Br. J. Pharmac. (1981), **72**, 5–7

HAEMODYNAMIC EFFECTS OF SULPHINPYRAZONE IN EXPERIMENTAL MYOCARDIAL ISCHAEMIA

D.C. RUSSELL

Department of Cardiology and University Department of Medicine,
The Royal Infirmary, Edinburgh EH3 9YW

The effect of sulphinpyrazone (30 mg/kg i.v.) on heart rate, blood pressure and ventricular arrhythmias was studied in open-chested anaesthetized dogs during sequential 10 min occlusions of the left anterior descending coronary artery. An increased duration of occlusion without ventricular fibrillation and reduction in epicardial activation delay in the central ischaemic region were observed after intravenous sulphinpyrazone ($n = 7$). These effects were associated with a progressive and significant reduction in intrinsic heart rate (up to 15 beats/min) but no change in blood pressure. These findings suggest that heart rate changes alone may account for the observed protective effect of sulphinpyrazone against early ventricular fibrillation during acute experimental myocardial ischaemia.

Introduction A striking antiarrhythmic effect of sulphinpyrazone has been suggested by clinical trial findings of a 43% reduction in the incidence of sudden cardiac death at 2 years following myocardial infarction (Anturane Reinfarction Trial Research Group, 1978). Effects of similar magnitude have not been observed with other inhibitors of platelet aggregation such as aspirin or dipyridamole (Elwood & Sweetham, 1979). The question therefore arises whether sulphinpyrazone may have an antiarrhythmic effect during myocardial ischaemia.

We have shown previously an acute haemodynamic effect of sulphinpyrazone on the response to exercise in man (Forfar, Russell & Oliver, 1980). The possible relation between such a haemodynamic effect and the genesis of lethal arrhythmias has been investigated further in an experimental canine preparation following repeated sequential coronary occlusions.

Methods Studies were performed on 14 mongrel dogs (body weights 12 to 15 kg), anaesthetized with intravenous pentobarbitone 30 mg/kg followed by a maintenance infusion of 3 mg kg^{-1} h^{-1} and ventilated on room air. The heart was exposed by left thoracotomy and suspended in a pericardial cradle. The proximal left anterior descending coronary artery was dissected free to allow repeated applications of a coronary occlusion clip for periods of up to 10 min or until onset of ventricular fibrillation; 30 min were allowed for recovery between occlusions. Ventricular fibrillation was managed by release of the coronary occlusion clip and immediate d.c. cardioversion. Arterial blood pressure was continuously monitored from a femoral arterial cannula and electrograms were recorded on tape (SE-84 FM recorder) from surface leads and local electrodes sutured to the epicardium in central-ischaemic, border-ischaemic and non-ischaemic regions. Signals were analysed for heart rate, ventricular arrhythmias and local activation delays determined from the timing of the intrinsic deflection of the surface electrograms.

Following three consecutive periods of coronary occlusion, dogs were given either sulphinpyrazone 30 mg/kg intravenously ($n = 7$) or an equivalent volume of placebo carrier ($n = 7$). Three further coronary occlusions were then performed starting 30, 70 and 110 min respectively after injection. Data from the first control coronary occlusion were not analysed as previous studies from our laboratory have shown reproducibility only during second and subsequent coronary occlusions.

Statistical analysis used Students' t test for paired observations. All data quoted are mean $\pm$ s.e. mean.

Results Comparable values were obtained before and during the second two control occlusions in both sulphinpyrazone and placebo-treated groups for heart rate, blood pressure, arrhythmia frequency and regional activation delay. Ventricular fibrillation was induced in similar numbers of animals in both groups.

The incidence of ventricular fibrillation after sulphinpyrazone treatment was reduced in the three subsequent occlusions (11 episodes), compared with placebo (16 episodes). The mean duration of occlusion without occurrence of ventricular fibrillation was prolonged, attaining significance ($P < 0.05$) after 110 min (Figure 1). No significant alterations in the frequency of ventricular premature beats during occlusions was noted in either treatment group.

