The distribution and irreversible tissue binding of practolol and its metabolites in the hamster

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The β-adrenoceptor antagonist practolol produces side effects associated with the eye, skin and intestine (Nicholls, 1976). Practolol is metabolised *in vitro* to metabolites which bind irreversibly to liver microsomes and the highest binding was to hamster microsomes (Case, Lindup, Lowery, Orton, Reeves & Whittaker, 1978). The distribution and tissue binding of practolol has therefore been studied *in vivo* in the hamster.

There was a dose-dependent linear increase in the total and irreversibly bound radioactivity in the eye (Table 1) and the control data suggest the involvement of metabolism in irreversible binding. The linear dose-response curve for irreversible binding contrasts with that of paracetamol which displays a threshold effect for liver binding once glutathione detoxification is exceeded. (Potter, Thorgeirsson, Jollow & Mitchell, 1974).

The ocular accumulation of practolol appears to be due to melanin binding which can occur with many basic drugs (Mason, 1977). There is no direct evidence that the increased levels of total and irreversibly bound radioactivity (7- and 14- fold respectively) after chronic administration could account for the precipitation of side-effects during long-term practolol therapy in man; in fact, no ocular toxicity has been observed after chronic administration to several animal species, including the hamster.

Table 1 Total and irreversibly bound concentrations of radioactivity in the eye and skeletal muscle of the male hamster 24 h after oral administration of [^{14}C]-practolol.

Dose of practolol (mg/kg)	*Tissue Concentration* (nmol [^{14}C]-practolol equivalents/g tissue) Total (T)*		*Bound (B)*		*% Bound in eye (B/T × 100)*
	Eye	*Muscle*	*Eye*	*Muscle*	
Control*†	269.6	11.8	0.8	n.d.	0.3
200	68.7 ± 16.3	1.9	7.4 ± 4.1	0.1	10.8
400	210.0 ± 40.7	1.8	10.2	0.2	4.9
600	240.1 ± 4.3	2.2	12.9 ± 3.2	0.2	5.4
800	403.8 ± 152.5	2.9	19.5 ± 2.2	0.3	4.8
400‡	1,438 ± 322	n.d.	145.3 ± 53.9	n.d.	10.1

* Results are expressed as mean ± s.d. and tissues from 2–5 hamsters studied; n.d. = not detectable.
† Eyes and skeletal muscle from two untreated hamsters were homogenized and [^{14}C]-practolol, 37.55 and 3.96 nmol respectively, added prior to extraction.
‡ Practolol (400 mg kg^{-1} day^{-1}; 2 μCi kg^{-1} day^{-1}) was administered for 22 days.

Single oral doses of [^{14}C]-practolol (400 mg/kg; 500 μCi/kg) were administered to male hamsters and the time-course of the tissue distribution of [^{14}C]-labelled material studied. The dose-dependence of distribution and irreversible binding of radioactivity was investigated 24 h after oral administration of 200–800 mg/kg (560 μCi/kg). The effect of 400 mg kg^{-1} day^{-1} for 22 days was also investigated. The irreversible binding and tissue distribution of drug and metabolites were measured by solvent extraction and scintillation counting.

The eye, skin and small intestine, in contrast to skeletal muscle retained radioactivity over the 168 h period studied. Radioactivity was highest in the eye and practolol was the major (80–84%) component present. Whole body autoradiography showed that the radioactivity was associated with pigmented areas of the uveal tract.

References

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