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SHORT COMMUNICATION

EFFECT OF FOOD ON THE BIOAVAILABILITY OF FEXOFENADINE HYDROCHLORIDE (MDL 16 455A)

MAXINE STOLTZ*, THANGAM ARUMUGHAM, CHRISTINA LIPPERT, DALE YU, VIJAY BHARGAVA, MARK ELLER AND SCOTT WEIR

Departments of Pharmacokinetics and Statistics, Hoechst Marion Roussel, Inc., Kansas City, MO, U.S.A.

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The hydrochloride salt of fexofenadine, the primary metabolite of terfenadine (Seldane®), is being developed for the treatment of symptoms associated with seasonal allergic rhinitis without producing sedation. Clinical safety and efficacy studies of fexofenadine hydrochloride were conducted using an immediate-release capsule formulation of the drug. A tablet containing the same granulation plus magnesium stearate is being developed as a supplementary dosage form. Because co-ingestion of food has been shown to effect the bioavailability of many drugs,[1,2] the present studies were conducted to evaluate bioavailability of fexofenadine hydrochloride given as capsules or tablets when administered with a high-fat meal. Previous studies with fexofenadine hydrochloride have shown that under fasted conditions the relative bioavailability of the capsule is 89–93% when compared to an oral solution. The bioequivalence of the tablets relative to the capsules has also been established under fasting conditions (unpublished data).

Two separate open-label, randomized crossover design studies were conducted where each subject received either (i) a single oral dose of 80 mg fexofenadine hydrochloride production-scale capsules (2×40 mg) following a 10 h fast and 30 min following a high-fat breakfast or (ii) a single oral dose of 120 mg fexofenadine hydrochloride production-scale immediate-release tablets (3×40 mg) after a 10 h fast and after ingestion of a high-fat breakfast. The high-fat breakfast consisted of two eggs fried in butter, two strips of bacon, two pieces of buttered toast, 2 oz hash browns, and 8 oz whole milk (55 g fat, 33 g protein, 58 g carbohydrate). A 6 d washout was allowed between treatment periods.

*Address all correspondence to Maxine L. Stoltz, Ph.D., Hoechst Marion Roussel, Inc., P.O. Box 9627, Kansas City, MO 64134-0627, U.S.A. Email: maxinestoltz@hmri.com

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Participants in these studies were healthy male nonsmokers, 18–43 years old, within 10% of ideal body weight and whose physical examinations, ECGs, and clinical laboratory tests were within normal limits and screens for HIV, hepatitis B antigen, and drug abuse were negative.

Serial blood samples were collected for 48 h after dosing for plasma fexofenadine assay using high-performance liquid chromatography–mass spectrometry. Pharmacokinetic parameters were calculated by standard, noncompartmental techniques. A three-way analysis of variance, with terms for subject, period, and treatment, was performed for each pharmacokinetic parameter. Least-squares means for each treatment, estimated treatment differences, and 90% confidence intervals for treatment differences were calculated.

Mean plasma fexofenadine concentration–time profiles are illustrated in Figure 1. When either capsules or tablets were administered, mean time to peak plasma concentration was 3 h, regardless of fed or fasted state. As shown in Table 1, co-ingestion of food with capsules decreased the mean AUC(∞) by 17% and C_{max} by 11%. When given food with the tablets, AUC(∞) and C_{max} were 24 and 25% less, respectively, than when given tablets under fasted conditions. Ingestion of capsules or tablets on a full or empty stomach did not have an effect on fexofenadine $t_{1/2}$. Maximal concentrations and areas under the plasma concentration–time curves were proportional in subjects given total

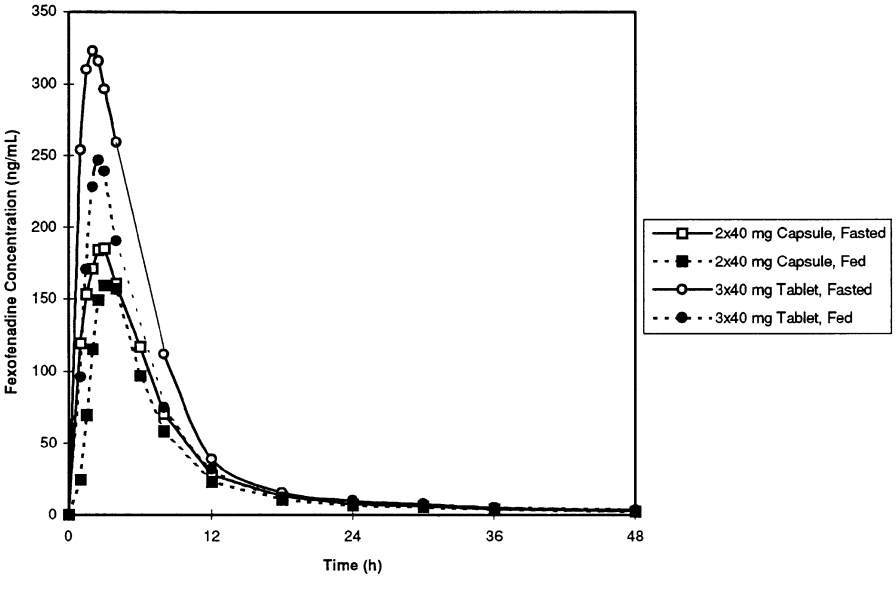

Figure 1. Plasma concentration–time profiles of fexofenadine after oral administration of fexofenadine hydrochloride capsules and tablets to fasted and fed subjects

