CARDIOVASCULAR EFFECTS IN MAN OF INTRAVENOUS PRIZIDILOL HYDROCHLORIDE (SK&F 92657); A NEW ANTIHYPERTENSIVE AGENT

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1 Cardiovascular responses to intravenous prizidilol hydrochloride (SK&F 92657) 0.86 mg/kg were studied in eight supine resting healthy volunteers. Five subjects were slow and the remaining three were fast acetylators of sulphamethazine. Compared with pre-infusion values, mean resting systolic and diastolic blood pressures were significantly reduced, while mean resting pulse rate was significantly increased at 30 min after the start of the twenty minute infusion.

2 During the 6 h study period the lowest mean $\pm$ s.e. mean systolic blood pressure (108.8 ± 1.7) was recorded 30 min after the start of the infusion. This represented a mean reduction of 5.2 mmHg. Reductions in mean diastolic blood pressure were greater and of longer duration, the lowest mean value (44.8 ± 2.0 mmHg) being recorded 3.5 h after the start of the infusion and representing a reduction of 18.5 mmHg from the pre-dosing value. At 6 h after the start of the infusion mean diastolic blood pressure was still significantly reduced (by 15.3 mmHg).

3 The maximum mean $\pm$ s.e. mean resting pulse rate (79.3 ± 4.4 beats/min) occurred 3 h after the start of the infusion, an increase of 23.0 beats/min over the pre-infusion value. At the end of the study the pulse rate was still significantly raised (by 17.7 beats/min).

4 The left ventricular ejection fraction, evaluated in five subjects, 45 min after the start of the infusion, was not altered by prizidilol hydrochloride, but the left ventricular area decreased significantly.

5 Intravenous prizidilol hydrochloride decreases resting blood pressure and left ventricular area, increases pulse rate and has virtually no effect on left ventricular ejection fraction.

Introduction

Prizidilol hydrochloride, dl-3-[2-(3-*t*-butylamino-2-hydroxypropoxy) phenyl]-6- hydrazinopyridazine (SK&F 92657), is a new blood pressure lowering agent with both pre-capillary vasodilator and β -adrenoceptor blocking activities whose hypotensive properties have been investigated in animal and man (Taylor, Roe & Slater, 1979; Bell *et al.*, 1980; Collier & Pitcher, 1980).

Experiments in anaesthetised rats, cats and dogs have shown that intravenous prizidilol hydrochloride (2-4 mg/kg) causes pronounced peripheral vasodilatation. Regional blood flow studies using radioactive microspheres have demonstrated a marked fall in the arterial blood pressure and total peripheral resistance, without any change in cardiac output, stroke volume or heart rate (Taylor *et al.*, 1979). The aim of this study was to evaluate the effects of 20 min intravenous infusion of prizidilol hydrochloride on resting pulse rate, blood pressure, electrocardiogram

(ECG), left ventricular ejection fraction and left ventricular area in normal healthy subjects in a single-blind fashion.

Methods

Study 1

Eight healthy male volunteers aged 18-27 years were studied initially. All gave their consent to participate in the study. The study was ethically approved by the Clinical Research Working Party of the Royal Navy. Acetylation phenotype was determined in each subject using the sulphamethazine clearance technique (Evans, 1969).

The subjects were first studied using 20 ml physiological saline as placebo. At least seven days later prizidilol hydrochloride was administered in an

identical fashion, by constant intravenous infusion at 1 ml/min for 20 min, to give a total dose of 0.86 mg/kg body weight. A baseline standard 12 lead ECG was recorded, the pre-dosing resting pulse and blood pressure measurements were made at 15 min intervals for 2 h. After the start of the infusion pulse and blood pressure recordings were made at regular intervals for 2 h on the first study day (placebo) and for 6 h on the second study day (prizidilol hydrochloride). Blood pressure measurements were made using an Accuson mercury sphygmomanometer.

