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DIFFERENTIAL EFFECTS OF THE CALCIUM-ANTAGONISTIC VASODILATORS, NIFEDIPINE AND VERAPAMIL, ON THE TRACHEAL MUSCULATURE AND VASCULATURE OF THE DOG

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In anaesthetized dogs the trachea *in situ* was perfused arterially with blood, and drugs were injected intra-arterially. Isoprenaline and the calcium-antagonistic vasodilators, nifedipine and verapamil, increased tracheal blood flow and decreased resting tone of the trachea. Isoprenaline was equi-effective in producing tracheal vasodilatation and tracheal dilatation. The two calcium-antagonistic vasodilators were less effective tracheal dilators than tracheal vasodilators.

Introduction The calcium-antagonistic vasodilator, verapamil or its methoxy analogue, D 600, has been shown to inhibit the electrical and mechanical activities of spontaneously contracting uterine (Fleckenstein, Grün, Tritthart & Byon, 1971; Reiner & Marshall, 1976) and intestinal (Golenhofen & Lammel, 1972) smooth muscle. The mechanism underlying these actions has been ascribed by these workers to an inhibition of the transmembrane influx of Ca^{2+}. Nifedipine, another calcium-antagonistic vasodilator, is also known to inhibit spontaneous uterine contractions by a similar mechanism (Ulmsten, Andersson & Forman, 1978; Fleckenstein, Fleckenstein-Grün, Byon, Haastert & Späh, 1979). However, no information is available as to whether calcium-antagonistic vasodilators are able to reduce resting tone of airway smooth muscle. Furthermore, there is no study comparing directly the effect of calcium-antagonistic vasodilators on the musculature and on the vascular bed of the airway. The present experiments were designed to elucidate these two points.

Method Experiments were carried out on 8 mongrel dogs weighing 10 to 15 kg, anaesthetized with pentobarbitone sodium (30 mg/kg i.v.). After the animal had been given heparin sodium (500 units/kg i.v.), the tracheal vascular bed was perfused *in situ* with arterial blood through the cannulated cranial thyroid arteries on both sides. Perfusion pressure was kept constant at a value approximately equal to mean systemic blood pressure. Blood flow through the arteries was measured with an electromagnetic flowmeter (Nihon Kohden, MF-46-3). The trachea was intubated by a tracheal tube with a water-filled cuff attached. Hydraulic pressure in the cuff was measured with a pressure transducer (Nihon Kohden, MPU-0.1) as intraluminal pressure of the trachea. Details of the preparation and the experimental methods have been given previously (Himori & Taira, 1976).

(−)-Isoprenaline hydrochloride (Nikken Kagaku) and (±)-verapamil hydrochloride (Knoll) were dissolved in 0.9% w/v NaCl solution (saline). Nifedipine (Bayer, 100 μg/ml in ampoule) was diluted with saline. The solvent of nifedipine (Bayer) was also used. All drug solutions (except for those corresponding to 10μg of nifedipine) were injected intra-arterially (i.a.) in volumes of 10 to 30 μl in 4 s. Doses refer to their bases. All values are expressed in terms of means ± s.e. mean (unless otherwise stated).

Results The mean blood flow through the canine tracheal vascular bed was 11.3 ± 1.3 ml/min at the average perfusion pressure of 153 ± 14.1 (s.d.) mmHg ($n = 8$). The average resting intraluminal pressure (resting tone) of the trachea was 34 ± 2.5 cmH_2O ($n = 8$).

Single intra-arterial injections of isoprenaline (0.03 to 0.3 μg) increased blood flow through the tracheal vascular bed (tracheal vasodilatation) and decreased resting tone of the trachea (tracheal dilatation) in a dose-dependent manner over the same dose range. A typical experiment and dose-response curves for peak tracheal dilatation and vasodilatation are shown in Figure 1. Nifedipine (0.3 to 10 μg, i.a.) also produced dose-dependent tracheal dilatation and vasodilatation (Figure 1). The dose-response curve to nifedipine for tracheal vasodilatation was roughly parallel to that to isoprenaline; nifedipine was about 20 times less potent than isoprenaline on a weight basis. Nifedipine was less effective in producing tracheal dilatation than tracheal vasodilatation; the threshold dose for producing the former was higher than that for the latter and the dose-response curve to nifedipine for tracheal dilatation was flatter than that to isoprenaline. Even with the highest dose of nifedipine the tracheal dilatation never attained the amplitude produced by 0.3 μg of isoprenaline. Essentially similar results to those with nifedipine were obtained with verapamil except that it was about 20 times less potent than nifedipine both on tracheal muscle and blood vessels (Figure 1).

