VASODILATOR EFFECT OF TRIMETAZIDINE ON CUTANEOUS MICROCIRCULATION OF NORMAL CONSCIOUS RABBITS

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Trimetazidine (TMZ), 1-(2,3,4-trimethoxy benzyl)-piperazine dihydrochloride, has been claimed to dilate arterioles in the periphery and brain as well as in the heart (1). Concerning the macrocirculatory effects of TMZ, a previous work (2) demonstrated in urethane-anesthetized rabbits a slight and transient fall of mean carotid arterial pressure after an intravenous administration in a dose of 10.0 mg/kg, though there was no change in doses below 5.0 mg/kg.

In the preliminary experiments of the present study in urethane-anesthetized rabbits (6 animals), an injection of 1.0–10.0 mg/kg (i.v.) of TMZ produced an immediate fall of mean femoral arterial pressure ranging up to -38 mmHg, but the blood pressure restored within a few minutes, and there was no change in the blood pressure after the fall. In addition, an immediate rise of carotid blood flow ranging up to $+15$ ml/min was observed by the same doses of TMZ when the blood pressure changes were observed. Accordingly the macrocirculatory effects of intravenous administrations of TMZ were transient. In the present study, we investigated microcirculatory changes in the cutaneous tissue following intravenous administration of TMZ in a single dose of 5.0 mg/kg by the use of intra-vital microscopy in conscious rabbits.

Male adult rabbits (7 animals) weighing about 3.0 kg were employed in the present

study. A transparent round-table chamber (rabbit ear chamber, REC (3)) was attached to the ear lobe, and the microcirculation of the ear lobe was observed through a binocular microscope-closed TV system at an ambient temperature of about 25°C . As a rule, the direct microscopy and photomicrography were performed at magnifications of $480\times$ or more. The microcirculation of the ear lobe was recorded by a video-tape-recorder, and the diameter of vessels visualized on a TV monitor by reproduction of the video-tape-recorder was measured with a slide caliper.

Under normal and basal conditions, the cutaneous microcirculation showed spontaneous rhythmic changes consisting of both an increase and decrease in the diameter of vessels as well as the volume and velocity of blood flow, suggesting the existence of vasomotion (4). The change in the diameter of vessels could be divided into four phases: first full dilatation, second initial constriction, third full constriction, and fourth initial dilatation. Since vascular diameter was maximum at the full dilatation phase, we measured the diameter of vessels at the full dilatation phase of vasomotion at appropriate time intervals following an intravenous administration of TMZ or saline (control) solution.

TMZ induced an appreciable vasodilatation not only of arterioles but also of venules and capillaries. A typical change in the diameter of vessels induced by TMZ is presented in

Fig. 1. In this case, an increase in the diameter of the arteriole(a) and venule(v) reached to 137% and 227% of the initial value, respectively. Successive measurements of arteriolar diameters during 1 hr following the administration of TMZ and saline are illustrated in Fig. 2. Although the level of arteriolar diameters at the full dilatation phase of vasomotion appeared to drift slightly from the base line even after saline administration (spontaneous shift of vasomotor tone), it was certain that TMZ produced a short-duration but definite vasodilator effect. Throughout the observation period, saline did not affect the normal microcirculatory state, but TMZ augmented the amplitude of vasomotion; arteriolar diameters increased at the full dilatation phase and increased both volume and velocity of blood flow, though the

increase in diameter was not observed at the full constriction phase. In addition, the frequency characteristic and phasic proportion of vasomotion were not altered by the injection of TMZ.

Intravenous administration of a coronary dilator drug, dilazep dihydrochloride, induces a similar microvascular dilating effect that does not interfere with vasomotion at lower doses (10–50 $\mu\text{g/kg}$) (5). Intravenous administration of an α -blocker vasodilator drug, phenoxybenzamine hydrochloride (5 mg/kg), however, has been demonstrated to induce a marked dilatation of arterioles, not only at the full dilatation phase but also at the full constriction phase, and abolish vasomotion completely for a long period of time (more than a few hours) (6). Similarly, a water-soluble vitamin vasodilator, nicotinic

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Fig. 1. Photomicrographs of a typical vasodilator effect of trimetazidine (TMZ). The full dilatation phase of vasomotion before (panel A) and 5 min after (panel B) administration of TMZ are presented. a, arteriole; v and v_{1-4} , venules. Identification, 20 μm .

Fig. 2. The dilator effect of trimetazidine (TMZ) on the arterioles. Percent increase or decrease in diameter of the arterioles is plotted as the ordinate and time after TMZ or saline injection is plotted as the abscissa. Mean and S.E. ($n=7$). * $P<0.05$, by analysis of variance. The control (before saline or TMZ) values of the arterioles ranged from 17 to 35 μ m in diameter.

acid, induces vasodilatation of arterioles with failure of vasomotion; but the effect of nicotinic acid subsides within 10 min after the administration (6).

The arteriolar dilatation with failure of vasomotion induced by phenoxybenzamine dihydrochloride and nicotinic acid may produce a remarkable depressor effect on blood pressure due to a continuous loss of the vascular resistance of arterioles. On the contrary, TMZ dilates arterioles rhythmically without affecting vasomotion, keeping their vascular tone. Therefore, the microcirculatory vasodilator effect of TMZ can be separated from the systemic blood pressure effect.

The results suggest that TMZ may exert

its vasodilator effect on the cutaneous microvasculature by a mechanism different from that of the vasodilator effect of phenoxybenzamine dihydrochloride or nicotinic acid. Moreover, the anti-nicotinic effect of TMZ on contraction of the isolated guinea pig atria (7) might have no connection with the microvascular dilating effect because the rhythmic movements of the atria and the arteriole are quite different from each other in nature.

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