

Regional brain concentration of propranolol and its hypotensive effect in the conscious rabbit

O.M. BAKKE, C.T. DOLLERY, P.J. LEWIS, M.G. MYERS* & J.L. REID

Department of Clinical Pharmacology, Royal Postgraduate Medical School

The mechanism of the antihypertensive effect of propranolol remains uncertain. Propranolol lowers plasma renin activity but the dose required is often less than that needed to reduce arterial pressure in hypertensive patients. Although the drug causes a decrease in cardiac output following acute intra-

after i.c.v. injection and regional brain levels of radioactivity were measured using a scintillation counter (Table 1). Preliminary data showed that 89% of the radioactivity was toluene extractable, that is, unchanged propranolol. In two other groups of rabbits, an i.v. loading dose of unlabelled (\pm)-propranolol (0.4 mg/kg) followed by i.v. infusion at a rate of 1.0 and 2.0 (mg/kg)/h resulted in plasma propranolol levels at 120 min of 209 ± 62 and 328 ± 44 ng/ml respectively and falls in mean arterial pressure of -13.2 ± 2.1 mmHg ($P < 0.01$) and -10.2 ± 4.4 mmHg ($P < 0.05$) below control. At the end of the 120 min infusion period, the animals were killed and brain propranolol levels (Table 1) were measured (Shand, Nuckolls & Oates, 1970).

Table 1 Regional brain concentration of propranolol ($\mu\text{g/g}$ brain tissue) following i.v. infusion and i.c.v. injection

	<i>Hypothalamus</i>	<i>Medulla-pons</i>	<i>Mid-brain</i>	<i>Cerebellum</i>	<i>Rest of brain</i>
AFTER 120 min I.V. INFUSION 1.0 (mg/kg)/h ($n = 4$)	3.40 ± 0.34	2.70 ± 0.09	2.68 ± 0.17	2.43 ± 0.08	1.54 ± 0.19
2.0 (mg/kg)/h ($n = 6$)	6.30 ± 0.60	4.57 ± 0.63	5.54 ± 0.53	5.57 ± 0.42	1.75 ± 0.28
TIME OF DEATH AFTER ICV INJECTION 530 μg					
60 min ($n = 3$)	10.30 ± 3.98	8.83 ± 2.54	4.28 ± 0.86	1.35 ± 0.26	10.51 ± 4.30
120 min ($n = 3$)	3.54 ± 1.49	7.72 ± 5.19	4.07 ± 1.22	0.98 ± 0.19	2.40 ± 1.13
240 min ($n = 4$)	1.52 ± 0.21	1.95 ± 0.62	0.97 ± 0.04	0.52 ± 0.03	2.10 ± 0.38

venous (i.v.) administration in man, there is no simultaneous fall in arterial pressure. In a recent communication, we have reported that propranolol can exert a hypotensive effect via the central nervous system in the conscious rabbit. Direct intracerebroventricular (i.c.v.) injections of ($-$)-propranolol (500 μg) caused a significant prolonged fall in mean arterial pressure between 60 and 240 min (maximum -16.8 ± 5.9 mmHg at 105 min). This response has been further studied by comparing regional brain concentrations of the drug following i.c.v. and i.v. injections.

Injections of ^{14}C (\pm)-propranolol (530 μg i.c.v.) were administered to conscious normotensive rabbits. Animals were killed 60, 120 and 240 min

The propranolol levels in the hypothalamus, midbrain and medulla-pons at the end of the i.v. infusions were similar to the propranolol content in these areas between 60 and 240 min after i.c.v. injection, the time of the maximum hypotensive response. Plasma propranolol levels during the i.v. infusions in the rabbits were within the effective therapeutic range of the drug in man.

Reference

- SHAND, D.G., NUCKOLLS, E.M. & OATES, J.A. (1970). Plasma propranolol levels in adults with observations in four children. *Clin. Pharmacol. Ther.*, 11, 112.