COMPARISON OF EFFECTS OF LOPERAMIDE, VERAPAMIL AND CALMODULIN ANTAGONISTS ON VASCULAR MUSCLE

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Loperamide, a widely used antidiarrhoeal drug, was shown to possess activity similar to that of the calcium channel blocker, verapamil (verap) in inhibiting agonist-induced contractions of guinea-pig ileum (Ali et al 1988). The calcium antagonist activity of loperamide (lop) was further investigated in vascular muscle (Bowes et al 1989). In these experiments concentrations of lop and verap which caused comparable reduction in maximal contractions to potassium (K) and noradrenaline (NA) in portal vein differentially affected aorta; lop reduced maximal contractions to both agonists whereas verap reduced only responses to K, suggesting that intracellular actions or opiate effects might contribute to the activity of lop. In the present experiments these possibilities were investigated.

Cumulative concentration-response curves to NA (10^{-10}-10^{-5}M) were constructed in rat aortic rings before and after exposure to lop (10^{-6}-10^{-5}M), verap (10^{-6}-10^{-5}M) or the calmodulin antagonists trifluoperazine (TFP) (10^{-7}-10^{-5}M) and N-(6-aminohexyl)-5-chloro-1-naphthalanesulphonamide (W7) (10^{-6}-10^{-4}M) in the presence or absence of naloxone (NAL) (10^{-6}M). Tissues were maintained in oxygenated Krebs' solution. Lop (3 x 10^{-6}, 10^{-5}M) caused concentration-related, non-competitive antagonism of responses to NA, maximal responses being reduced by 40±3 and 78±10% respectively. This reduction was unaffected by NAL (10^{-6}M); NAL alone had no effect on responses to NA. Verap (10^{-6}-10^{-5}M) did not modify responses to NA in the presence or absence of NAL (10^{-6}M). Both TFP and W7 caused concentration-related antagonism of NA responses which was similar to that produced by lop. TFP (10^{-6}, 10^{-5}M) decreased maximal NA responses (NA_{max}) by 54±8 and 91±5% respectively and W7 (10^{-5}, 10^{-4}M) decreased NA_{max} by 34±5 and 67±13% respectively.

In further experiments stable, submaximal contractions were induced by addition of 1 x 10^{-3}M $CaCl_2$ in rat aortic rings maintained in calcium-free, depolarising (4 x 10^{-2}M KCl) Krebs' solution. Single doses of lop (10^{-5}-10^{-4}M) or verap (10^{-7}-10^{-5}M) were applied in the absence or presence of NAL (10^{-5}M). Lop and verap fully relaxed calcium-induced contractions, the time taken for 100% relaxation being concentration-dependent. Verap relaxed aorta more rapidly than lop; relaxation time for verap (10^{-5}M) being ≤ 3 mins whereas lop (10^{-5}M) required 20 mins for full relaxation. These effects were unaffected by NAL; NAL alone had no effect on calcium contractions.

These results indicate that opiate effects do not contribute to the actions of lop on vascular muscle. Rather they suggest that calcium antagonism is a significant property of the drug and that the antagonism is likely to be intracellular. Although the actions of lop and verap appeared similar in ileum, the different profile of activity observed in the present study emphasises that more than one approach is needed in studying these actions.

Ali, I.M. et al (1988) Br. J. Pharmac. 95: 605P
Bowes M.A. et al (1989) Br. J. Pharmac. 98: 875P