PHARMACOKINETICS OF ISOTRETINOIN IN THE ANAESTHETIZED RAT FOLLOWING INTRAVENOUS ADMINISTRATION OF AN EMULSION

R Nankervis, M S Cheema, S S Davis, N H Day[§] & P N Shaw.
Department of Pharmaceutical Sciences, University of Nottingham, Nottingham, UK and
[§]Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK.

Isotretinoin (13-*cis* retinoic acid) is a retinoid used clinically for the oral therapy of severe acne and is also recommended for severe Gram-negative folliculitis and rosacea not responding to traditional therapy (Orfanos et al 1987). The aim of the study was to characterise the previously unreported intravenous pharmacokinetics of 13-*cis* retinoic acid in the anaesthetized rat.

Two groups of 5 male Wistar rats (200-250g) were anaesthetized with sodium pentobarbitone ($90 mgkg^{-1}$). Isotretinoin ($0.264 mgkg^{-1}$, 0.2mL, or $0.792 mgkg^{-1}$, 0.6mL) was administered via the left jugular vein in an emulsion of soya oil (10%), egg lecithin (1%) and water (89%). Blood samples were collected over a period of 210 minutes from the right carotid artery.

Samples were analysed by HPLC. The column was a Spherisorb 5µm ODS-2 (125 x 4.6mm), with a mobile phase of 70% acetonitrile and 30% ammonium acetate (0.1M), pH6.0, at a flow rate of $1 mLmin^{-1}$. The detection wavlength was 350nm.

Plasma (0.1mL) was extracted by a direct protein precipitation method (Kabra et al 1977; Chu et al 1980; Stofford et al 1980) involving the addition of 0.2mL of acetonitrile containing the internal standard Ro 11-5036. After vortex mixing (20sec) the samples were centrifuged and the supernatant layer was directly injected onto the HPLC column.

Dose ($mgkg^{-1}$)	0.264		0.792		
AUC ($\mu gmL^{-1}min$)	55	± 31	317	± 34	$P < 0.001$
Clearance ($mLmin^{-1}kg^{-1}$)	6.0	± 3.4	2.5	± 0.25	$P < 0.05$
Elimination $t_{½}$ (min)	48.1	± 5	61.1	± 7	$P < 0.01$
V_D ($mLkg^{-1}$)	421	± 227	222	± 19	$P < 0.05$
	n = 5		n = 5		

From the data in the table, a non-proportional increase in AUC was observed with increasing dose, resulting from a decrease in both total body clearance and the volume of distribution. The elimination half-life also varied with increasing dose.

Considerable inter-subject variation was seen in the pharmacokinetic data. This finding is consistent with studies in the dog (Cotler et al 1983).

Chu S Y et al (1980) Clin. Chem. **26**: 521
Cotler S et al (1983) Drug Metab. Disp. **11**: 458-462
Kabra P M et al (1977) Clin. Chem. **23**: 1284-1288
Orfanos C E et al (1987) Drugs **34**: 459-503
Stofford B E et al (1980) Clin. Chem. **26**: 1366

The authors are grateful to the Science and Engineering Research Council and Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK, for their financial support.