonate showed the highest adsorptive effect, the extent of adsorption being up to 83%. Only 4% of Hf adsorbed by the antacid could be eluted with 0.1 M HCl while no detectable elution occurred with water. Other antacids investigated were magnesium trisilicate and aluminium hydroxide and these had Hf-adsorption capacities of 23 and 43%, respectively. The effect of magnesium carbonate on the bioavailability of Hf was evaluated in seven healthy volunteers. The subjects were administered with 500 mg oral dose of Hf–HCl or the same dose of the drug in combination with 1 g of magnesium carbonate, in a crossover fashion. Blood samples were collected at predetermined time intervals and were analysed for Hf and its major metabolite, desbutylhalofantrine (Hfm), using high-performance liquid chromatography method. The results showed that magnesium carbonate significantly prolonged ($P < 0.05$) the time to reach maximum plasma concentration (T_{max}) of Hf. Also the maximum plasma concentrations (C_{max}) of Hf and Hfm were significantly reduced ($P < 0.05$). Furthermore, there was a reduction in the area under the curve (AUC) values of Hf and this was as high as 56% (range 1–56%). Results of this study suggest that it may not be advisable to concomitantly administer Hf with an antacid like magnesium carbonate.

Keywords: Halofantrine; Magnesium carbonate; Interaction; Altered pharmacokinetics

1. Introduction

The spread of drug-resistant *Plasmodium falciparum* malaria has emphasised the need for alternative drugs for the treatment of the disease. Halofantrine (Hf) is a blood schizonticide which is effective against both chloroquine-sensitive and multi-drug resistant strains of *P. falciparum* [1–3]. Some malaria patients on therapy with Hf could also have other indications like ulcer and non-ulcer dyspepsia requiring treatment with antacids. Before a concomitant administration of Hf and antacids could be recommended, it would be necessary to determine whether a significant in vivo interaction occurs between both compounds. The importance of such a study is underscored by the fact that antacids have been reported to markedly reduce the bioavailability of a broad range of drugs [4–6]. Also, increased gastrointestinal absorption have been demonstrated with some drugs when co-administered with antacids [7]. On the other hand, antacids do not alter the bioavailability of some other drugs [8,9]. Thus, it is apparent that the effect of antacids on gastrointestinal drug absorption varies with the type or nature of the drug.

The systemic availability of Hf is significantly increased in the presence of food [10] but, there is no information in the literature on the effect of antacids on the bioavailability of the drug. Therefore, the purpose of this study was to determine whether Hf interacts with antacids in vitro and also to evaluate the effect of the antacid on the pharmacokinetics of the drug in man.

2. Materials and methods

2.1. In vitro adsorption and elution experiments

Preliminary experiments were performed to determine

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0939-6411/98/$19.00
PII S0939-6411(98)00029-0

the equilibration time for the adsorption of Hf by antacids. One hundred millilitre volumes of 40 μg/ml concentration of Hf were prepared separately in 1% w/v aqueous suspensions of aluminium hydroxide, heavy magnesium carbonate and magnesium trisilicate. Flasks containing these preparations were placed in a water-bath at 37.5°C and 5 ml aliquots were taken at 0.25, 0.5, 1, 2, 3, 4, 5, and 6 h. The samples were centrifuged at 5000 rpm for 5 min and concentrations of Hf in the supernatants were determined spectrophotometrically. Maximum Hf adsorption and equilibration were found to occur after 4 h of interaction with the antacids. Consequently, the adsorption and elution studies were carried out at 37.5°C and the antacid-Hf mixtures were allowed to equilibrate for 4 h. Other procedures adopted for the adsorption and elution experiments have been reported [11]. In brief, a duplicated series of flasks containing 100 ml of different concentrations of Hf in 1% w/v aqueous antacid suspensions were prepared. The Hf concentration in the antacids ranged from 5 to 40 μg/ml. After equilibration, the contents of the flasks were centrifuged to obtain the supernatants which were assayed spectrophotometrically for Hf. The adsorption curves were generated. For the elution experiment, 100 ml of 1% w/v suspension of magnesium carbonate with a Hf concentration of 40 μg/ml was equilibrated. Elution of the adsorbed Hf was carried out by extracting the residue left after centrifugation with 100 ml of 0.1 M HCl or water. Concentrations of the extracted Hf were monitored over a 6-h period. Triplicate runs were carried out.