Changes in pulse rate and blood pressure between pre-dosing measurements and those obtained at specific times after the start of the infusion were analysed using the two-tailed Student's *t*-test. Electrocardiographic tracings were recorded every 10 min for the first post-infusion hour, and every 30 min thereafter. Blood samples were taken on the second study day prior to dosing and at frequent intervals for the subsequent 6 h for measurements of concentration of prizidilol plus acid labile metabolites. Prizidilol is not stable in alkaline conditions.

The *p*-methoxybenzaldehyde (anisaldehyde) hydrazone derivative of prizidilol is formed under acidic conditions. After extraction this derivative is separated by high pressure liquid chromatography and assayed by ultra-violet spectrophotometry. In the acidic conditions used in the derivitization the acid labile metabolites of prizidilol are converted back to prizidilol (Taylor & Cresswell, personal communication).

Study 2

The effects of prizidilol hydrochloride 0.86 mg/kg on left ventricular ejection fraction and left ventricular area were later studied in five of the eight subjects on a separate occasion. Insertion of intravenous cannulae and pre-dosing recordings of pulse, blood pressure and ECG were made as for the earlier study. However, 45 min before the start of the infusion of 0.86 mg/kg prizidilol hydrochloride (20 ml) radio-nuclide cardiac scans were performed on each subject.

An intravenous bolus injection of approximately 5mCi 99m TcO₄ (pertechnetate) was given, and the passage of the isotope through the heart was followed by a gamma camera connected to a Varian 76 computer. Left ventricular function was determined using the 'first pass' (ungated) technique (Kriss, Freedman & Enright, 1971), and the left ventricular ejection fraction (LVEF) was calculated from the equation:

$$\text{LVEF (\%)} = (\text{end diastolic counts} - \text{end systolic counts}) / (\text{end diastolic counts}).$$

Mean left ventricular area (LVA) was calculated by counting the number of cells of scintillation over the

left ventricle at end-systole and end-diastole, and by taking the mean of the count obtained.

Regular measurements of pulse and blood pressure, and recordings of ECG were made following the start of the infusion of prizidilol hydrochloride. A second cardiac scan was performed at approximately 45 min after the start of the infusion. The difference in LVEF and LVA between the pre-dosing measurements and those made 45 min after the start of the infusion were analysed using Student's *t*-test.

Results

1 Pulse rate and blood pressure

Changes in resting supine pulse rate and blood pressure following intravenous administration of prizidilol hydrochloride 0.86 mg/kg were virtually identical in the two studies. The results from study 1 are presented here.

A comparison has been made between pre-dosing measurements and those obtained at specific times after the start of the infusion.

i) *Pulse rate (Figure 1)* When subjects received saline, supine pulse rate remained virtually unchanged throughout the period of observation. Infusion of prizidilol hydrochloride, on the other hand, led to a statistically significant rise in the mean resting supine pulse rate after 30 min. The mean pulse rate rose from 56.3 ± 2.7 to 66.5 ± 3.6 beats/min, an increase of 18% ($P < 0.05$). The maximum rise (41%) was observed 3 h after the start of the infusion. At 6 h after dosing the mean pulse rate was still significantly elevated ($P < 0.05$).

ii) *Blood pressure (Figure 1)*. Infusion of saline led to an insignificant rise in the resting supine systolic and diastolic (phase V) blood pressure. At 2 h after dosing the mean systolic blood pressure increased from 117.8 ± 2.5 to 122.0 ± 3.5 mmHg (3.6%) and the mean diastolic blood pressure from 66.6 ± 3.0 to 73.1 ± 3.5 mmHg (9.7%).

At 30 min after the start of the infusion of prizidilol hydrochloride the mean resting systolic blood pressure was significantly lowered ($P < 0.05$). A statistically significant fall in diastolic blood pressure was similarly noted at 30 min after the start of the infusion. The resting diastolic blood pressure decreased (12.6%) from 63.3 ± 2.8 to 55.3 ± 3.4 mmHg ($P < 0.05$). The maximum fall in the resting diastolic blood pressure (29.2%) was observed at 3.5 h following the start of the infusion. At 6 h after dosing the diastolic pressure was still significantly decreased at 48.0 ± 2.3 mmHg ($P < 0.05$).

