Short communications

Isoprenaline- and exercise-induced tachycardia in the assessment of β-adrenoceptor blocking drugs; a comparison between tolamolol, practolol and propranolol

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The effects of tolamolol, propranolol and practolol on both isoprenaline- and exercise-induced tachycardia have been studied in conscious dogs. Tolamolol was approximately equipotent to propranolol and 50 times more potent than practolol in antagonizing exercise-induced tachycardias, but was approximately 12 times less potent than propranolol and 8 times more potent than practolol in blocking isoprenaline-induced tachycardia. It is suggested that antagonism of the tachycardia induced by exercise affords a more meaningful assessment of the possible therapeutic potential of β-adrenoceptor blocking drugs than does that induced by isoprenaline.

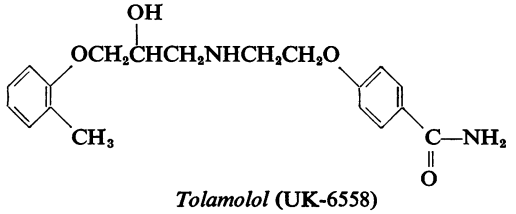
The assessment of β-adrenoceptor blocking compounds by their ability to antagonize the tachycardia produced by isoprenaline has been widely used in both animals and man. Difficulties arise, however, when assessing, in the conscious animal, cardioselective β-adrenoceptor blocking compounds, such as practolol, where the depressor effect of isoprenaline on the peripheral vasculature is unaffected or only partially antagonized. In such cases a reflex tachycardia persists, due to reduction in vagal activity, even after total blockade of myocardial β-adrenoceptors (Dunlop & Shanks, 1968; Brick, Hutchison, McDevitt, Roddie & Shanks, 1968; Barrett, Crowther, Dunlop, Shanks & Smith, 1968). For this reason it was considered that the relative potencies of cardioselective and non-selective β-adrenoceptor blocking compounds might be better compared by their ability to antagonize the tachycardia produced by exercise than by their antagonism of tachycardia caused by isoprenaline. This communication describes the effects of propranolol and practolol and of tolamolol, a β-adrenoceptor blocking agent (Augstein, Cox, Ham, Leeming & Snarey, 1973) for which cardioselectivity has been demonstrated in man (Briant, Dollery, Fenyvesi & George, 1973) and in the anaesthetized dog (Boyles, personal communication), in blocking the tachycardia produced by isoprenaline and by exercise in the conscious dog.

Methods.—Nine male beagles (10–14 kg) with exteriorized carotid loops were used in these experiments. Heart rates were derived from carotid artery pressure pulses, obtained from a miniature strain gauge held against the carotid loop.

The effect of isoprenaline (3 μg i.v.) on heart rate was determined before, and 45 min after, an intravenous dose of the β-adrenoceptor blocking agent under test.

In the exercise study, dogs were trained to exercise on a treadmill which was inclined 10% from the horizontal. The running speed was varied according to the exercise capability of individual dogs, and the exercise tachycardia measured before, and 45 min after, an intravenous dose of the β-adrenoceptor blocking agent under test.

The mean resting heart rate was 81 ± 1 (S.E.M.) beats/min and mean control increases in response to isoprenaline and exercise were 127 ± 17 beats/min and 123 ± 12 beats/min respectively. The reduction of the tachycardia by the compound under test was expressed as a percentage of the control tachycardia.