2.2. Subjects and drug administration

Seven healthy male volunteers between the ages of 24 and 31 years and weighing between 57 and 67 kg participated in this investigation after giving their informed consent. None of the volunteers was receiving any other drugs for at least 2 months before this study and all of them were non-smokers. The volunteers were not allowed to take alcohol or any other medications throughout the duration of the study. The study protocol received the approval of the Ethics Committee of the Obafemi Awolowo University Teaching Hospital. After an overnight fast, 500 mg of Hf–HCl (two tablets of Halfan®, Smithkline Beecham, Lagos, Nigeria), was administered with 100 ml of water to each of the seven volunteers. After a wash-out period of 2 months, each of these subjects again received the same dose of Hf–HCl tablets concomitantly with 1 g of magnesium carbonate suspended in 100 ml of water.

2.3. Sample collection and analysis

Venous blood samples (4 ml) were drawn before and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 168 and 336 h following administration of Hf alone and Hf–antacid combination. The blood samples were collected by venipuncture from the forearm and were placed in heparinised tubes. The blood samples were centrifuged immediately for 15 min at $2000 \times g$ to obtain the plasma which was transferred into plastic tubes and stored at −20°C until analysed.

The plasma samples were analysed for Hf and its major metabolite, desbutylhalofantrine (Hfm), using a sensitive high-performance liquid chromatography (HPLC) method recently developed in this laboratory [12]. In the method, sample treatment involved protein precipitation with acetonitrile followed by extraction with hexane–diethylether (1:1, v/v) under alkaline condition. The organic layer was transferred into a tapered-end tube and evaporated to dryness over a stream of nitrogen at 40°C. The extract was reconstituted in acetonitrile–1 M HCl (90:10) and injected onto the HPLC through a Varian manual loop valve injector fitted with a 50 μl loop. A Varian (Palo Alto, CA) model 5000 liquid chromatograph fitted with a fixed wavelength (254 nm) UV detector was used. Chromatographic separation was achieved on a 10-μm particle size C-18 column (200×4.6 mm i.d.) (Hewlett Packard, Avondale, PA) using a mobile phase consisting of methanol–0.05 M potassium dihydrogen phosphate (70:30, v/v) with 55 mmol/l perchloric acid. The pH of the mobile phase was 3.1 and it was pumped through the column at a flow rate of 1.3 ml/min. The detection limits for Hf and Hfm were 2.5 and 2.0 ng/ml, respectively. The intra- and inter-assay coefficients of variation for both compounds were less than 7% ($n = 6$) at plasma concentrations of 40 and 400 ng/ml. The recovery of both compounds at the same concentrations was not less 87%. The accuracy of the method assessed by the deviation of the determined concentration from the actual concentration was less than 8% ($n = 6$) for both Hf and Hfm at concentrations of 40 and 400 ng/ml.

2.4. Data analysis

The maximum plasma drug concentrations (C_{max}) and the time to reach these concentrations (T_{max}) were estimated by visual inspection of the concentration − time data. The area under the curve (AUC) up to the last determined plasma drug concentration was obtained using the linear trapezoidal method. The extrapolated AUC was estimated from the ratio of C_t to β, where C_t is the last determined plasma drug concentration and β is the elimination rate constant. Total AUC (AUC_T) was the sum of the AUC up to the last determined concentration and the extrapolated AUC. β was determined by linear regression analysis of at least three points on the terminal elimination portion of the log concentration versus time profiles. The elimination half-life ($T_{1/2}\beta$) was calculated from the ratio: $0.693/\beta$. The Wilcoxon matched pairs signed-rank test (two-tailed) was used to evaluate the difference between pairs of data. A P-value of <0.05 was considered significant. Also, the difference in the extent of Hf gastrointestinal absorption in the presence and absence of the antacid was further evaluated using the confidence interval approach [13].

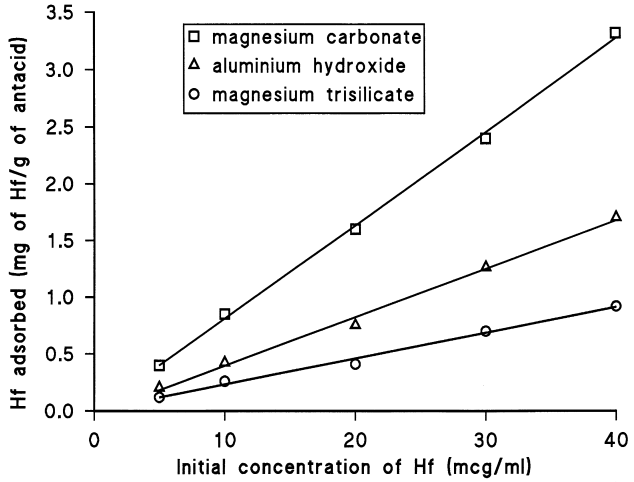

Fig. 1. Adsorption of different concentrations of halofantrine (Hf) by 100 ml of 1% w/v antacid preparations at 37.5°C. Each point is an average of two determinations.

