

## THE ANTIDYSRHYTHMIC AMINOSTEROID, ORG 6001, REDUCES THE ST-SEGMENT ELEVATION PRODUCED BY CORONARY OCCLUSION IN THE DOG

R.J. MARSHALL & J.R. PARRATT

Department of Physiology & Pharmacology, University of Strathclyde, Glasgow

ST-segment elevation following temporary coronary artery occlusion was measured from nine epicardial leads in open-chest anaesthetized dogs. This was greatly reduced by the prior administration of the anti-dysrhythmic aminosteroid, ORG 6001. It is suggested that this effect is related either to a reduction in the extent and degree of myocardial ischaemia or to prevention of K<sup>+</sup> egress from ischaemic cells.

**Introduction** We have previously demonstrated that 3 $\alpha$ -amino-5 $\alpha$ -androstan-2 $\beta$ -ol-17-one (ORG 6001) administered intravenously or orally is capable of preventing the early ventricular dysrhythmias that result from coronary artery ligation in anaesthetized greyhounds (Marshall & Parratt, 1975). In addition, there was evidence that some of the metabolic indices of myocardial ischaemia (e.g. CO<sub>2</sub> and lactate production, K<sup>+</sup> efflux) were reduced in dogs treated with ORG 6001. The present study is an attempt to answer the question as to whether these beneficial metabolic effects of ORG 6001 result secondarily from the reduction in ventricular dysrhythmias, since these *per se* decrease myocardial perfusion (Marshall, Parratt & Ledingham, 1974) or whether the drug has some other more direct effect on the ischaemic myocardium. We have approached this problem by assessing the effects of ORG 6001 on the extent of myocardial injury (assessed from epicardial ST-segment changes) produced by temporary coronary occlusion in a canine model, devoid of dysrhythmic activity.

**Methods** Six mongrel dogs of either sex and weighing between 11–19 kg were anaesthetized with sodium thiopentone (30 mg/kg, i.v.) followed by  $\alpha$ -chloralose 85 mg/kg. The dogs were ventilated with 100% O<sub>2</sub> and catheters placed in the descending aorta, pulmonary artery, right atrium and coronary sinus for pressure measurements and for blood sampling as previously described (Marshall *et al.*, 1974). After thoracotomy the heart was slung in a pericardial cradle and a Mersilk thread passed around the left anterior descending coronary artery (l.a.d.) about 2 cm from its origin. A triangular sheet of rubber in which were embedded nine silver electrodes (impedance 600–1200  $\Omega$ ) was sutured to the anterior

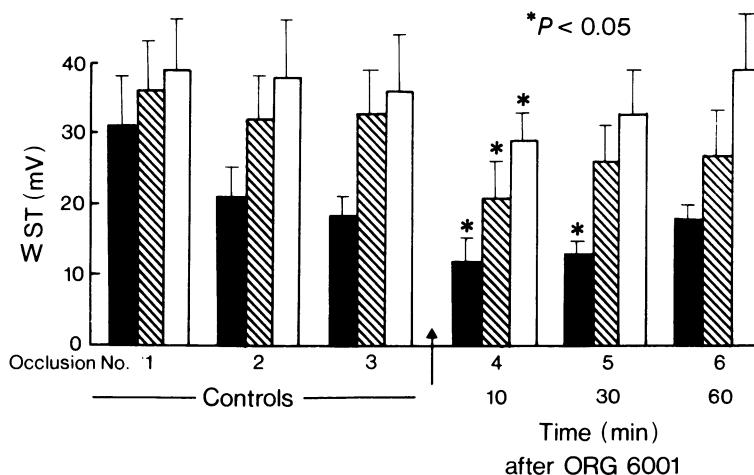
surface of the left ventricle so that at least six of the electrodes lay in areas supplied by the artery to be occluded (Marshall & Parratt, 1977). Care was taken to keep the epicardium moist with normal saline throughout the experiment. Aortic blood pressure, pulmonary artery pressure and epicardial electrocardiograms (ECGs) were recorded on a Mingograph ink-jet recorder.

After baseline haemodynamics, blood gases and epicardial ECGs had been obtained, the l.a.d. was occluded and epicardial ECGs at each of the nine sites were recorded by means of a rapid switching circuit (at a paper speed of 50 mm/s) at 1, 2 and 3 min after occlusion. Only short (i.e. 3 min) occlusions were used because occlusion of the artery for longer periods occasionally resulted in ventricular dysrhythmias and conduction defects; both of which mask shifts in the ST-segment. In each dog, three control occlusions were performed and occlusions were repeated 10, 30 and 60 min after injection of ORG 6001 (10 mg/kg) into the right atrium. The results were analysed statistically using the Student's *t* test for paired data.