Figure 1 Mean and s.e. mean pulse rate and blood pressure for eight subjects after infusion of prizidilol hydrochloride 0.86 mg/kg (●) and after infusion of saline (○) in Study 1. Each infusion lasted 20 min.

2 Left ventricular ejection fraction (Table 1)

At 45 min after the start of the infusion, a decrease in the left ventricular ejection fraction was seen in four

of the five subjects studied, the fall ranging from 4% to 6%. In the remaining subject the LVEF rose by 6%. The values for all subjects were in the normal range (58–70%) at 45 min after the start of the infusion of prizidilol hydrochloride and the changes were not statistically significant.

3 Left ventricular area (Table 1)

Mean left ventricular area, the chief determinant of left ventricular volume, decreased in all subjects following intravenous administration of prizidilol hydrochloride. At 45 min after the start of the infusion, the mean decrease was 20.8 ± 5.54 cells (36.4%), a statistically significant change ($P < 0.05$). The individual post-dosing values for left ventricular area were below the lower limit of the normal range.

4 Electrocardiographic evaluation

The ECG tracings remained normal throughout the study.

5 Unwanted signs and symptoms

All five subjects in study 2 and one of eight subjects in study 1 developed flushing of the face between 30 and 60 min after the start of the infusion. Three subjects (study 1) experienced a sensation of facial warmth. One subject complained of a headache which developed simultaneously with facial flushing, 45 min after the infusion. Two others noted palmar sweating following administration of prizidilol hydrochloride, one of whom also had cold extremities.

6 Pulse and blood pressure response and acetylator phenotype (Figure 2)

No significant differences were obtained between the responses of slow and fast acetylators to prizidilol hydrochloride.

Table 1 Left ventricular ejection fraction and left ventricular area before and 45 min after start of infusion of prizidilol hydrochloride

Subject	Left ventricular ejection fraction (%)			Left ventricular area (cells)		
	Before prizidilol hydrochloride	After prizidilol hydrochloride	Change	Before prizidilol hydrochloride	After prizidilol hydrochloride	Change
1	63	58	-5	58	37	-21
2	68	64	-4	61	41	-20
3	71	77	+6	71	41	-30
4	71	67	-4	52	35	-17
5	70	64	-6	44	28	-16
Mean ($\pm$ s.e. mean)	68.6 ($\pm$ 1.5)	66.0 ($\pm$ 3.1)	-2.6	57.2 ($\pm$ 4.5)	36.4 ($\pm$ 2.4)	-20.8 ($P < 0.05$)

Figure 2 Mean pulse rate and blood pressure for three fast (■—■) and five slow (●—●) acetylators of sulphamethazine after infusion of prizidilol hydrochloride (0.86 mg/kg) in Study 1. S.e. mean values are included at 1 h 15 m and 4 h and 30 m after start of infusion.

7 Plasma concentrations of prizidilol (Figure 3) and acid labile metabolites

Plasma concentrations of the drug-related material were measured in seven subjects. Peak plasma concentrations ranged between 1.3 $\mu\text{g/ml}$ and 4.5 $\mu\text{g/ml}$. The time of peak plasma concentration was 15 min after the start of the infusion in four subjects, 20 min in another two, and 30 min in the remaining subject.

Discussion

Intravenous infusion of prizidilol hydrochloride 0.86 mg/kg led to a significant rise in mean resting pulse rate, and a fall in systolic and diastolic blood pressure at 30 min after dosing.