3. Results

3.1. In vitro studies

The adsorption of Hf by 1% w/v antacid preparations at 37.5°C is shown in Fig. 1. The percentages of Hf adsorption, at an initial drug concentration of 40 μg/ml were 23, 43 and 83% by magnesium trisilicate, aluminium hydroxide and magnesium carbonate, respectively. It was observed from the elution experiment that only 4% of the Hf adsorbed by magnesium carbonate could be eluted within 6 h by 0.1 M HCl, whereas, no detectable elution occurred with water.

3.2. In vivo studies

Mean plasma concentrations versus time profiles of Hf and Hfm in the seven volunteers after oral administrations of 500 mg of Hf–HCl alone, and with 1 g of magnesium carbonate, to each of the subjects, are shown in Fig. 2. The figures show that the antacid caused a significant decrease ($P < 0.05$) in the C_{max} of both Hf and Hfm. The C_{max} values of Hf were 571 ± 315 ng/ml (mean ± SD) and 294 ± 92 ng/ml, without and with antacid co-administration, respectively, while the corresponding values for Hfm were 305 ± 162 ng/ml and 158 ± 47 ng/ml, respectively. Also, the T_{max} of Hf was significantly prolonged ($P < 0.05$) by the antacid co-administration (4.3 ± 1.3 vs. 12.9 ± 7.5 h, without and with antacid, respectively). Tables 1 and 2 present the absorption and dis-position characteristics of Hf and Hfm following oral administrations of Hf alone and Hf–antacid combination to the subjects. The mean AUC values of Hf and Hfm obtained after administration

