

Cardiovascular effects of diltiazem, a calcium antagonist, on isolated heart muscle preparations and in anaesthetized and pithed rats

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Diltiazem (d-cis-isomer of 3-acetoxy-2,3-dihydro-5-(2-(dimethylamine)-ethyl)-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one.HCl) has been shown to produce myorelaxant effects in several tissues such as the isolated ileum contracted with various spasmogens (Nagao, Sato, Iwasawa, Takada, Ishida, Nakajima & Kiyomoto, 1972) and canine coronary arteries depolarized with potassium (Nagao, Ikeo & Sato, 1977).

In man, the compound has been reported to decrease cardiac work, an effect which is beneficial in the relief and prevention of angina (Kusukawa, Kinoshita, Shimono, Tomonaga & Hoshino, 1977).

The present study describes the cardiovascular effects of diltiazem in several *in vitro* and *in vivo* preparations.

In the rat spontaneously beating right atrium diltiazem (10 μ M), in contrast to ($\pm$)-propranolol, produced a non-competitive antagonism of isoprenaline positive chronotropic responses.

In the electrically paced (100 beats/min) rat heart, perfused with Tyrode solution (5 ml/min) using the technique of Langendorff, the dose of diltiazem exerting 50% inhibition of the baseline contractile force was 6.7 μ M. The same effect was produced by decreasing the extracellular calcium concentration from 2.2 to 0.62 mM. The negative inotropic effect of 10.0 μ M diltiazem was partially antagonized (70–80%) by doubling the normal calcium ion concentration of the Tyrode solution.

In paced (60 beats/min) rabbit heart (prepared as the rat heart) diltiazem (1.0 μ M; perfusion flow: 20

ml/min) decreased left ventricular pressure by 50% and perfusion pressure by 12% at the end of the 10 min infusion. The duration (at 0 and –60 mV) of the left ventricular epicardial action potential (AP) and the resting potential were not significantly changed by diltiazem. However, the rate of rise of the AP as well as the overshoot was significantly decreased.

Finally, in the intact pentobarbital anaesthetized rat, diltiazem (156 μ g kg⁻¹ min⁻¹ for 60 min) induced a significant and sustained fall in carotid blood pressure and heart rate. In the pithed rat, the same dose of diltiazem reduced significantly the increases in blood pressure and heart rate elicited by i.v. noradrenaline, 5-hydroxytryptamine and angiotensin II as well as electrical stimulation of the spinal cord.

These results suggest that diltiazem may affect the excitation-contraction coupling. An effect on intracellular free calcium, essential for contractile processes, is probable since the phase of the ventricular action potential depending on the calcium membrane permeability was not significantly modified. This conclusion is consistent with the results obtained by Nakajima, Hoshiyama, Yamashita & Kiyomoto (1975) using the isolated guinea-pig papillary and ventricular muscles exposed to diltiazem (1.0 μ M).

References

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The sensitivity of superfused bioassay tissues

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Some authors (e.g. Ferreira & De Sousa Costa, 1976) have overestimated the sensitivity of superfused tis-

suess by assuming that the response is proportional to the total dose. The present work confirms the statement by Gaddum (1953) that the response is proportional to the concentration, and shows in addition that the contact time can be important. Strips of rat gastric fundus were set up at 37°C in oil baths and superfused by Krebs solution as described by Ferreira & De Sousa Costa (1976), using a variable-rate peristaltic pump (LKB 2120 Peripex). The Krebs solution contained antagonists (Gilmore, Vane & Wyllie, 1968)