Tiracizine disposition in healthy volunteers with reference to the debrisoquine oxidation phenotype

Tiracizine is an antiarrhythmic agent with class IA, IB and IV properties according to the Vaughan-Williams classification [1]. The drug is extensively metabolised and undergoes substantial hepatic first-pass elimination in man [2, 3]. Three major metabolites (M1, M2 and M3) are detected in human serum (Figure 1) and are generated by hepatic microsomal enzymes [4]. M1 and M2 are pharmacodynamically active and contribute with pure class IB properties to the net antiarrhythmic effect of tiracizine [1]. In human volunteers, marked interindividual differences in serum concentrations of tiracizine and its metabolites as well as of the respective pharmacokinetic characteristics have been observed. There is evidence from *in vitro* studies that the carbamic acid amide bond cleavage might be under genetic control of CYP2D6 in man [4]. To determine whether or not the CYP2D6 polymorphism is responsible for the observed interindividual differences, the serum kinetics of the antiarrhythmic agent, tiracizine, and three of its metabolites (M1, M2, M3), obtained from 10 healthy volunteers after single oral administration of 50 mg tiracizine hydrochloride tablets (Arzneimittelwerk Dresden GmbH, Germany), were assessed.

The study was carried out in 10 healthy volunteers (six male, four female, age 22–33 years, and body weight 60–76 kg). Each subject was phenotyped for metabolic oxidation status with debrisoquine as described previously [5]. Nine subjects were EM and one subject was PM (metabolic ratio debrisoquine/4-hydroxydebrisoquine [MR] = 20.1) of debrisoquine. The MR of one of the EMs was distinctly higher (3.72) compared with the range of the remaining (between 0.13 and 0.17) EMs. Tiracizine and its metabolites were measured by h.p.l.c. as described previously [3] and the following pharmacokinetic parameters were calculated: AUC, $C_{\max}$, $t_{\max}$ and $t_{1/2,z}$ of the parent compound as well as AUC(0,t), $C_{\max}$ and $t_{\max}$ of the metabolites. Moreover, the AUC ratios between parent compound and metabolites were calculated.

Tiracizine AUC of the PM could be classified as an outlier with regard to the random sample of the AUC of all individuals studied (tiracizine AUC = 1287 $\mu\text{mol ml}^{-1} \text{ h}$ in the PM vs 442.9 $\mu\text{mol ml}^{-1} \text{ h}$, 95% CI: 236–580 in EMs). Moreover, for the following parameters the PM markedly exceeded the 95% confidence interval (CI) of the mean of the EMs: tiracizine $t_{1/2,z}$ = 4.7 h in the PM vs 2.4 h, 95% CI: 2.0–2.9 in the EMs; AUC-ratio M1/tiracizine = 5.4 in the PM vs 19.1, 95% CI: 16–22 in EMs; AUC-ratio

M2/tiracizine = 1.9 in the PM vs 5.4, 95% CI: 4.2–6.5 in EMs; AUC-ratio M3/M2 = 0.13 vs 0.08, 95% CI: 0.06–0.10 in EMs and M3/M1 = 0.05 vs 0.02, 95% CI: 0.017–0.021 in EMs. Interestingly, the EM with the higher MR showed a markedly higher tiracizine AUC, and $C_{\max}$ with regard to the range of the remaining EMs. The serum concentration ratios of tiracizine/M1 were about three times higher in the PM compared with EMs up to 12 h after drug intake, and were markedly enhanced in the EM with the higher MR during the first hour after drug administration (Figure 1).

The results of the present study clearly emphasise the need for kinetic data from some more PMs. Therefore, the results are only preliminary in nature with respect to the debrisoquine hydroxylation status of the volunteers. Nevertheless, it is possible that the PM represents a distinct population in comparison to the EMs with regard to both debrisoquine and tiracizine metabolism. Moreover, comparing the parent compound/metabolite AUC ratios, our results indicate that the cleavage of the carbamic acid amide bond (Tiracizine $\rightarrow$ M1; M3 $\rightarrow$ M2) but not *N*-demethylation of tiracizine to be at least partially under genetic control of the debrisoquine hydroxylation polymorphism. Given the fact that M1 and M3 formation are the major clearance pathways, deficiency of the mentioned metabolic pathway of tiracizine could account for longer half-lives and higher AUC of tiracizine, lower AUC-ratios of M1/tiracizine, M2/tiracizine and the higher ratio of M3/M2 observed in PM.

Our results are in accordance with theoretical considerations and the results from *in vitro* metabolic studies with human liver. Tiracizine is structurally closely related to other substrates of CYP2D6 enzymes such as tricyclic antidepressants. Its steric conformation can be superimposed with dextromethorphan in a 3D model. Further, the metabolites M1 and M2 were formed from tiracizine and M3, respectively, *in vitro* in cells expressing the CYP2D6 enzyme [4]. The generation of M1 from tiracizine and of M2 from M3 correlated well with bufuralol 1'-hydroxylation in human liver microsomes. The formation of M3 by *N*-demethylation of tiracizine, however, was not related to CYP2D6 levels. Finally, the CYP2D6 specific inhibitor quinidine significantly inhibited M1 formation [4].

Our data in healthy volunteers give support to the *in vitro* studies indicating that the cleavage of the carbamic acid amide bond but not *N*-demethylation of tiracizine is under the genetic control of CYP2D6.

Figure 1 Chemical structure and metabolic pathway of tiracizine; Tiracizine/metabolite 1 serum concentration ratio vs time after single oral administration of 50 mg tiracizine HCl in the 10 human volunteers (Δ : poor metaboliser (MR 20.7, $\bullet$: extensive metaboliser (MR 3.7), remaining: extensive metabolisers of debrisoquine (MR 0.13–0.68): --- mean of the group of extensive metabolisers).

Further studies with a larger number of PMs are required to draw final conclusions on the pharmacokinetics of tiracizine in deficient metabolizers, and to elucidate the clinical implications of the polymorphic metabolism.

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