Epicardial activation delays in the central ischaemic regions after 4 min of ischaemia showed a small, significant ($P < 0.01$) reduction at both 70 and 110 min after sulphinpyrazone (39 $\pm$ 3, 39 $\pm$ 3 ms com-

0007-1188/81/010005-03 $01.00

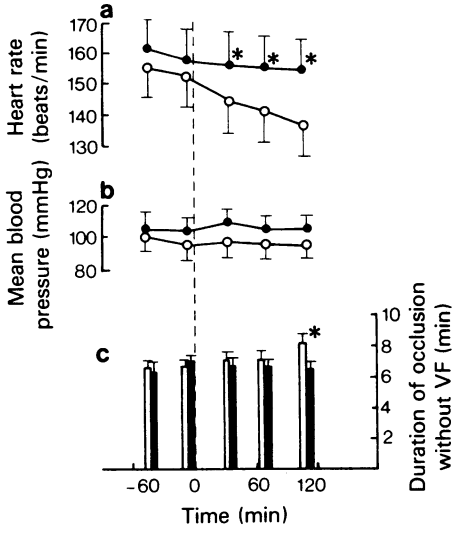

Figure 1 Mean changes in heart rate (a), blood pressure (b) and duration of coronary occlusion before ventricular fibrillation (VF) (c) prior to 30, 70 and 110 min after intravenous sulphinpyrazone 30 mg/kg ($n = 7$) or placebo ($n = 7$) in open-chested dogs. The time of injection is shown by the dotted line. Sulphinpyrazone-treated animals are shown by the open circles and columns and placebo animals by closed circles and columns. Duration of occlusion was prolonged ($P < 0.05$) and heart rate reduced ($P < 0.01$) 110 min after sulphinpyrazone.

pared with control 44 ± 4 ms) and this was not observed after placebo. No significant effects were observed in border-ischaemic regions or in the non-ischaemic myocardium.

Following administration of sulphinpyrazone a significant fall in heart rate was observed (Figure 1) from 154 ± 10 to 145 ± 11 beats/min after 30 min ($P < 0.01$). This was more marked at 70 and 110 min after sulphinpyrazone. Placebo treatment had no significant effects.

No significant blood pressure effects were observed before or during ischaemia either after sulphinpyrazone or placebo.

Discussion This study has demonstrated a small, but significant anti-arrhythmic effect of sulphinpyrazone during coronary occlusion 110 min, but not during occlusions 30 or 70 min after the drug. These findings, together with the small reductions in central ischaemic zone conduction abnormalities are explicable on the basis of the observed reductions in intrinsic heart rate (of the order of 15 beats/min) at this time.

Although in the non-ischaemic heart a reduction in heart rate may reduce the arrhythmia threshold (Han, Millet, Chizzonitti & Moe, 1966), under conditions of ischaemia the effect of increasing severity of ischaemia with increasing heart rate offsets any rate-dependent electrophysiological effect and results in an enhanced vulnerability to arrhythmias (Kent, Smith, Redwood & Epstein, 1973). We have shown previously that a reduction in heart rate of 20 beats/min reduces the incidence and delays the onset of ventricular fibrillation following proximal left anterior descending coronary occlusion in the dog, and also ameliorates underlying electrophysiological abnormalities in action potential morphology and conduction (Russell, Smith & Oliver, 1979). The observed amelioration in conduction of around 5 ms would be consistent with these findings.

Similar heart rate effects of sulphinpyrazone in association with a reduced incidence of early ventricular arrhythmias following coronary occlusion, are described in both the anaesthetized cat preparation (Kelliker, Dix, Jurkiewicz & Lawrence, 1980) and anaesthetized dog preparation (Povalski, Olson, Kopia & Furness, 1980) although no significance was attached by the authors to this observation. In these two studies sulphinpyrazone was given either intravenously (100 mg/kg) or by oral pretreatment respectively. However, in the conscious dog, although oral pretreatment had no significant effects on resting heart rate, the expected increase in heart rate 15 min following coronary artery occlusion was significantly reduced with associated reduction in the incidence of ventricular ectopic beats. This rate effect was not sustained, being limited to the early period of enhanced ventricular vulnerability to arrhythmias and infarct size remained unaffected. Sulphinpyrazone has been shown to reduce myocardial ischaemic injury and electrolyte loss and improve collateral blood flow in ischaemic myocardium in the dog (Moschos, Escobinas, Jorgensen & Regan, 1979). Reduction in ST segment elevation is known to be highly rate-dependent.

Moschos, Escobinas & Jorgensen (1980) describe significant reduction in arrhythmic deaths in the anaesthetized dog preparation during a 4 h period of coronary occlusion after oral sulphinpyrazone pretreatment associated with a significant reduction in afterload, as determined by aortic pressure. Heart rate values are not given. It is possible therefore that in this present study a small blood pressure effect may have been masked by the small numbers employed.

