Absence of central nervous system effects of practalol [ICI 50,172; 4-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide], a new adrenergic β-receptor blocking drug

Practalol [ICI 50,172; 4-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide] is a potent adrenergic β-receptor blocking agent which, in contrast to some older drugs from this group {propranolol, Kö 592 [1-(isopropylamino)-3-(*m*-tolyloxy)-2-propanol HCl]}, is almost free from local anaesthetic properties (Dunlop & Shanks, 1968). Since it has been shown that several β-receptor blocking drugs, like propranolol, Kö 592, and 2-isopropylamino-1-(p-nitrophenyl) ethanol (INPEA), exhibit marked effects on the central nervous system, ranging from central depression to central stimulation (Ammon & Estler, 1968; Leszkovszky & Tardos, 1965; Murmann, Almirante & Saccani-Guelfi, 1966), we examined the central nervous system effects of practalol in white mice. (±)-Propranolol was used for comparison in some of the tests.

Male NMRI-mice, which had free access to standard diet (Altromin R, obtained from Altromin GmbH, Lage/Lippe, Germany) and tap water, were used.

Spontaneous motor activity of single mice. The animals were placed into circular activity cages of 14 cm diameter. In each cage two photo-cells and light beams were installed. When the animals moved along the circular path they interrupted the light beams, and the number of interruptions per time unit was measured. Recordings were made for 2 h after the animals had received 1, 5, or 20 μg/g of practalol or the same doses of (±)-propranolol subcutaneously. Activity was measured in counts/30 min.

Spontaneous orientational hypermotility of grouped mice. Groups of 5 mice were placed into a Basile activity cage. The floor of this cage is made up of steel bars insulated from each other and charged with a low current. When moving around the animals close the electric circuits and the contacts per time unit are counted. The activity was measured for 15 min after the animals had received 1, 5, or 20 μg/g practalol subcutaneously. Activity was measured as contacts/15 min.

Traction test. This test (Julou, 1956) measured sedation and muscular relaxation in mice treated with 1, 5, or 20 μg/g practalol or propranolol subcutaneously 45 min beforehand.

Effect on hexobarbitone anaesthesia. Mice were pretreated subcutaneously with 1, 5, or 20 μg/g practalol or (±)-propranolol. 30 min later, 120 μg/g of hexobarbitone was injected intraperitoneally, and the sleeping time measured. Sleeping time was equated with absence of righting reflexes.

Effect on propanidid anaesthesia. Mice were pretreated subcutaneously with 1, 5, or 20 μg/g practalol or (±)-propranolol. 30 min later they were injected with 40 μg/g propanidid intraperitoneally, and the sleeping time was measured as before.

Effect on leptazol seizures. Mice were pretreated subcutaneously with 20 μg/g practalol or the same dose of (±)-propranolol. 30 min later leptazol was given intravenously in increasing doses from 50–120 μg/g. The number of animals that exhibited tonic extensor spasms and died within 30 min was recorded. From these data the LD50 for leptazol was calculated (Litchfield & Wilcoxon, 1949).

It is obvious (Table 1) that the effects of practalol differ in most respects from those of propranolol. Like Leszkovszky & Tardos (1965), we found propranolol to increase the seizure threshold and the LD50 of leptazol and to prolong hexobarbitone anaesthesia. In the same way, the sleeping time after propanidid was prolonged by 20 μg/g (±)-propranolol. Practalol, on the other hand, did not significantly affect the hexobarbitone and propanidid anaesthesia and the LD50 of leptazol. Both

Table 1. *Central nervous system effects of practalol and (±)-propranolol*

Test	Time after injection of drug (min)	Saline	Practalol (μg/g s.c.)			(±)-Propranolol (μg/g s.c.)		
			1	5	20	1	5	20
Spontaneous motility of single mice (counts/30 min) ..	0–30	120 ± 12 (28)	155 ± 14* (28)	195 ± 17* (28)	167 ± 13* (28)	138 ± 23 (20)	134 ± 14 (24)	119 ± 12 (24)
	30–60	38 ± 6 (28)	56 ± 12 (28)	114 ± 22* (28)	45 ± 11 (28)	68 ± 23 (20)	60 ± 11 (24)	51 ± 9 (24)
	60–90	23 ± 5 (28)	37 ± 11 (28)	78 ± 20* (28)	43 ± 10 (28)	18 ± 4 (20)	37 ± 7 (24)	29 ± 6 (24)
	90–120	23 ± 7 (28)	30 ± 11 (28)	63 ± 21 (28)	14 ± 6 (28)	14 ± 3 (20)	32 ± 9 (24)	27 ± 8 (24)
Orientational hypermotility of grouped mice (counts/15 min)	0–15	615 ± 61 (20)	813 ± 46* (20)	809 ± 52* (20)	795 ± 53* (20)	—	—	—
Sleeping time after 120 μg/g hexobarbitone i.p. (min)	30	51 ± 5 (16)	47 ± 5 (16)	45 ± 5 (14)	51 ± 4 (14)	53 ± 9 (9)	53 ± 12 (8)	75 ± 6* (21)
Sleeping time after 40 μg/g propanidid i.p. (min)	30	1·8 ± 0·2 (10)	2·1 ± 0·2 (10)	1·8 ± 0·2 (9)	2·1 ± 0·2 (13)	2·2 ± 0·2 (9)	2·2 ± 0·2 (10)	2·6 ± 0·2* (15)
LD50 of leptazol and confidence limits (μg/g i.p.) ..	45	75 68–86	—	—	68 56–83	—	—	92* 79–105

Results are expressed as mean values ± s.e. The number of animals is given in parentheses.
* Values significantly different from control, $P \leq 0{\cdot}05$.

drugs had no effect on the behaviour of animals in the traction test. The only significant effect of practalol was on spontaneous motility. All doses tested increased the orientational hypermotility of grouped mice. In single animals motility was increased for 90 min after a dose of 5 μg/g practalol and for only 30 min by 1 and 20 μg/g, whereas propranolol did not markedly influence the spontaneous activity of single mice.

Thus, (±)-propranolol shows central depressant properties (Leszkovszky & Tardos, 1965; Murmann & others, 1966), whereas practalol exerts only weak, if any, central stimulant effects.

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