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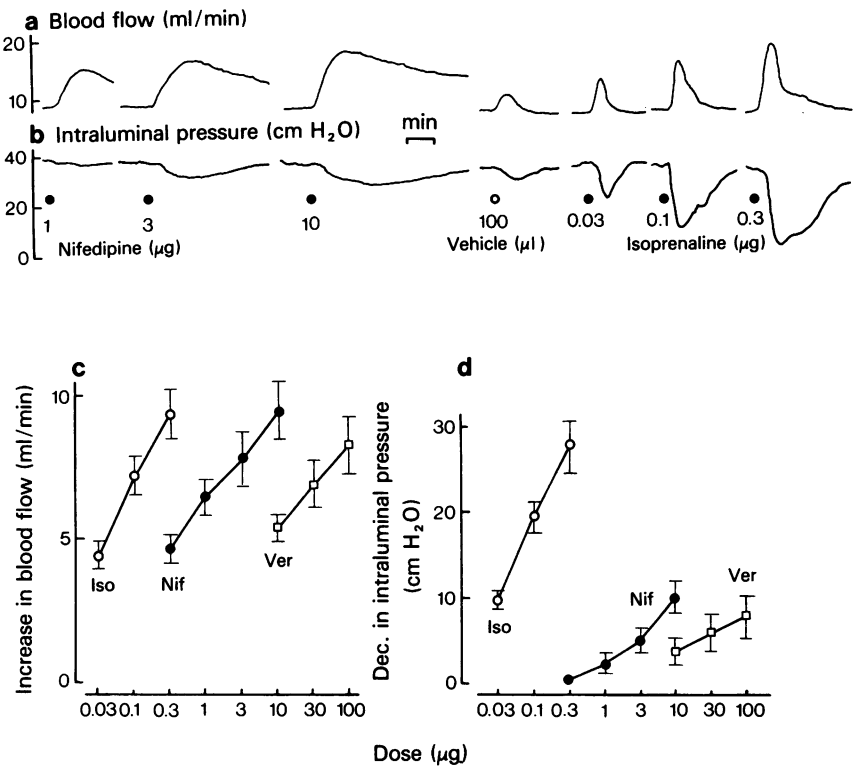

Figure 1 Effects of intra-arterial nifedipine and isoprenaline on (a) blood flow through the tracheal vascular bed and (b) intraluminal pressure of the trachea of a dog. Vehicle was solvent for nifedipine. (c) Dose-response curves for increase in tracheal blood flow to isoprenaline (Iso), nifedipine (Nif) and verapamil (Ver). (d) Similar dose-response curves but for decrease in tracheal intraluminal pressure. Each point represents the mean value and vertical bars show s.e. mean. The number of dogs is 6 for isoprenaline, 5 for nifedipine and 4 for verapamil.

Discussion In the present experiments isoprenaline and the two calcium-antagonistic vasodilators, nifedipine and verapamil, produced tracheal vasodilatation and tracheal dilatation. Unlike isoprenaline which was similarly effective in each tissue, the two other drugs were less effective in producing tracheal dilatation than tracheal vasodilatation.

In smooth muscle, the cytosolic Ca^{2+} responsible for maintaining tone is derived from the extracellular fluid and from membrane and intracellular storage sites. The relaxant actions on smooth muscle of nifedipine (Ulmsten *et al.*, 1978; Fleckenstein *et al.*, 1979) and verapamil (Fleckenstein *et al.*, 1971; Golenhofen & Lammel, 1972) are ascribed to an inhibition of the transmembrane influx of Ca^{2+}. Thus, the present results suggest that, for the maintenance of resting tone, vascular smooth muscle depends upon the transmembrane Ca^{2+} influx more than does tracheal smooth muscle.

It has been shown that contractions of dog tracheal smooth muscle produced by low concentrations of acetylcholine are inhibited by verapamil and suggested that such contractions are produced primarily by the transmembrane Ca^{2+} influx (Farley & Miles, 1978). In contrast, tracheal contractions produced by high concentrations of acetylcholine are completely resistant to calcium-antagonistic vasodilators (Coburn, 1977; Farley & Miles, 1978). Taken together with these earlier findings the present results suggest that the use of calcium-antagonistic vasodilators as bronchodilators in the treatment of bronchial asthma is limited.

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