Tolamolol (UK-6558)
4-[2-(2-hydroxy-3-*o*-tolyloxypropylamino)ethoxy] benzamide

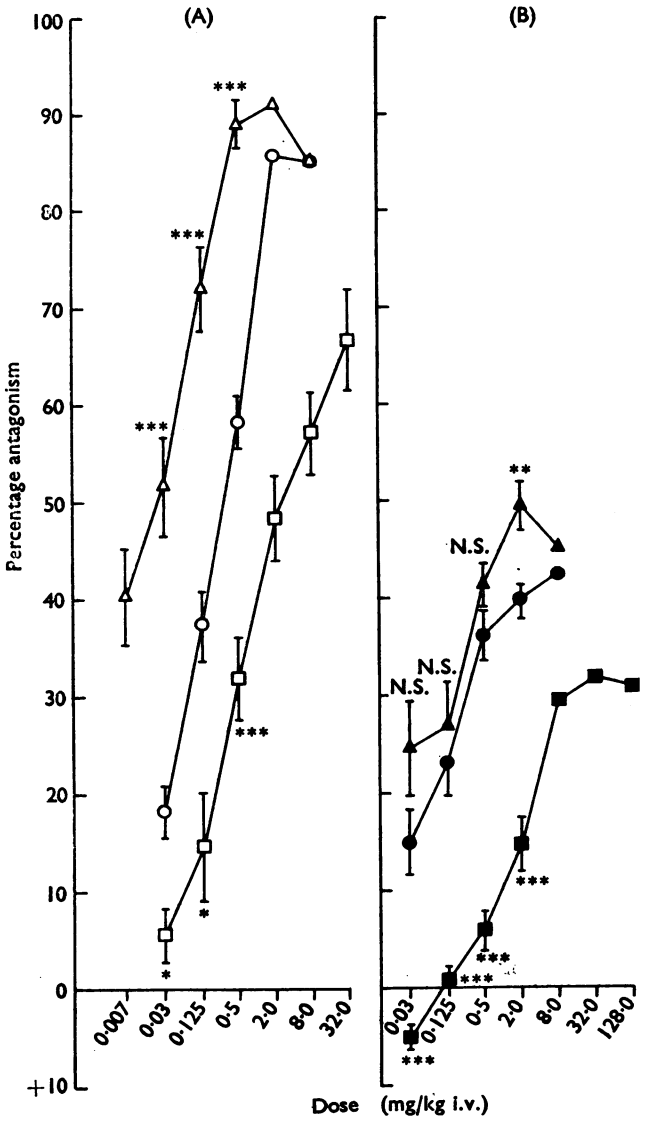


FIG. 1. Comparison of the effects of tolamolol (●, ○), practolol (□, ■), and propranolol (△, ▲) in the conscious dog against (A) isoprenaline-induced tachycardia and (B) exercise-induced tachycardia. Significance of difference from tolamolol at equal dose, *=$P<0.05$, **=$P<0.01$, ***=$P<0.001$, N.S.=not significant.

Results.—The effects of propranolol, practolol and tolamolol on isoprenaline- and exercise-induced tachycardia are shown in Figure 1. Propranolol was approximately 12 times more potent than tolamolol and 100 times more potent than practolol in antagonizing isoprenaline-induced tachycardia. Against exercise-induced tachycardia, however, propranolol and tolamolol were virtually equipotent and 50–60 times more potent than practolol. The lowest dose level of practolol investigated (0·03 mg/kg) enhanced the exercise-induced tachycardia, possibly due to its sympathomimetic properties; this effect was not observed with propranolol or tolamolol.

Maximum blockade (approximately 90%) of isoprenaline-induced tachycardia was achieved with propranolol and tolamolol at a dose level of 2·0 mg/kg and increasing amounts produced no further

antagonism. With practolol, however, an antagonism of only 66% was obtained at the high dose level of 32 mg/kg.

The maximum blockade of the exercise-induced tachycardia, after propranolol and tolamolol, was about 45% ; this maximum was achieved with doses of 2·0 mg/kg and 8·0 mg/kg respectively. Practolol produced only 30% blockade at a dose level of 8·0 mg/kg and further increases in dose produced no further antagonism.

Discussion. — Propranolol has been shown to possess approximately four times the potency of practolol in inhibiting the cardiac responses to isoprenaline in anaesthetized cats and dogs (Dunlop & Shanks, 1968). In our laboratories, in anaesthetized dogs, propranolol was approximately 5 times more potent than practolol but only half as potent as tolamolol in this respect (Boyles, personal communication). In the current experiments in conscious dogs, however, propranolol was approximately 12 times more potent than tolamolol and approximately 100 times more potent than practolol in antagonizing isoprenaline tachycardia. The latter result correlates reasonably with that found in a recent study in man where tolamolol was approximately 5 times more potent than practolol against isoprenaline tachycardia (Briant *et al.*, 1973). Dunlop & Shanks (1968) also found practolol to be much less active than propranolol in conscious dogs, while Brick *et al.* (1968), in human studies, failed to obtain a significant antagonism of isoprenaline tachycardia after practolol (20 mg i.v.).

It has been suggested that the increase in heart rate elicited by isoprenaline in conscious animals results from both a direct stimulation of the sino-atrial node and a reflex reduction in vagal activity in response to the vasodepression (Barrett *et al.*, 1968 ; Dunlop & Shanks, 1968). Cardioselective agents, such as tolamolol and practolol, do not block the fall in arterial pressure produced by isoprenaline and the reflex component of the tachycardia remains even after complete blockade of the direct effects of isoprenaline on the heart. This accounts for their lower potencies compared with propranolol in conscious animals and man. In dogs anaesthetized with pentobarbitone, however, the baroreceptor reflexes are depressed and the β-adrenoceptor blocking potencies of tolamolol and practolol are much higher relative to propranolol.

The increase in heart rate produced by severe muscular exercise results from an increase in sympathetic activity, a reduction in vagal activity and an undefined non-nervous mechanism (Donald & Shepherd, 1963 ; Jose, 1966 ; Chamberlain, Turner & Sneddon, 1967). β-Adrenoceptor blocking compounds reduce only the sympathetic component by their action on the cardiac β-adrenoceptors and therefore only partial antagonism of the exercise tachycardia can be obtained. It would be expected, however, that the relative potencies of tolamolol, practolol and propranolol against exercise tachycardia would more closely resemble those found in anaesthetized animals against isoprenaline and be independent of the cardioselective properties of these agents. Our experiments show that tolamolol and propranolol are approximately equipotent against the tachycardia produced by exercise but that practolol is approximately 50 times less potent. In fact, the maximum percentage antagonism achieved after practolol was markedly less than that achieved after tolamolol or propranolol.

The unexpectedly low efficacy of practolol against exercise tachycardia cannot be explained at present, but might be due in part to its intrinsic sympathomimetic activity, a property not possessed by tolamolol and propranolol. However, Brick *et al.* (1968), who reported somewhat similar results for practolol in man in a comparison with propranolol, discounted the relative differences in local anaesthetic activity and intrinsic sympathomimetic activity between propranolol and practolol as being causative.

Although we have no ready explanation for the results obtained with practolol, we suggest that β-adrenoceptor blocking agents are better compared, in conscious dogs, by their ability to antagonize exercise-induced tachycardia than by antagonism of tachycardia elicited by intravenous administration of isoprenaline.

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