Several features of the effects of intravenous prizidilol hydrochloride on the cardiovascular system are similar to those produced by hydralazine. There is commonly a delay in the onset of blood pressure lowering effect after intravenous hydralazine, and the cardiovascular changes persist for at least 6 h (Koch-Weser, 1975). This delay in onset and duration of action has also been demonstrated by prizidilol hydrochloride in this study. The tachycardia associated with hydralazine may occur even after intravenous doses as small as 0.1 mg/kg (Falch & Norman, 1978). It is due to the baroreceptor reflex initiated by reduction of total peripheral resistance consequent upon arteriolar vasodilatation. Although hydralazine

Figure 3 Mean and s.e. mean plasma concentrations of prizidilol and acid labile metabolites ($\mu\text{g/ml}$) for seven subjects in Study 1.

and other vasodilators can reduce peripheral vascular resistance by at least 50%, their hypotensive effect is limited by the subsequent rise in cardiac output (Koch-Weser, 1975). The facial flushing and sensation of warmth noticed by some subjects after intravenous infusion of prizidilol hydrochloride suggest that cutaneous vasodilation is caused by the drug. Although the coronary, cerebral and splanchnic circulations are important sites of action of hydralazine (Koch-Weser, 1976) the cutaneous vascular bed is also affected (Sannerstedt *et al.*, 1972). It has recently been suggested that hydralazine may also have a direct positive inotropic effect (Opie, 1980; Khatri *et al.*, 1977).

Studies in animals (Brunner, Hedwall & Meier, 1967) and normotensive and hypertensive man (Sannerstedt *et al.*, 1971) have demonstrated the attenuating effects of β -adrenoceptor blocking agents on hydralazine-induced tachycardia. Oral administration of prizidilol hydrochloride at a dose of 5 mg/kg has significantly lowered systemic blood pressure without increasing standing heart rate (Bell *et al.*, 1980).

β -adrenoceptor curbing of isoprenaline induced rises in heart rate has been demonstrated following administration of a single oral dose of 200 mg prizidilol hydrochloride (Pitcher, Curry & Trounce, 1980). In contrast to these observations, intravenous infusion of prizidilol hydrochloride led to a significant rise in resting pulse rate. This may be due to the route of administration. Collier & Pitcher (1980) found that at low doses of 100 and 500 ng/min, intravenously administered prizidilol hydrochloride attenuated the dilator effects of locally infused isoprenaline on vessel walls. At doses of 400 μ g and 1600 μ g administered intra-arterially, dose-dependent vasodilatation was demonstrated, evidenced by mean increases in fore-

arm blood flow of 59% and 40.3% respectively. In the present study the dose of intravenous prizidilol hydrochloride was of the order of 3 mg/min and it is likely that the β -adrenoceptor blocking effects of the drug was masked by its vasodilator activity.

Changes in the left ventricular ejection fraction following intravenous administration of prizidilol hydrochloride were slight and clinically non-significant. Ulrych *et al.* (1968) have shown that intravenous propranolol (10 mg) leads to a significant 20% fall in cardiac output. Hydralazine given in intravenous doses of 0.15–0.40 mg/kg has been shown to increase cardiac output (Wilkinson, Backman & Hecht, 1952). Although the left ventricular ejection fraction remained virtually unchanged, the left ventricular area fell significantly, from a mean of 57.4 ± 4.5 to 36.4 ± 2.4 cells after infusion of prizidilol hydrochloride. This suggests that while myocardial function was not impaired by the drug, incomplete cardiac filling in diastole occurred as a result of significant rises in pulse rate.

Significant decreases in supine heart rate without changes in blood pressure have been shown to occur in normotensive man after intravenous administration of propranolol (Ulrych *et al.*, 1968). The decrease in blood pressure following intravenously administered hydralazine is associated with a secondary rise in heart rate (Falch & Norman, 1978). Though prizidilol hydrochloride possesses both β -adrenoceptor antagonist and pre-capillary vasodilator activities, the changes in resting cardiovascular parameters seen in this study are predominantly due to its pre-capillary vasodilator moiety.

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