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LETTER TO THE EDITORS

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Influence of food intake on the bioavailability of thioctic acid enantiomers

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Introduction

Recent controlled clinical trials have demonstrated that long-term administration of 600 mg thioctic acid (TA, *R*(+)-TA, *S*(−)-TA; α-lipoic acid), once daily, can improve symptoms of peripheral and autonomic neuropathy in patients with diabetes mellitus (Ziegler et al. 1995). In diabetic patients the bioavailability of drugs may be decreased by delayed gastric emptying (due to autonomic neuropathy) *and* the interaction of drugs with food retained in the stomach. Therefore, the present trial investigated whether a pharmacokinetic interaction between food and TA takes place.

Subjects and methods

The trial (randomised, open, two-period crossover) was approved by the local Ethics Committee, and all subjects [healthy, six females, six males; mean age 26.3(5.2) years] gave their written consent. Each volunteer received two single oral doses of 600 mg racemic TA (one tablet of Thioctacid 600). One dose was administered after a 12-h fasting period, the other immediately after a standardised heavy breakfast (two fried eggs, three strips of bacon, two slices of toast, 20 g butter, 25 g jam, 150 ml decaffeinated coffee). This equals 863 kcal: 101 kcal protein (12%), 358 kcal fat (41%), 404 kcal carbohydrates (47%). Plasma concentrations of the TA enantiomers were measured by an enantiospecific reversed-phase high-performance liquid chromatography (HPLC) method with fluorescence detection as described previously (Hermann et al. 1996).

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The area under the plasma concentration-time curve from 0 up to the last measured plasma concentration ($AUC_{0-t\,(last)}$, linear trapezoidal rule), maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were determined for both TA enantiomers. $AUC_{0-t\,(last)}$ and C_{max} were analysed by analysis of variance (ANOVA) after logarithmic transformation. Relative bioavailability was assessed by the geometric means of the ratio fed/fasted $AUC_{0-t\,(last)}$ and C_{max}. The decision in favour of a lack of food interaction was accepted when 90% confidence intervals (CI) did not exceed the limits of 80% and 125% for $AUC_{0-t\,(last)}$ ratios, and 70% and 143% for C_{max} ratios (Steinijans et al. 1991). For t_{max}, means and differences between means and their interval estimates were calculated and subjected to Wilcoxon's test.

Results and conclusions

The plasma concentration time curves are shown in Fig. 1. The values of $AUC_{0-t\,(last)}$ and C_{max} of the *R*(+)-TA are higher than those for *S*(−)-TA (Table 1). Administration of racemic TA after food ingestion reduced the $AUC_{0-t\,(last)}$ and C_{max} values of both enantiomers (Table 1). The geometric means for the ratio $AUC_{0-t\,(last)}$ fed/fasted were 76.5% (90% CI 64.1, 91.2) for *R*(+)-TA and 83.3% (90% CI 69.9, 99.3) for S(−)-TA. The geometric means for the ratio of C_{max} were 65.4% (90% CI 46.7, 91.5; $P < 0.05$) for *R*(+)-TA and 70.9% (90% CI 50.4, 99.6; $P < 0.05$) for *S*(−)-TA. The mean difference of t_{max} was 1.5 h (90% CI 0.9, 2.1; $P < 0.05$) for both enantiomers.

As shown previously (Gleiter et al. 1995), in the present study the bioavailability of *S*(−)-TA was lower than that of *R*(+)-TA. Food may significantly decrease TA bioavailability. Data on metabolites or excretion balance are not available in order to further elucidate reduction. It has been shown that the bioavailability of both enantiomers of TA is reduced in *fasted* diabetic patients with *delayed gastric emptying* (Gleiter et al. 1995). As therapy with TA is a typical long-term treatment, it appears particularly important that the *extent* of absorption remains unaltered. In order to achieve maximal absorption, it is recommended to ingest the drug while the stomach is empty.

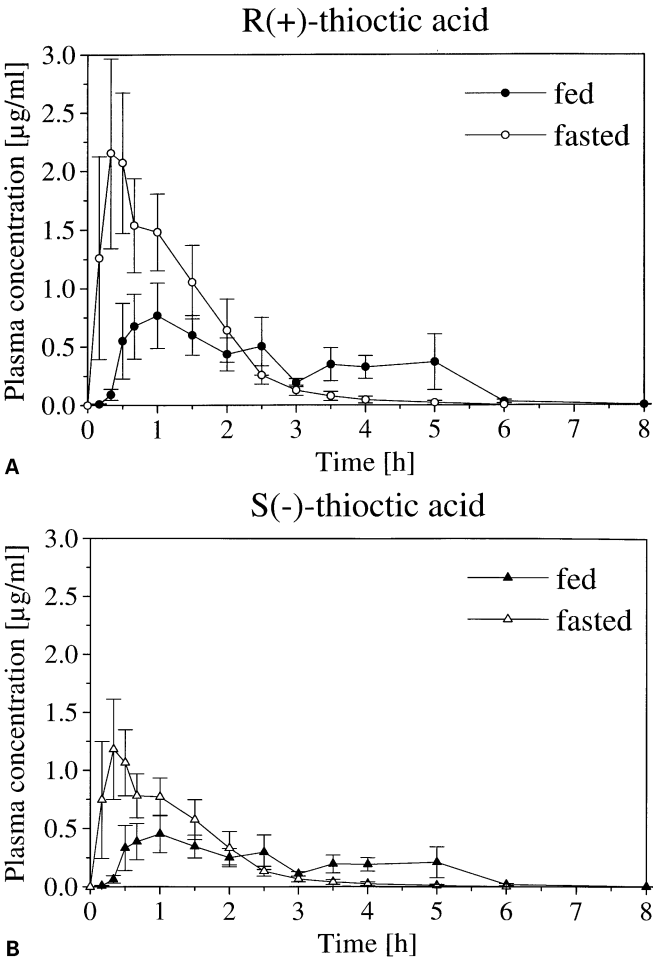

Fig. 1A, B Plasma concentrations of the *R*(+)- and *S*(−)-enantiomers of thioctic acid following a single oral dose of 600 mg racemic thioctic acid administered in fed and fasted healthy volunteers (arithmetic means with SEM, $n = 12$)

Table 1 Pharmacokinetic variables for the assessment of bioavailability of the *R*(+)- and *S*(−)-enantiomers of thioctic acid following a single oral dose of 600 mg racemic thioctic acid administered in fed and fasted healthy volunteers ($AUC_{0-t(last)}$ and C_{max}: geometric means and coefficient of variation; t_{max}: arithmetic means with SEM, $n = 12$)

	R(+)-thioctic acid		*S*(−)-thioctic acid	
	Fasted	Fed	Fasted	Fed
$AUC_{0-t(last)}$ ($ng \cdot ml^{-1} \cdot h$)	2518	1926	1361	1134
CV (%)	49	38	46	37
C_{max} ($ng \cdot ml^{-1}$)	2654	1735	1415	1003
CV (%)	88	54	87	55
t_{max} (h)	1.01(0.22)	2.47(0.43)	1.00(0.23)	2.47(0.43)

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