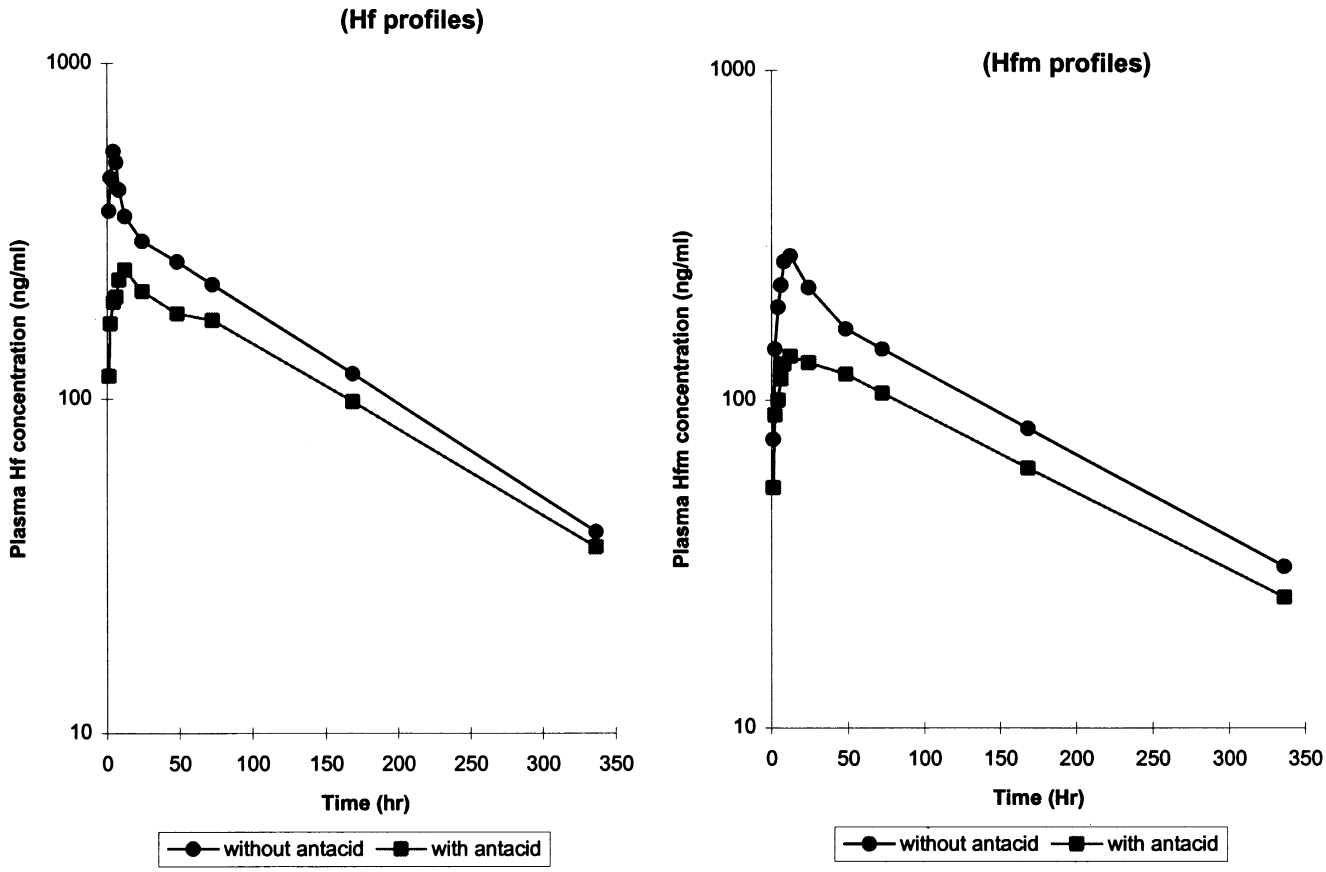

Fig. 2. Mean plasma concentrations versus time profiles of halofantrine (Hf) and desbutylhalofantrine (Hfm) following oral administration of 500 mg of Hf–HCl alone, and with 1 g of magnesium carbonate, to each of seven volunteers.

Table 1

Absorption and disposition characteristics of halofantrine following oral administration of 500 mg dose of hydrochloride salt of the drug alone, and with 1 g of magnesium carbonate, to each of seven volunteers

Drug	Volunteer	T_{max} (h)	C_{max} (ng/ml)	AUC_T (μg/ml per h)	$T_{1/2}\beta$ (h)
A	I	6	345	30.15	87
	II	6	550	43.72	107
	III	4	390	59.10	106
	IV	4	420	82.76	108
	V	2	370	70.95	108
	VI	4	600	76.77	118
	VII	4	1320	67.70	123
	Mean	4.3	571	61.59	108
	SD	1.3	318	17.39	11
B	I	12	197	26.02	120
	II	6	270	31.22	137
	III	6	240	33.99	122
	IV	6	300	58.99	138
	V	12	195	21.72	99
	VI	24	410	75.0	120
	VII	24	445	64.74	107
	Mean	12.9	294	44.53	120
	SD	7.5	92	19.63	13
	Test of Significance	*	*	n.s.	n.s.

A, 500 mg halofantrine hydrochloride; B, 500 mg halofantrine hydrochloride plus 1 g magnesium carbonate.
*Significant difference ($P < 0.05$); n.s., no significant difference ($P > 0.05$).
T_{max}, C_{max}, $T_{1/2}\beta$ and AUC_T are as defined in the text.

of Hf–antacid combination were lower ($P > 0.05$) than the corresponding values derived following dosing with Hf alone. The values for Hf were 61.59 ± 17.39 and 44.53 ± 19.63 (μg/ml per h), without and with antacid combination, respectively, while the corresponding Hfm values were 29.89 ± 8.89 and 22.62 ± 5.30 (μg/ml per h), respectively. Further analysis of the data using the confidence interval approach shows that the antacid caused a decrease in the extent of absorption of Hf that was as low as 1% and as high as 56%.

4. Discussion

The in vitro adsorption of Hf by the different antacids showed that magnesium carbonate exhibited the highest adsorptive capacity. For a variety of other drugs, magnesium trisilicate appeared to possess the highest adsorptive effect [11,14,15]. It has been demonstrated that the extent of drug adsorption by antacids depends on the structure of both the antacid and the drug, the pH of the antacid suspension, and the polarity of the drug in such pH [16]. Therefore, no trend can be expected to be generally obtainable in the adsorptive capacities for drugs by antacids. For example, magnesium oxide has a higher adsorptive capacity than magnesium trisilicate for chloramphenicol while the reverse is the case for doxycycline [16].

