Effects of Propranolol and Oxprenolol on the Vasoconstrictor Response to Noradrenaline in the Superficial Hand Vein in Man

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Summary. The effects of oxprenolol and propranolol on the vasoconstrictor response to noradrenaline were studied in healthy volunteers by measuring superficial dorsal hand vein diameter at a standard congesting pressure. In 8 subjects dose response curves to noradrenaline (20–1280 ng/ml) were obtained with noradrenaline alone, with noradrenaline plus propranolol 10 µg/ml, with noradrenaline plus propranolol 10 µg/ml plus oxprenolol 3 µg/ml, and with noradrenaline plus propranolol 13 µg/ml according to a double blind balanced randomised design. Propranolol 10 µg/ml significantly (P<0.05) potentiated the vasoconstrictor response to noradrenaline and the addition of oxprenolol significantly (P<0.05) reversed the potentiation giving a response similar to that seen with noradrenaline alone. The higher concentration of propranolol did not produce further potentiation, the response being similar to that obtained with the lower concentration of propranolol. It is suggested that the effect of oxprenolol may be attributable to alpha blocking properties, to partial beta agonism or to its membrane stabilising properties.

Key words: Propranolol, oxprenolol, noradrenaline-induced vasoconstriction

Law et al. (1974) concluded from studies in the rabbit isolated ear artery that oxprenolol had alpha adrenoreceptor blocking properties and Meier (personal communication) obtained similar findings in vivo in the cat.

It had previously been shown by White and Udwadia (1975) that propranolol potentiated the vasoconstrictor response to noradrenaline in the superficial dorsal hand vein in man and the present study was designed to establish whether oxprenolol would reverse that potentiation.

Material and Methods

Superficial dorsal hand vein diameter (HVD) was measured using the technique described by White and Udwadia (1975). The subject lies horizontal on a couch with the hand supported above the level of the heart on a rigid wood and metal frame sloping at an angle of 35° from the horizontal. The hand is fixed at the wrist by pressure on the ulna and radial styloid processes and the fingers rest on a metal cylinder, the palm being held away from the surface of the support to minimise the contribution which the swelling of the whole hand could make to HVD readings. A Devices optical wedge displacement transducer is held on a Prior micromanipulator so that the tip of an attached metal arm rests on a marked spot over the selected dorsal hand vein. A continuous trace of the vein's position is obtained on a Devices M2 chart recorder. A sphygmomanometer cuff is placed around the upper arm and readings are taken by inflating the cuff to a pressure of 40 mm Hg for a 2 minute period, or for longer if required to obtain a plateau in vein size. The cuff is then deflated and the HVD taken as the distance from the plateau height just before deflation to the collapsed vein position. Infusions were given through a Gillette 25G needle inserted into a selected vein. The point for measurement was 10–12 mm from the tip of the needle. Each concentration of drug was infused for 5 min before duplicate readings were taken. Subjects abstained from tea, coffee, smoking for at least 2 h before study and rested in position for at least 20 min before measurements began. The ambient temperature was maintained above 26°C.
In 8 healthy volunteers, 7 male and 1 female, dose response curves were obtained to noradrenaline at an initial concentration of 2 ng/ml with subsequent doubling of concentration up to 1280 ng/ml. Dose response curves were obtained to noradrenaline alone, to noradrenaline with the addition of propranolol 10 μg/ml, to noradrenaline with the addition of propranolol 10 μg/ml plus oxprenolol 3 μg/ml and to noradrenaline with the addition of propranolol 13 μg/ml according to a double blind balanced randomised design. These solutions were infused at a constant rate of 0.1 ml/min with a Sage syringe pump model 355 using normal saline as diluent with the addition of 10 μg/ml ascorbic acid to inhibit oxidation of noradrenaline.

ED50 values were determined from the regression of the response given as percentage change from saline control against log dose. The variance for each treatment was similar and the regressions highly significant.

Results

The results are shown in Table 1. The addition of 10 μg/ml propranolol significantly (P<0.05) potentiated the vasoconstrictor response to noradrenaline. The addition of 3 μg/ml oxprenolol reversed the potentiation seen with 10 μg/ml propranolol alone. The ED50 obtained in the presence of oxprenolol did not differ significantly from that obtained with noradrenaline alone but did differ significantly (P<0.05) from the ED50 obtained with noradrenaline plus 10 μg/ml propranolol. The ED50 for noradrenaline plus 13 μg/ml propranolol was intermediate between the values obtained for noradrenaline plus propranolol plus oxprenolol and for noradrenaline plus 10 μg/ml propranolol but did not differ significantly from the value obtained with the lower concentration of propranolol.

Discussion

The results confirm the finding of White and Udwadia (1975) that 10 μg/ml propranolol significantly potentiated the vasoconstrictor response to noradrenaline and similar findings have been reported for adrenaline in human hand veins (Collier et al., 1972) and forearm arteries (Glover and Hutchinson, 1965). White and Udwadia (1975) concluded that the probable mechanism of this effect was abolition by propranolol of the beta agonist vasodilator activity of noradrenaline while alpha adrenergic vasoconstrictor activity was unopposed. Possibly there is a concentration of propranolol at which this beta blockade is maximal and this might explain the failure of the higher concentration of propranolol to produce further potentiation. Alpha blockade with propranolol in vitro has been reported (Burks and Cooper, 1967) though only at concentrations 1000 times greater than those required to block beta receptors; this could possibly explain the finding with the higher concentration of propranolol.

Several mechanisms might be responsible for the reversal of potentiation produced by oxprenolol. Alpha blockade with oxprenolol has been reported (Law et al., 1974), on the basis of increased noradrenaline release but decrease in the vasoconstrictor response of the rabbit isolated ear artery on sympathetic nerve stimulation and in response to exogenous adrenaline but not to histamine. Mazurkiewicz-Kwilecki (1970) demonstrated that oxprenolol gave significant protection against alpha adrenergic blockade induced by phenoxybenzamine. Meier (personal communication) compared the relative alpha and beta adrenoreceptor blocking activities of labetolol and oxprenolol in the cat in the terms of heart rate increase and contraction of the nictitating membrane induced by stellate ganglion stimulation. He found that oxprenolol and labetolol were equipotent as alpha blockers but oxprenolol was more potent as a beta blocker. The dose ratio alpha blockade : beta blockade was 10 for labetolol and 30 for oxprenolol.

Barrett and Carter (1970) demonstrated that oxprenolol but not propranolol had partial beta agonist activity in catecholamine depleted rats. If partial agonism were the explanation here then it must have occurred despite the beta blockade due to propranolol.

Local anaesthetic or membrane stabilising activity has been reported for both propranolol and oxprenolol, oxprenolol being half as active as propranolol as a local anaesthetic on the basis of its effects in reducing the height of the action potential in the frog's sciatic nerve and its effects on intracellular cardiac potentials (Vaughan Williams and Papp,