AN IN VITRO COMPARISON OF PRAZOSIN AND ITS CONGENERS UK-18596 AND UK-33274 ON VASCULAR MUSCLE

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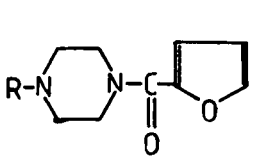
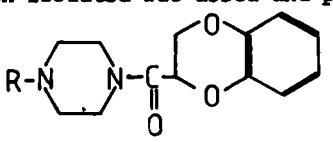
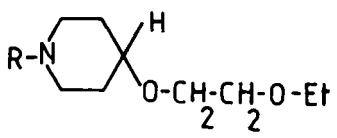
Timmermans et al (1980) investigated the hypotensive effect of prazosin and its congeners UK-18596 and UK-33274 in the pithed rat and cat and found a potency order prazosin > UK-18596 > UK-33274. They attributed the hypotensive action entirely to blockade of vascular adrenoceptors. Since it has been reported that prazosin has qualitatively different effects upon venous and arterial muscle (Cohen & Wiley 1979) we have studied the relative potencies of prazosin, UK-18596 and UK-33274 on isolated rat aorta and portal vein.



Prazosin



UK-33,274



UK-18,596

R = 4-Amino-6,7-dimethoxyquinazolin-2-yl

Longitudinal preparations of portal vein and helical strips of descending thoracic aorta were obtained from male Wistar rats (180-240g), suspended in Krebs bicarbonate solution at 37°C and gassed with 5% CO_2 in oxygen with resting tensions of 0.5g and 1.0g respectively. In experiments with portal vein, propranolol (10^{-6}M), β-oestradiol (10^{-5}M) and cocaine (10^{-5}M) were added to the bathing solution. Isometric contractions to noradrenaline were obtained and dose response curves constructed over concentration ranges of 2.5×10^{-10}M to 10^{-5}M for aorta and 10^{-8}M to 10^{-5}M for veins. The responses of the portal vein were expressed as the integral of contraction. The effect of prazosin and its congeners, each at a concentration of 2.5×10^{-8}M, was determined as the log shift of each curve measured at the agonist ED_{50}.

On portal vein the shift with prazosin (1.49 ± 0.06)(mean ± s.e.mean, n=6) was significantly greater than that observed with either UK-33274 (0.964 ± 0.033, n=6) or UK-18596 (0.858 ± 0.05, n=6)($p < 0.001$), but there was no significant difference between the effect of the two congeners. Similarly on aorta, prazosin caused a significantly greater shift (2.6 ± 0.08, n=6) than either of the congeners ($p < 0.001$) but the shift due to UK-33274 (1.94 ± 0.11, n=6) was significantly greater than that of UK-18596 (1.29 ± 0.09, n=6)($p < 0.001$). Thus the order of potency of prazosin, UK-18596 and UK-33274 on rat venous and arterial muscle in vitro differs from the previously reported relative hypotensive potencies in vivo. On both aorta and portal vein the antagonism due to prazosin, UK-18596 and UK-33274 appeared competitive with a parallel shift of the noradrenaline curve to the right and no change in maximum response. In contrast, Cohen et al (1979) reported a non-competitive blockade by prazosin on the circular muscle of rat portal vein. The shift due to prazosin on aorta was significantly greater than that on portal vein ($p < 0.001$) which suggests a preferential action upon arterial muscle. This is in accord with the findings of Pedersen et al (1979) on human arterial and venous muscle in vitro but inconsistent with the findings of Collier et al (1978) on human muscle in vivo.

We are grateful to Pfizer U.K. for the gift of prazosin and its congeners.

Cohen, M.L. et al (1979) Blood vessels 16: 144-154
Collier, J.G. et al (1978) Br. J. Clin. Pharm. 5: 35-44
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