Table 1. Plasma fexofenadine pharmacokinetic parameters following treatment with fexofenadine hydrochloride in healthy male volunteers

Parameter[a]	Treatment	Mean ($N=24$)	%CV	Pairwise comparison	Ratio (%)[b]	Confidence interval[b]
2×40 mg capsules						
$t_{1/2}$ (h)	Fasted	14·43	39·48			
	Fed	14·03	25·74	Fed/Fasted	98·19	85·9, 112·3
C_{max} (ng mL^{-1})	Fasted	209·84	38·08			
	Fed	180·02	30·99	Fed/Fasted	89·06	79·4, 99·9
t_{max} (h)	Fasted	2·88	37·77			
	Fed	3·88	21·74	Fed/Fasted	111·46	93·2, 133·3
AUC(∞) (ng h mL^{-1})	Fasted	1583·92	40·18			
	Fed	1253·66	26·39	Fed/Fasted	83·05	74·7, 92·4
3×40 mg tablets						
$t_{1/2}$ (h)	Fasted	15·49	30·34			
	Fed	17·45	32·45	Fed/Fasted	111·71	99·6, 125·3
C_{max} (ng mL^{-1})	Fasted	382·30	39·04			
	Fed	267·75	29·94	Fed/Fasted	75·27	66·9, 84·7
t_{max} (h)	Fasted	2·60	56·45			
	Fed	2·63	30·38	Fed/Fasted	106·76	89·7, 127·1
AUC(∞) (ng h mL^{-1})	Fasted	2524·25	31·22			
	Fed	1843·53	26·24	Fed/Fasted	75·97	69·0, 83·7

[a]$t_{1/2}$, half-life; C_{max}, maximum concentration; t_{max}, time to maximum concentration; AUC, area under the curve.
[b]Ratio and confidence intervals calculated using adjusted means.

doses of 80 mg fexofenadine as capsules to those given total doses of 120 mg as tablets, suggesting that food does not change the proportionality of fexofenadine pharmacokinetics.

Food can influence drug absorption as a result of physiological changes in the GI tract or physical or chemical interactions between particular food components and drug molecules.[1] Drug absorption may be reduced, delayed, increased, or not affected, by concomitant food intake.[1] For terfenadine, food was found to delay absorption by 0·9 h but had no effect on the extent of absorption of the drug, i.e., mean fexofenadine AUC values were essentially identical after administration of terfenadine in the fasted or fed state;[3] consequently there are no labeling restrictions regarding timing of meals and ingestion of terfenadine.[4] However, the bioavailability of astemizole, another second-generation antihistamine, was reduced by 60% when taken with meals. According to 1995 labeling, astemizole should be administered at least 2 h after meals and additional food intake should be delayed for 1 h after dosing.[5] In contrast, food increased the bioavailability of loratadine by 40%, resulting in a labeling restriction that loratadine be administered on an empty stomach.[6]

Although results of the present studies reveal that ingestion of a high-fat breakfast decreased AUC(∞) and C_{max} values for both fexofenadine hydrochloride capsules and tablets, the changes are smaller than those observed with astemizole or loratadine. The proposed therapeutic clinical dose of fexofenadine hydrochloride is 60 mg twice daily although a dose level of 40 mg has also been shown to be effective. Therefore, a 25% decrease in exposure to drug due to ingestion of a high-fat meal would not decrease the efficacy of the drug. Furthermore, no other pharmacokinetic parameters measured (t_{max}, $t_{1/2}$) were altered by food intake. It is concluded that food ingestion has no clinically significant effect on the rate or extent of fexofenadine hydrochloride absorption.

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REFERENCES

1. R. D. Toothaker and P. G. Welling, The effect of food on drug bioavailability. *Annu. Rev. Pharmacol. Toxicol.*, **20**, 173–199 (1980).
2. A. Melander, D. Lalka and A. McLean, Influence of food on the presystemic metabolism of drugs. *Pharmacol. Ther.*, **38**, 253–267 (1988).
3. M. G. Eller, B. J. Walker, L. Yuh, K. K. Antony, B. E. McNutt and R. A. Okerholm, Absence of food effects on the pharmacokinetics of terfenadine. *Biopharm. Drug Disposit.*, **13**, 171–177 (1992).
4. In *Physicians' Desk Reference*, Seldane®, 49th edn, Medical Economics Data Production Company, Montvale, NJ, 1995, pp. 1428–1430.
5. In *Physicians' Desk Reference*, Hismanal®, 49th edn, Medical Economics Data Production Company, Montvale, NJ, 1995, pp. 1183–1184.
6. In *Physicians' Desk Reference*, Claritin®, 49th edn, Medical Economics Data Production Company, Montvale, NJ, 1995, pp. 2246–2247.