PY 108-068, a dihydropyridine derivative, and verapamil interact differently with the ouabain effects on the heart and the peripheral circulation

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Summary

In previous experiments PY 108-068 (PY) has been found to have more potent calcium antagonistic effects on vascular smooth muscle than on myocardial tissue. We now investigated the effects of PY and verapamil (V) on the increases in myocardial contractile force (measured with a strain gauge) and regional vasoconstriction (measured with tracer microspheres) effected by an infusion of 40 μg/kg ouabain into anaesthetized cats. Ouabain significantly increased contractile force of the left ventricle and caused vasoconstriction in the heart, stomach, small intestine, pancreas, spleen and skin, but not in the kidneys, brain, adrenals and liver. PY (30 μg/kg i.v.) and V (0.3 mg/kg i.v.) antagonized the vasoconstrictor effects of the glycoside in all organs except the skin, i.e. also in organs, where the calcium antagonists normally do not cause vasodilatation. However, PY did not affect the increase in contractile force, whereas V attenuated both the cardiac and peripheral vascular effects of ouabain. The results demonstrate the preferential action of PY on peripheral blood vessels as opposed to left ventricular myocardial tissue. Heart rate was decreased by both PY and V but the PQ-interval was lengthened only by V suggesting that PY in contrast to V preferentially acts on the sinus node rather than A-V conduction. A combination of PY with a glycoside might be beneficial in the treatment of cardiac failure, since this calcium antagonist apparently does not antagonize the positive inotropic action of ouabain on the heart while reducing afterload and reversing the undesirable vasoconstriction induced by cardiac glycosides.

Key words: calcium antagonists, ouabain, interaction, cardiac function, regional circulation

Introduction

Calcium antagonists are peripheral vasodilators and thus reduce afterload. Nifedipine has been used for the treatment of chronic congestive heart failure in man (4, 23). Calcium antagonists might offer more than symptomatic improvement. The genetic cardiomyopathy of Syrian hamsters can be prevented by prolonged treatment with V (6, 22, 27) and theoretically at least some forms of human cardiomyopathies could be due to microvascular spasms (5).

All calcium antagonists have an inherent cardiodepressant activity related to their mechanism of action (8). This might limit their usefulness for the treatment of heart failure. Fortunately, however, the cardiodepressant effects do not necessarily correlate with effects on vascular smooth muscle or on the sinus node (20, 26).

An inhibitory interaction between cardiac glycosides and calcium antagonists on myocardial and smooth muscle has been described almost together with the initial description of the calcium antagonistic mechanism of action of the first compounds (8–10). The vasoconstrictor effect of cardiac glycosides has also been shown to be sensitive to calcium antagonists in
experiments in vivo (13, 33). Fleckenstein has mentioned in this review (8) that coronary artery preparations were more sensitive to the action of calcium antagonists than the myocardium.

Finally, both cardiac glycosides and calcium antagonists prolong atrioventricular conduction and the effects of both classes of compounds may be additive (24).

We now report on experiments designed to study the potentially beneficial and detrimental interactions between ouabain and two different calcium antagonists in anaesthetized cats. Myocardial force, surface ECG and changes in regional vascular beds were measured simultaneously in order to ascertain that the doses of the drugs used had the desired effect (increase in myocardial force for ouabain and coronary dilatation for the calcium antagonists). We then assessed, how two calcium antagonists with different haemodynamic (14) and myocardial (20) activity, verapamil (V) and the dihydropyridine derivative PY 108-068 (PY), (16, 19, 20, 29) interacted with the ouabain effects.

Methods

The preparation of the experimental animals and the use of the microsphere method have been described previously in detail (14, 15, 17, 21). The differences described below were kept as small as possible to facilitate the comparison of the “anti-vasoconstrictor” effects in the present experiments with the vasodilator effects reported previously (14, 16).

Mongrel cats were anaesthetized (chloralose, 43 mg/kg and urethane, 430 mg/kg injected intramuscularly), tracheotomized and ventilated with a Loosco MK2 infant ventilator. Room air was used and a positive end-expiratory pressure was applied as soon as the thorax was opened. The ventilation was adjusted to keep the end-expiratory CO$_2$ between 4.2 and 4.7 volume percent and the arterial blood gases were checked regularly. Catheters were placed in the lower abdominal aorta, the inferior vena cava, the right atrium and, through a thoracotomy, in the left atrium. A flowprobe was placed on the aortic root. The phasic flow signal was integrated to obtain mean aortic flow, and differentiated to obtain $dQ/dt$, i.e. acceleration of blood in the aorta, which we use as an ejection phase parameter of myocardial function (15). Myocardial function was also assessed by measuring contractile force with a Walton-Brodie strain gauge sewn onto the left ventricle in parallel to the superficial muscle fibres. The electromagnetic flow probe was calibrated in vivo by the reference flow method at the time of the last microsphere injection. Total peripheral conductance (TPC) was calculated by dividing cardiac output by mean arterial pressure, neglecting the small central venous pressure (shown in table 1).

Needle electrodes were placed subcutaneously on the extremities and lead II of the ECG was recorded at the speed of 50 mm/s on a Schwarzer recorder. The PQ-interval of 10 complexes was measured for each period.

Regional blood flow was determined by injecting about $1.5 \times 10^5$ microspheres with one of the following labels: $^{125}$I, $^{14}$Ce, $^{51}$Cr, $^{85}$Sr or $^{46}$Sc. In order to avoid systematic errors due to small differences between different batches of microspheres, spheres with different labels were rotated, so that each label was used for each measuring period. The spheres were flushed into the left atrium with 2 ml of 0.9 % saline. This procedure had no effect on blood pressure, heart rate or aortic flow.

At the end of the experiment the animals were killed with an overdose of pentobarbital and the organs to be counted were dissected and weighed. Samples of skeletal muscle were obtained from the hindlegs. All other organs mentioned were counted in toto. The heart was dissected to obtain samples of the free wall of the left ventricle, which was then divided into 3 layers as described in detail elsewhere (14). The papillary muscles were weighed and counted together with the subendocardial layer. The samples were counted in a Packard gamma counter (Mod 5921) and the spectra processed on a PDP 11/34 minicomputer as described previously (17, 28).

Experimental protocol: During a stabilization phase of at least 90 minutes all drug solutions were prepared fresh for infusion. Ouabain (Sandoz) was diluted in glucose 5 % and PY (Sandoz) and V (Knoll) were dissolved in a mixture of ethanol and polyethylene glycol 400, 1 ml/mg of substance. This stock solution was then further diluted with 5 % glucose. Thus both drugs were dissolved in the same amount of solvent so that only one control group was needed for treatment with the vehicle. After