Comparison of some haemodynamic changes between central and intravenous administration of (±)-propranolol in anaesthetized dogs

JANINE K. CARTER,* H.W. MITCHELL & R.H. POYSER

Beecham Research Laboratories, Medicinal Research Centre, The Pinnacles, Harlow, Essex

Propranolol has found clinical use as an anti-hypertensive agent, and recent work has shown that it has a hypotensive effect in animals when injected into the central nervous system (Kelliher & Buckley, 1970; Stern, Hoffman & Braun, 1971; Day & Roach, 1972, 1973; Srivastava, Kulshrestha, Singh & Bhargava, 1973; Dollery, Lewis, Myers & Reid, 1973). In the present study we have further explored this central action by comparing some of the haemodynamic changes produced on administering propranolol to anaesthetized dogs by the following routes: intracerebroventricular (i.c.v.), intracisternal (i.c.), into the right vertebral artery (i.v.a.) which supplies mainly the hind brain region, and i.v. (femoral vein). No changes in B.P. were observed when saline was injected by any route.

Propranolol caused falls in mean arterial pressure (MAP) by all routes (Table 1), but responses following both doses i.c. and the large dose i.v.a. were significantly greater ($P < 0.02$) than the respective falls i.v. Prior to the hypotension, short-lived pressor responses were often observed with i.c.v. and i.c. administration, whereas a transient depressor effect preceded the prolonged hypotension to propranolol i.v.a.

All injections of propranolol caused bradycardia and a reduction in cardiac output (CO), measured with an electromagnetic flow probe as total aortic flow minus coronary flow. These responses differed only slightly between routes in contrast to the marked differences observed in blood pressure changes. Consequently, total peripheral resistance (TPR = MAP/CO) tended to increase following i.c.v. and i.v. propranolol but was decreased by i.c. and i.v.a. administration.

The significantly larger falls in mean arterial pressure obtained following i.c. and i.v.a. propranolol, in relation to i.c.v. and i.v. dosing, provide further evidence for an action of the drug in the hind brain region to lower blood pressure. This hypotension in the anaesthetized dog has been shown to be a consequence of reduced total peripheral resistance in addition to a decrease in cardiac output. This is unlike the hypotensive effect in many in which there is no evidence of a fall in peripheral resistance.

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Table 1 Effects of propranolol administered by four different routes on mean femoral arterial pressure (MAP), heart rate (HR), cardiac output (CO) and calculated total peripheral resistance (TPR) in pentobarbitone-anaesthetized dogs. Different groups of dogs were used for each route and in all experiments the larger dose (1.0 mg/kg) of propranolol was administered at least 2 h after the smaller dose (0.3 mg/kg). Values are means ± standard errors.

Route and dose (mg/kg)	*MAP (mm Hg where 1 mm Hg = 1.33 mbar) n = 5*		*HR (beats/min) n = 5*		*CO (litres/min) n = 4*		*TPR (dynes cm^{-5} sec x 10^{-3}) n = 4*	
	Pre-dose	*Post-dose*	*Pre-dose*	*Post-dose*	*Pre-dose*	*Post-dose*	*Pre-dose*	*Post-dose*
Intravenous								
0.3	109 ± 11	98 ± 8	154 ± 16	130 ± 8	1.74 ± 0.4	1.5 ± 0.3	4.65 ± 1.0	5.34 ± 1.1
1.0	94 ± 9	87 ± 10	127 ± 7	117 ± 7	1.44 ± 0.06	1.26 ± 0.02	4.75 ± 0.59	4.94 ± 0.7
Intracerebroventricular								
0.3	114 ± 3	103 ± 4	155 ± 11	124 ± 10	1.73 ± 0.3	1.36 ± 0.2	5.71 ± 1.1	6.53 ± 1.1
1.0	111 ± 4	93 ± 8	120 ± 11	107 ± 10	1.09 ± 0.2	0.88 ± 0.2	8.43 ± 1.1	8.94 ± 1.4
Intracisternal								
0.3	106 ± 9	77 ± 12	152 ± 9	131 ± 9	2.04 ± 0.28	1.56 ± 0.29	4.5 ± 0.67	4.41 ± 0.69
1.0	89 ± 10	31 ± 7	137 ± 14	109 ± 12	1.74 ± 0.37	1.02 ± 0.35	4.55 ± 0.84	2.96 ± 0.8
Intravertebral artery								
0.3	111 ± 7	93 ± 10	145 ± 7	113 ± 8	1.66 ± 0.2	1.44 ± 0.2	5.64 ± 0.5	5.34 ± 0.85
1.0	96 ± 10	46 ± 13	115 ± 8	86 ± 7	1.35 ± 0.06	1.01 ± 0.2	5.67 ± 0.8	3.45 ± 1.1