centrations continued to increase (week 6 mean-week 5 mean, $t_{23} = 4.6$, $P < 0.001$) followed by a significant fall when the drug was withdrawn (week 7 mean, $t_{23} = 2.6$, $P < 0.02$). Patient 4 developed nausea, nystagmus and a positive Romberg's test consistent with phenytoin intoxication during the second week of cimetidine treatment. Her peak plasma phenytoin concentration at that time was 114 μmol/l (therapeutic range 40–80 μmol/l) in contrast to a peak of 59 μmol/l found during the second week of ranitidine administration when no adverse effects had been noted.

These results show that standard therapeutic doses of ranitidine, unlike cimetidine, produced no change in plasma phenytoin concentrations in these four patients. The extent of the increase during cimetidine administration varied considerably from patient to patient with a mean increase in phenytoin concentrations of 70% (range from 22% to 280%) similar to that reported by Neuvonen *et al.* (1981) following 3 weeks' cimetidine. This is a greater effect than the 13–33% increase in mean plasma phenytoin concentrations that we found after 6 days' cimetidine treatment of a different group of patients (Hetzel *et al.*, 1981).

The clinical importance of the interaction is illustrated by patient 4 who developed symptoms, signs and plasma concentrations consistent with phenytoin intoxication after 14 days of cimetidine treatment. No adverse effects were seen during ranitidine treatment. Caution is necessary when adding cimetidine to phenytoin treatment, while ranitidine in these standard doses produced no significant increase in plasma phenytoin concentrations. Ranitidine may be a more suitable histamine $H_2$-receptor antagonist when this treatment is necessary for epileptic patients receiving phenytoin.

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# THE INTERACTION OF CIMETIDINE WITH METOPROLOL, ATENOLOL, PROPRANOLOL, PINDOLOL AND PENBUTOLOL

Cimetidine is known to influence plasma level time curves of various drugs, because of an inhibition of drug metabolism and/or a reduction of liver blood flow (Somogyi & Gugler, 1982). The recent study of Houtzagers *et al.* (1982), titled 'The effect of pretreatment with cimetidine on the bioavailability and disposition of atenolol and metoprolol', deals with plasma levels and plasma half-lives of atenolol and metoprolol (*after a single oral dose* to seven patients suffering from various diseases) and the influence of cimetidine on them. Although propranolol and several other drugs eliminated by oxidative metabolism are known to interact with cimetidine, the authors did not find any influence of cimetidine on the kinetics of metoprolol, which is mostly eliminated by (oxidative) biotransformation. Their results con-

cerning an increased half-life of atenolol, which is almost totally excreted renally as unchanged atenolol, can be regarded as very surprising. All these results do completely contradict, as the authors noticed correctly at the end of their paper, those obtained by our group by *investigating steady state levels* (Kirch *et al.*, 1981). We could not find any influence of cimetidine on atenolol kinetics, but did find an effect on metoprolol kinetics. Houtzagers *et al.* (1982) attributed the discrepancies between the investigations mentioned to not sufficiently selective analytical methods in our study.

It should be unnecessary to say, that we proved our methods and that t.l.c. is one of the standard methods for the analysis of biological materials. Therefore the analytical methods which we used cannot be looked upon as a reason for the different results. Besides we performed the same study on propranolol, and our results, an average increase of the AUC of 90%, are very similar to those obtained by other authors (e.g. Reimann *et al.*, 1981). Furthermore Houtzagers *et al.* (1982). were astonished about our finding, that the pharmacodynamic action of metoprolol was not altered significantly by concomitant administration of cimetidine, although the mean plasma levels were significantly higher than during monotherapy. The shallow plasma concentration-response curve that exists at the observed metoprolol plasma levels, as far as the reduction of exercise induced tachycardia is concerned, makes it difficult to demonstrate statistically significant differences in small numbers of volunteers.

In the meantime we also investigated the influence of cimetidine on pindolol, which is partly, and penbutolol, which is almost totally eliminated by biotransformation. Pindolol plasma levels were determined using a fluorodensitometric method with nadolol as internal standard (fluorescence measurements after extraction from plasma and t.l.c. separation) (Spah & Mutschler, in preparation). Concentrations of penbutolol, 4-hydroxypenbutolol, penbutololglucuronide and 4-hydroxypenbutololglycuronide were determined by an h.p.l.c. method with spectrophotometric detection. (The glucuronides were determined after having treated the samples with glucuronidase) (Hajdú & Damm, in preparation). The plasma levels of these β-adrenoceptor blockers were slightly elevated, but the AUC values were not significantly influenced. The inhibition of exercise-induced tachycardia was also not influenced by cimetidine. Looking at the results with penbutolol one could conclude that the interaction of cimetidine with other drugs, as Houtzagers *et al.* (1982), believe, is difficult to evaluate. However the investigation (h.p.l.c. assay!) of the penbutolol metabolites shows the reasons to the attentive observer: The main metabolite of penbutolol is penbutololglucuronide, a phase-II metabolite. Minor metabolites are 4-hydroxypenbutolol and 4-hydroxypenbutololglucuronide. Plasma levels of penbutololglucuronide were not affected by concomitant administration of cimetidine in healthy volunteers during chronic treatment, whereas the levels of the 4-hydroxylated compounds significantly decreased ($P < 0.01$; Figure 1). Therefore the conclusion can be drawn, that

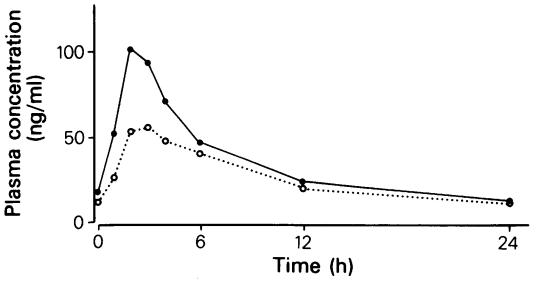


**Figure 1** Mean plasma levels of 4-hydroxylated compounds in seven healthy volunteers (4-hydroxypenbutolol plus 4-hydroxypenbutololglucuronide, calculated as 4-hydroxypenbutolol equivalents) on the seventh day of chronic treatment with penbutolol as monotherapy (●) and penbutolol + cimetidine (○).

cimetidine interactions occur and can be predicted with a high probability, if cimetidine is given together with substances mainly metabolised by the cytochrome P-450 system.

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