POSTER COMMUNICATIONS

Disposition and pharmacokinetics of phenytoin in rats with acute renal failure

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The unbound fraction (f) of phenytoin in plasma from patients with renal insufficiency is increased and so too is the apparent volume (V_d) of distribution, whereas the plasma half-life ($T_{\frac{1}{2}}$) is decreased (Odar-

ment open model (Colburn & Gibaldi, 1977). Results from the tissue distribution studies showed that, despite the decrease in intrinsic clearance, renal failure did not affect the hepatic uptake of phenytoin. Phenytoin concentrations were significantly higher in the skeletal muscle, liver and brain of uraemic rats. Comparison of the tissue phenytoin/plasma unbound phenytoin concentration ratio of control and uraemic rats indicated that in renal failure binding to skeletal muscle and the heart was decreased, while the liver and brain were unaffected.

Table 1 Pharmacokinetics of phenytoin in rats with acute renal failure. [^{3}H]-Phenytoin (10 mg/kg; 10 μCi/rat) was administered via the femoral vein to male Wistar albino rats (about 300 g) anaesthetized with pentobarbitone sodium (50 mg/kg; i.p.). Blood samples (0.4 ml) were collected from the carotid artery at intervals up to 180 min.

	f	AUC ($\mu g\ ml^{-1}\ min^{-1}$)	$T_{\frac{1}{2}}$ (min)	Cl_t ($ml\ min^{-1}\ kg^{-1}$)	Cl_i ($ml\ min^{-1}\ kg^{-1}$)	V_d (ml/kg)
Control	0.19 ± 0.01	103.1 ± 5.6	40.3 ± 2.0	35.3 ± 1.4	185.6 ± 10.5	2053 ± 224
Uraemic	0.29 ± 0.01	73.9 ± 3.5	33.0 ± 3.5	44.3 ± 1.7	147.5 ± 8.6	2110 ± 235
P value	<0.001	<0.05	<0.001	<0.001	<0.001	>0.05

Results are mean ± s.e. mean of 3–4 rats.
AUC = area under the plasma concentration versus time curve; Cl_t = total plasma clearance.
Cl_i = intrinsic clearance.

Cederlöf & Borgå, 1974). The reason for the decreased $T_{\frac{1}{2}}$ was unknown but may have been due to increased rates of both elimination and diffusion into tissues. We have therefore investigated the fate of phenytoin in rats with acute renal failure.

Renal failure was produced in male rats as previously described (Bowmer & Lindup, 1979) and the pharmacokinetics of [^{3}H]-phenytoin investigated 48 h after the injection of glycerol. A terminal blood sample was taken 180 min after administration of phenytoin, and then the brain, liver, heart and a sample of skeletal muscle removed for analysis of phenytoin and metabolites (Gerber, Weller, Lynn, Rangno, Sweetman & Bush, 1971; Colburn & Gibaldi, 1977).

Plasma concentrations of phenytoin in rats with renal failure were significantly lower at all times up to and including the first 90 min after injection. Thereafter there was no difference. Metabolites of phenytoin accumulated so that, from 120 min onwards, the total concentration of radioactivity was significantly higher in the plasma of rats with renal failure. Table 1 lists the results of a preliminary pharmacokinetic analysis of the data using a two compart-

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