Influence of Pizotifen and Ergotamine on the Venoconstrictor Effect of 5-Hydroxytryptamine and Noradrenaline in Man

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Summary. The influence of locally infused pizotifen (80 ng) and ergotamine (16 ng and 4 ng) on the compliance of superficial hand veins in man, and their interactions with the venoconstrictor effects of noradrenaline and 5-hydroxytryptamine (5-HT), were investigated in a placebo-controlled study in healthy volunteers. Pizotifen alone reduced venous compliance and produced a parallel displacement to the right of the 5-HT dose-response curve suggestive of competitive antagonism. The venoconstrictor effect of noradrenaline was not influenced by pizotifen. This confirms the selective antagonism of 5-HT by pizotifen and supports the existence of specific 5-HT receptors on human veins. After infusion of 16 ng ergotamine, which by itself reduced venous compliance and produced a parallel displacement to the right of the 5-HT dose-response curve suggestive of competitive antagonism. The venoconstrictor effect of noradrenaline was not influenced by pizotifen. This confirms the selective antagonism of 5-HT by pizotifen and supports the existence of specific 5-HT receptors on human veins. After infusion of 16 ng ergotamine, which by itself reduced venous compliance, the venoconstrictor effects of the lower doses of 5-HT and of all doses of noradrenaline were larger but still never exceeded the arithmetic sum of the separate effects of noradrenaline or 5-HT and ergotamine. A lower dose of ergotamine (4 ng) induced only a small venoconstriction and did not influence the constrictor effect of noradrenaline. Therefore, in contrast to previous observations, no potentiation of the venoconstrictor effect of noradrenaline by ergotamine was observed under the present experimental conditions. The additive effect of noradrenaline and ergotamine may well explain its therapeutic action in the treatment of migraine.

Key words: pizotifen, ergotamine, venous tone; 5-hydroxytryptamine, noradrenaline, venous compliance, venous constriction

5-Hydroxytryptamine (5-HT) and noradrenaline are physiological amines considered to be involved in the initiation and the course of attacks of migraine. Much, however, is still not known about the pathophysiology of migraine and the different factors leading to an attack. Studies of the different clinical pharmacological effects of drugs shown to be effective in the treatment or in the prevention of migraine attacks may help us to understand more about their mode of action, and the pathophysiological mechanisms of the disease.

Pizotifen (Sandomigran) is a 5-HT antagonist effective in the prevention of migraine attacks (Lance et al. 1970). Its antagonistic action on 5-HT has been demonstrated, for instance, on canine and human arteries in vitro (Müller-Schweinitzer 1976, 1983) and on superficial human veins in situ (Sicuteri et al. 1964; Aellig 1978), where it reduces the venoconstrictor action of 5-HT. Ergotamine, an ergot alkaloid with strong arterioconstrictor and venoconstrictor activity in vitro and in vivo (Clark et al. 1978), is used for the treatment of acute migraine attacks. In studies on isolated perfused human temporal and rabbit ear arteries, Carroll et al. (1974) found that low doses of ergotamine but not of pizotifen potentiated the venoconstrictor action of noradrenaline. No such interaction studies between ergotamine and noradrenaline have previously been carried out in man, but Fanciullacci et al. (1976) reported potentiation of the venoconstrictor effect of 5-HT on superficial human veins in vivo after low doses of ergotamine.

By means of a relatively simple technique for recording changes in the compliance of superficial hand veins after direct local infusion of constrictor agonists, the influence of low doses of locally infused ergotamine and pizotifen on the venoconstric-
Fig. 1. Reduction in hand vein diameter (ΔHVD) during local infusion of noradrenaline and 5-hydroxytryptamine before (●) and after (▲) local infusion of placebo. (mean ± SEM, n = 5)

Fig. 2. Reduction in hand vein diameter (ΔHVD) during local infusion of noradrenaline and 5-hydroxytryptamine before (●) and after (▲) local infusion of 80 ng pizotifen. (mean ± SEM, n = 5)

Materials and Methods

The study was carried out in 9 healthy male volunteers. Written informed consent was obtained after full explanation of the experimental procedures involved. The ages, weights and heights of the subjects are given in Table 1.

Changes in venous compliance were determined by recording the diameter of superficial hand veins at a constant subdiastolic congestion pressure of 45 mmHg. The method, which is based on the use of a linear variable differential transformer, has been described in detail elsewhere (Aellig 1981).

The various drugs were administered by local infusion through a small needle (27 G) inserted into the vein about 10 mm distal to the point of measurement. Immediately after insertion of the needle an infusion of physiological saline (0.1 ml/min) was started and was maintained throughout the entire experiment except for the periods of drug administration, when it was replaced by infusion of the drug dissolved in physiological saline (0.1 or 0.2 ml/min). Room temperature was kept constant at 24 ± 0.5 °C throughout the experiment. Measurements were not started earlier than 40 min after the end of the preparation of the subject for the study to allow complete adaptation to room temperature and the experimental conditions.

In the first part of the study dose-response curves for locally infused 5-hydroxytryptamine sulphate...