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PRELIMINARY COMMUNICATIONS

THE EFFECTS OF AMIODARONE (L 3428), AN α AND β RECEPTOR ANTAGONIST, ON OVERFLOW OF TRANSMITTER AND UPTAKE OF NORADRENALINE IN THE CAT SPLEEN

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Introduction

The benzofuran derivative amiodarone (2-butyl-3-(4-diethylamino-ethoxy-3, 5-diiodobenzoyl)-benzofuran hydrochloride)*, has been reported to have beneficial therapeutic effects in patients with angina pectoris. Both α and β effects of catecholamines on heart and blood vessels are antagonised in a non-competitive manner [1] but amiodarone has no demonstrable effect on the catecholamine content of both heart and adrenals [2]. The present study was undertaken to determine whether this drug would elevate the overflow of transmitter from the cat spleen following nerve stimulation in the same way as a pure α antagonist such as hydergine [3].

Materials and Methods

Isolated cat spleens were perfused with blood [4]. Three trains of 200, 0.5ms impulses at 20V were given to the splenic nerves at a frequency of 10Hz followed by trains of 200 impulses at 30Hz every 10 min. Transmitter overflowing from the third and subsequent stimulations at 30Hz was collected and bioassayed [5]. The plasma levels of

* Labaz, L 3428

amiodarone had no effect upon the responses of the pithed rat to noradrenaline.

Uptake of 7-^{3}H-(-)-noradrenaline from infusions was estimated as previously described[6].

7-^{3}H-(-)-noradrenaline (8.1 mCi/μM): Radiochemical Centre, Amersham. Amiodarone hydrochloride: Labaz Laboratories. Phenoxybenzamine hydrochloride: Smith, Kline & French Laboratories Limited. Heparin (mucus): Boots Pure Drug Company. Prostaglandin E_1: Dr John E. Pike, Upjohn, Kalamazoo. Amiodarone and phenoxybenzamine were dissolved in a few drops of ethyl alcohol and diluted with 10ml of 0.9% saline just before addition to the blood.

Where appropriate, results are expressed as the mean $\pm$ S.E. of the mean, significance is estimated by the two tailed t-test.

Results

a. Effect of Amiodarone on Transmitter Overflow.

Overflow of transmitter collected in the 4 periods of stimulation before the drug remained essentially constant. In all 9 experiments amiodarone reduced the responses of the spleen[7] and produced a dose dependent ($r = .903$; $P<0.001$) inhibition of overflow reaching a plateau after 30-40 min (Fig. 1). The estimated ED_{50} for amiodarone was 0.17 mg/g (wet wt. spleen).

b. Effect of Amiodarone on Transmitter Liberation[8].

In 9 experiments phenoxybenzamine (30 μg/ml) was added to the blood immediately after the 8th collection period and allowed to act for 30 min without nerve stimulation. Overflow of transmitter following 200 stimuli at 10Hz was then measured. Amiodarone prevented the increase of transmitter overflow normally produced by phenoxybenzamine[4] and the effect was dose dependent ($r = .688$; $P<0.02$). The estimated ED_{50} was 0.17mg/g.

c. Effect of Amiodarone on Uptake of ^{3}H-(-)-noradrenaline.

Amiodarone at a dose of 1000 μg/g (wet wt. spleen) had no effect on the removal

of ^{3}H-(-)-noradrenaline presented to the spleen as an infusion of 345 ng/min. At steady state, amiodarone treated spleens removed 44.4 ± 2.7% (n = 5) of the (-)-noradrenaline infused, compared with 42.8 ± 3.2% (n = 4), in controls (P>0.7).

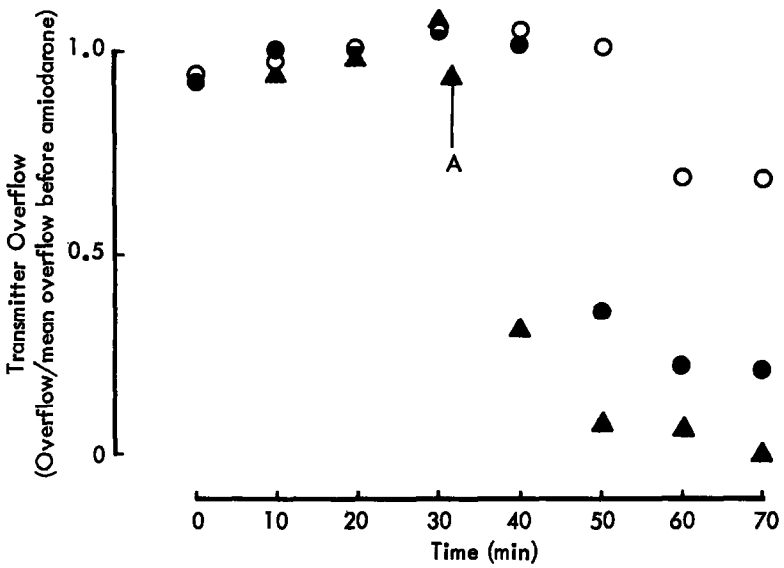

Fig. 1. The effect of amiodarone (A); 71 μg/g (wet wt. spleen) (O); 270 μg/g (●); and 857 μg/g (▲), on transmitter overflow from the cat spleen in 3 typical experiments. Splenic nerves were stimulated at 10 min intervals with trains of 200 supramaximal stimuli at 30Hz. Transmitter overflow is expressed as a fraction of the mean overflow of the 4 pre-drug stimulations in each experiment.

Discussion

The effect of amiodarone, a non-competitive α and β antagonist, upon the overflow of the sympathetic transmitter is opposite to that of the all tested pure

α antagonists [8]. The reduction in overflow after amiodarone could be due to several factors: increased inactivation of transmitter, a depletion of the nerve terminal, a reduction in transmitter liberation, either directly or indirectly via an α agonist effect upon postulated presynaptic α receptors [9], or a local anaesthetic effect. We can exclude any increase in transmitter inactivation since we have found no increase in the ability of the spleen to remove exogenous noradrenaline. Other workers have looked for but not found any catecholamine depleting effect of the drug [2] or local anaesthetic action [10]. We must, therefore, assume that the drug has either a direct effect on transmitter liberation or an indirect inhibitory action mediated via presynaptic α receptors. It is not known what part the β antagonising actions of amiodarone play in this system.

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