Other anti-arrhythmic mechanisms deserve mention since sulphinpyrazone has no known direct electrophysiological effect (Cowan & Vaughan-Williams, 1980). An indirect action by promoting coronary collateral blood flow to the ischaemic zone, possibly by reducing platelet microthrombosis or microembolus

formation has been suggested. Although implicated in the pathology of sudden death (Haerem, 1974), there is little evidence to date to support a role of platelets in arrhythmogenesis. Alternatively, the balance in the coronary vasculature may be modulated between the thromboxane (vasoconstrictor and platelet pro-aggregatory) and prostacyclin (vasodilator and platelet anti-aggregatory) derivatives of prostaglandin synthetic pathways.

We conclude that sulphinpyrazone can induce minor haemodynamic effects which alone could account for a protective action against the early ventricular fibrillation of experimental acute myocardial ischaemia.

Part of this work was supported by a grant from Ciba-Geigy, Pharmaceutical Division, Horsham, England. Thanks are due to Professor M.F. Oliver for advice in the preparation of this manuscript and to Dr J. Lawrie and Mrs J. Samuel for technical support.

References

ANTURANE REINFARCTION TRIAL RESEARCH GROUP (1978). Sulphinpyrazone in the prevention of cardiac death after myocardial infarction. *New Engl. J. Med.*, **298**, 289–295.

COWAN, J.C. & VAUGHAN-WILLIAMS, E.M. (1980). The Anturane Reinfarction Trial. *New Engl. J. Med.*, **303**, 48–49.

ELWOOD, T.C. & SWEETHAM, P.M. (1979). Aspirin and secondary mortality after myocardial infarction. *New Engl. J. Med.*, **298**, 289–295.

FORFAR, J.C., RUSSELL, D.C. & OLIVER, M.F. (1980). Haemodynamic effect of sulphinpyrazone on exercise responses in normal subjects. *Lancet* (in press).

HAEREM, J.W. (1974). Mural platelet microthrombi and major acute lesions of main epicardial arteries in sudden coronary death. *Atherosclerosis*, **19**, 529–541.

HAN, J. (1969). Ventricular vulnerability during acute coronary occlusion. *Am. J. Cardiol.*, **24**, 857–864.

HAN, J., MILLET, D., CHIZZONITTI, B. & MOE, G.K. (1966). Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate. *Am. Heart J.*, **71**, 481–487.

KELLIKER, G.J., DIX, R.K., JURKIEWICZ, N. & LAWRENCE, T.L. (1980). Effect of sulphinpyrazone on arrhythmia and death following coronary occlusion in cats. In *Cardiovascular Actions of Sulphinpyrazone*. ed. McGregor, M., Mustard, J.F., Oliver, M.F. & Sherry S. pp. 193–207. Miami: Symposia Specialists Inc.

KENT, K.M., SMITH, E.R., REDWOOD, D.R. & EPSTEIN, S.E. (1973). Electrical stability of acutely ischaemic myocardium. *Circulation*, **47**, 291–298.

MOSCHOS, C.B., ESCOBINAS, A. & JORGENSEN, O.B. Jr. (1980). Effects of sulphinpyrazone on ischaemic myocardium. *Cardiovascular Actions of Sulphinpyrazone*. ed. McGregor, M., Mustard, J.F., Oliver, M.F. & Sherry, S. pp. 175–187. Miami: Symposia Specialists Inc.

MOSCHOS, C., ESCOBINAS, A., JORGENSEN, O. Jr. & REGAN, T. (1979). Effect of sulphinpyrazone on survival following non-thrombotic coronary occlusion. *Am. J. Cardiol.*, **43**, 372.

POVALSKI, H.J., OLSON, R., KOPIA, S. & FURNESS, P. (1980). Comparative effects of sulphinpyrazone and aspirin in the coronary occlusion—reperfusion dog model. In *Cardiovascular Actions of Sulphinpyrazone*. ed. McGregor, M., Mustard, J.F., Oliver, M.F. & Sherry, S. pp. 153–171. Miami: Symposia Specialists Inc.

RUSSELL, D.C., SMITH, H.J. & OLIVER, M.F. (1979). Transmembrane potential changes and ventricular fibrillation during repetitive myocardial ischaemia in the dog. *Br. Heart J.*, **42**, 88–96.

(Received September 22, 1980.)