Since in vitro drug adsorption by antacids do not always translate into significant in vivo interaction [17,18], it was deemed necessary in this study to carry out an in vivo evaluation of the Hf–magnesium carbonate interaction, in addition to the in vitro adsorption experiments. Magnesium carbonate was selected for an evaluation of in vivo interaction with Hf because the antacid demonstrated the highest in vitro adsorptive capacity, and hence, the possibility of the occurrence of a significant in vivo interaction may be comparatively higher than with the other antacids. However, further studies are required to definitely establish that magnesium trisilicate and aluminium hydroxide have less influence than magnesium carbonate on the pharmacokinetics of Hf. The absorption and disposition characteristics of Hf obtained when the drug was administered alone (Table 1) indicate that the T_{max}, C_{max} and $T_{1/2}\beta$ values of the drug are within the range of literature values [10,19] and they also demonstrate wide intersubject variability as previously reported [20]. Co-administration of magnesium carbonate with Hf resulted in a significant decrease ($P < 0.05$) in the rate of absorption of Hf as is evident in the T_{max} values which were significantly prolonged. Hf is known to have a

Table 2

Disposition characteristics of desbutylhalofantrine following oral administration of 500 mg of halofantrine hydrochloride alone, and with 1 g of magnesium carbonate, to each of seven volunteers

Drug	Volunteer	T_{max} (h)	C_{max} (ng/ml)	$AUC_{0-336\ h}$ (μg/ml per h)
A	I	12	160	24.09
	II	12	260	16.03
	III	12	230	35.16
	IV	24	125	34.83
	V	12	560	20.87
	VI	24	260	42.43
	VII	6	540	35.80
	Mean	14.6	305	29.89
	SD	6.3	162	8.89
B	I	12	105	18.97
	II	6	208	15.97
	III	6	120	25.65
	IV	12	95	25.06
	V	12	165	14.77
	VI	24	200	26.62
	VII	12	210	29.09
	Mean	12.0	158	22.62
	SD	5.6	47	5.30
	Test of Significance	n.s.	*	n.s.

A, 500 mg halofantrine hydrochloride; B, 500 mg halofantrine hydrochloride plus 1 g magnesium carbonate.
*Significant difference ($P < 0.05$); n.s., no significant difference ($P > 0.05$).
T_{max}, C_{max} and AUC are as defined in the text.

poor water solubility, especially at high pH [20]. Thus, the slow rate of absorption of Hf in the presence of the antacid may be attributable to a most probable decrease in the dissolution rate of the drug at the high pH known to be induced by the antacid. The significant reduction ($P < 0.05$) in the peak plasma concentrations of Hf following antacid co-administration may have clinical implications since it has been asserted that the clinical efficacy of Hf is influenced by its peak plasma concentration [20]. Thus, the marked reduction in the C_{max} of Hf may adversely affect the therapeutic efficacy of the drug if it is concurrently administered with the antacid. The AUC values (Table 1) show that there was a wide intersubject variability in the extent of absorption of Hf, and this is consistent with previous reports [19]. Although a statistically insignificant ($P > 0.05$) decrease in the extent of Hf absorption was caused by the antacid co-administration, data analysis by the confidence interval approach which reveals that the extent of decrease in Hf absorption could be as high as 56%, indicates the need for a caution in allowing a combined administration of both agents. It is pertinent to note that the results of drug–antacid in vivo interaction studies are influenced by the dose and type of antacid employed [18]. The 1 g dose of the antacid used in this study is within the range of medium-dose antacid therapy [21]. The antacid did not affect the elimination kinetics of Hf as is evident in the $T_{1/2}\beta$ values which did not change significantly ($P > 0.1$) (Table 1).

It was found necessary in this study to monitor the Hfm plasma levels and to evaluate how they are affected by the antacid because, Hfm also has antimalarial activity which is equipotent to Hf [1]. Magnesium carbonate affected the C_{max} and AUC of Hfm in a similar way as it affected the corresponding parameters for Hf (Table 2). Thus, the significantly reduced peak plasma levels of Hfm may also contribute to the potential effect of the decreased C_{max} of Hf in adversely affecting the efficacy of treatment with Hf, if the drug is co-administered with the antacid.

In conclusion, magnesium carbonate, when administered in the amount used for medium-dose antacid therapy, significantly decreases the rate of absorption of Hf. Also, the antacid markedly reduces the peak plasma concentrations of the drug and its major metabolite, Hfm. Since the clinical efficacy of Hf is influenced by its peak plasma concentrations, co-administration of magnesium carbonate with Hf may affect therapeutic success with the antimalarial. Therefore, a concomitant administration of Hf with magnesium carbonate does not appear advisable.

Acknowledgements

We are grateful to Smithkline Beecham Pharmaceuticals, Welwyn, UK, for the supply of halofantrine hydrochloride and desbutylhalofantrine hydrochloride powders. We also thank Smithkline Beecham, Lagos, Nigeria, for providing us with Halfan® tablets.

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