PHARMACOKINETICS OF TOCAINIDE HYDROCHLORIDE IN HEALTHY VOLUNTEERS, AND ELDERLY PATIENTS WITH VENTRICULAR ARRHYTHMIAS

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The pharmacokinetics of tocainide were investigated in 6 healthy volunteers (aged 22 to 32 yr) and eight elderly patients (aged 59 to 76 yr) with ventricular arrhythmias each of whom received tocainide hydrochloride 7.5 mg kg^{-1} by intravenous infusion over 15 min. Blood samples were collected for up to 48 hr post-infusion, into heparinised plastic tubes, via an indwelling cannula in the antecubital or cephalic vein of the arm contralateral to the infusion site. The blood was centrifuged immediately to harvest the plasma which was stored at -20° pending analysis. Urine was collected for 24 hours following drug administration and pooled for analysis. The clinical protocol for this study was approved by the Ethics Committee, Lidcombe Hospital, N.S.W. Aust. and carried out in accordance with the guidelines laid down by the National Health and Medical Research Council of Australia.

Tocainide in plasma and urine was extracted with dichloromethane and quanitified by gas-liquid chromatography using 2-amino-N-(2,6-dimethyl phenyl) butanamide hydrochloride as internal standard and flame ionisation detection (interassay CV = 3.0%, detection limit = 0.03 $\mu g ml^{-1}$). Postinfusion plasma concentration-time data were fitted by a polyexponential equation using the nonlinear least squares regression programme Funfit (Veng Pedersen, 1977). Estimates of the coefficients were corrected for the duration of infusion by the method of Loo & Riegelman (1970). Pharmacokinetic parameters (Table 1) were calculated by standard methods (Gibaldi & Perrier, 1982). In one elderly patient and 2 volunteers plasma concentration-time profiles contained discontinuities which were attributed to extravascular administration of the drug. In these individuals pharmacokinetic parameters were obtained by area analysis (Gibaldi & Perrier, 1982).

Table 1. Mean (±SD) pharmacokinetic parameter estimates for tocainide HCl in healthy volunteers and elderly patients with ventricular arrhythmias

	Cardiac Patients	Healthy Volunteers	
$t_{\frac{1}{2}}$ (hr)	16.5 (range 11.2 to 19.5)	9.1 (range 7.5 to 11)	$p<0.05$*
Cl (ml $min^{-1}kg^{-1}$)	1.68 ± 0.42	3.0 ± 0.84	$p<0.05$
Cl_R (ml $min^{-1}kg^{-1}$)	0.57 ± 0.20	1.21 ± 0.40	$p<0.05$
V_β (l kg^{-1})	2.32 ± 0.22	2.31 ± 0.43	NS
V_{ss} (l kg^{-1})†	2.22 ± 0.25	2.11 ± 0.47	NS

* Mann-Whitney U; † elderly patients n=7, healthy volunteers n=4.

In the elderly subjects the mean total plasma clearance of tocainide was approximately 60% of that observed in healthy volunteers while the volumes of distribution V_β and V_{ss} were not different between the groups. Furthermore mean renal clearance in the elderly was approximately half that found in the young subjects. It would thus appear that the prolonged $t_{\frac{1}{2}}$ in the elderly subjects results from diminished capacity to eliminate tocainide. These findings suggest that in elderly subjects with ventricular arrhythmias, comparable plasma levels of tocainide may be achieved at dosages appreciably lower than those required in young healthy subjects.

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