Anti-arrhythmic and local anaesthetic activity of some β-receptor blocking compounds

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The ability of propranolol, 1-(isopropylamino)-3-(*o*-phenoxyphenoxy)-2-propanol, HCl (Ph QA 33) (Hermansen, 1968), and 2-isopropylamino-1-(*p*-nitrophenyl) ethanol HCl (INPEA) to abolish ouabain-induced ventricular fibrillations in guinea-pigs was compared with their local anaesthetic and β-receptor-blocking potency.

INPEA has previously been reported to be devoid both of local anaesthetic activity and of an effect against ouabain-induced ventricular tachycardia (Somani & Lum, 1965). With a different technique we found that INPEA has a significant reversing action on ouabain-induced fibrillations and also some local anaesthetic effect. The following values were obtained with the three compounds: antiarrhythmic effect (ED50 I.V.): propranolol 0.3 mg/kg, Ph QA 33 0.5 mg/kg, INPEA 1–3 mg/kg; local anaesthetic effect (ED50): propranolol 1.2 mg/ml., Ph QA 33 3.5 mg/ml., INPEA 18 mg/ml.; beta-receptor blocking effect (ED50 I.V.): propranolol 8.0 μg/kg, Ph QA 33, 7.5 μg/kg, INPEA 1–3 mg/kg. The order of potency demonstrates the close relationship between local anaesthetic activity and effect against non-catecholamine-induced arrhythmia. Furthermore, the results confirm the lack of correlation between anti-arrhythmic and β-receptor blocking effect as also shown with some other β-receptor antagonists.

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On the mechanism of the pressor response due to propranolol

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Occasional rises of systemic blood pressure with small doses of propranolol, and rise of perfusion pressure in the hind limb of the dog have been observed by various workers (Kayaalp & Kiran, 1966; Kayaalp & Turker, 1967). We have observed a consistent and moderate rise of blood pressure following propranolol (1–20 μg) in the rat (380 to 430 g) anaesthetized with urethane. The pressure was recorded from the common carotid artery with a Condon manometer; all injections were made into the cannulated femoral vein in volumes of 0.1 ml., followed by 0.2 ml. of normal saline.

The response on the blood pressure was immediate—the peak rise varied from 15 mm to 30 mm Hg. With propranolol (1–2 μg) the duration of the pressor response was 5 to 15 min; with 20 μg, the response was persistent and rarely returned to the pre-injection level, even after an hour or more. Development of tachyphylaxis occurred with repeated doses, the greater the dose, the earlier being the loss of response.

There was also a slight increase in the heart rate lasting for about 10–15 min (with 3 μg, 336–348/min). A positive inotropic and a slight chronotropic effect was also obtained with propranolol (0.4 μg) on Langendorff's preparation of the rabbit's heart. Thus the pressor response may be partly due to a direct or indirect effect on the heart.

The pressor response with propranolol was not prevented when the rats were treated with hexamethonium bromide (15 mg/kg I.V.). The response was also consistently obtained when the α-receptors for adrenaline had been blocked with phenoxybenzamine