Coronary Dilator Effect of MCI-176, a New Calcium Channel Blocker, in Dogs

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— Effects of MCI-176, 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethyl-aminoethyl)-6-isopropoxy-4 (3H)-quinazolinone hydrochloride, on coronary and aortic blood flows, mean blood pressure and heart rate were investigated in comparison with those of diltiazem in anesthetized dogs. MCI-176, like diltiazem, dose-dependently increased coronary and aortic blood flows and decreased mean blood pressure. In producing these effect MCI-176 was slightly but significantly more potent than diltiazem. Heart rate tended to increase with MCI-176, whereas it tended to decrease with diltiazem. ——— MCI-176; calcium channel blocker; coronary blood flow; dog

MCI-176, of which chemical structure is shown in Fig. 1, is a new potent calcium channel blocker selected from many quinazolinone derivatives (Sekiya et al. 1986*). The present article reports preliminarily its effects on coronary flow and cardiohemodynamics in anesthetized dogs. Mongrel dogs of either sex weighing 9-15 kg were anesthetized with pentobarbital sodium 35 mg/kg, i.v. Under artificial respiration the chest was opened at the fourth intercostal space. Blood flows through the left circumflex coronary artery and ascending aorta were measured with non-cannulating type probes. Mean blood pressure was measured with an electromanometer at the femoral artery. Heart rate was measured with a tachometer triggered by pulse pressures. In 12 dogs, both MCI-176 and diltiazem (30 and 100 μ g/kg i.v., respectively) were administered into the same animals. The data

Fig. 1. Chemical structure of MCI-176.

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Fig. 2. Peak changes induced by MCI-176 (●—●) and diltiazem (○—○) in coronary flow (CF), aortic blood flow (AF), mean blood pressure (MBP) and heart rate (HR). Each value represents the mean $\pm$ s.e. of 12 dogs. * significant difference between values obtained with MCI-176 and those with diltiazem ($p < 0.05$).

obtained were analyzed by the paired *t*-test. The basal coronary and aortic blood flows, mean blood pressure and heart rate were 37 ± 4 ml/min and 1.6 ± 0.5 liter/min, 104 ± 5 mm Hg, and 174 ± 7 beats/min, respectively. As shown in Fig. 2, MCI-176 increased coronary flow by 14.7 ml/min at 30 μ g/kg and by 24.1 ml/min at 100 μ g/kg. It increased aortic flow by 250 ml/min at 30 μ g/kg and by 390 ml/min at 100 μ g/kg and heart rate by 1.9 beats/min at 30 μ g/kg and by 2.5 beats/min at 100 μ g/kg. MCI-176 decreased mean blood pressure by 19 mm Hg at 30 μ g/kg and 25 mm Hg at 100 μ g/kg. Essentially similar results were obtained with diltiazem, although heart rate tended to decrease with diltiazem. In producing these effects, however, MCI-176 was slightly but significantly ($p < 0.05$) more potent than diltiazem. The coronary dilator effects of both drugs lasted about 4 min at 30 μ g/kg and 8 min at 100 μ g/kg. The difference in potency between MCI-176 and diltiazem is thought to derive from the difference in calcium antagonistic potencies judging from the results obtained in our laboratory (unpublished observations).