**Results** Coronary artery occlusion resulted in a time-related elevation of the ST-segment in the epicardial leads overlying the ischaemic area (Figure 1); the ST-segment in leads lying outside the affected area remained unchanged. Heart rate and pulmonary artery pressure remained unchanged throughout occlusions but there was always a small (5–15 mmHg) fall in aortic blood pressure. As previously reported (Wendt, Canavan & Michalak, 1974), there was evidence that the first occlusion resulted in more marked ST-changes than subsequent occlusions. However, these subsequent occlusions (up to six) produced similar changes in the ST-segment elevation in control dogs.

The total ST-segment elevation (assessed at 3 min) in five control, untreated dogs was  $34 \pm 4$  mV (first occlusion),  $26 \pm 3$  mV (second occlusion),  $25 \pm 4$  mV (third occlusion),  $31 \pm 4$  mV (fourth occlusion) and  $36 \pm 2$  mV (fifth occlusion). There was no significant difference in control dogs between the second, third, fourth or fifth successive occlusions.

Administration of ORG 6001 (10 mg/kg) caused similar transient haemodynamic changes to those



**Figure 1** Total ST-segment elevation produced at 1 min (solid columns), 2 min (hatched columns) and 3 min (open columns) after acute occlusion of the left anterior descending coronary artery in anaesthetized dogs. At the arrow ORG 6001 (10 mg/kg) was administered intravenously. Histograms and bars represent the means and standard errors respectively of six observations.

already reported (Marshall & Parratt, 1975) and all parameters had returned to normal within 5 min of the injection. At this dose, ORG 6001 significantly reduced ST-segment elevation throughout the occlusion (Figure 1) and in addition reduced the mean number of leads showing  $>2$  mV elevation (Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971) from  $6.6 \pm 0.3$  to  $5.1 \pm 0.2$  ( $P < 0.05$ ). These effects of ORG 6001 were relatively short-lasting and ST-elevation induced by occlusion returned towards control values 30 to 60 min after drug administration (Figure 1).

**Discussion** Although the mechanisms underlying ST-segment changes are still incompletely understood, many experimental studies have demonstrated that epicardial ECG mapping can be used to assess the degree and extent of myocardial ischaemia. Changes in the ST-segment correlate well with the subsequent depletion of CPK (Maroko *et al.*, 1971), with the degree of change in coronary blood flow and with the extent of anaerobic metabolism (Karlsson, Templeton & Willerson, 1973).

This present study has shown that an aminosteroid antidysrhythmic drug, ORG 6001, is capable of reducing ST-segment elevation produced by short coronary occlusions. Previous studies (Maroko *et al.*, 1971; Smith, Singh, Nisbet & Norris, 1975; Wendt *et al.*, 1975) have demonstrated that  $\beta$ -adrenoceptor antagonists and verapamil, which decrease myocardial oxygen requirements, decrease ST elevation produced by coronary artery occlusion. Clearly ORG 6001 does not share this mechanism of action since the drug is devoid of  $\beta$ -blocking activity and does not reduce

myocardial oxygen consumption (Marshall & Parratt, 1975).

There are two other possible explanations for this decrease in ST-elevation. Firstly, at the dose used in this study, ORG 6001 prevents  $K^+$  efflux from ischaemic myocardial cells into coronary venous blood (Marshall & Parratt, 1975). Potassium efflux *per se* would be expected to elevate the ST-segment (Fozzard & DasGupta, 1976) and indeed we have unpublished data which show a good relationship between extracellular  $K^+$  level and ST-segment elevation. A second and possibly related mechanism concerns the electrical events causing ST-segment elevation. Since ST elevation is a reflection of the injury potential generated *between* normally perfused and ischaemic tissue (Cohen & Kaufman, 1975) any agent which normalizes action potential characteristics in these areas would be expected to decrease ST-segment elevation. Of interest are findings (Salako, Vaughan Williams & Wittig, 1976) that ORG 6001 shortens the action potentials in rabbit ventricular conducting system so that duration is uniform along this system.

The ability of ORG 6001 to reduce ST-segment elevation may have clinical relevance to its antidysrhythmic properties since a good correlation has been shown between infarct size and the incidence of ventricular ectopics in patients with recent myocardial infarcts (Roberts, Husain, Ambos, Oliver, Cox & Sobel, 1975). It would be of considerable interest to investigate whether other antidysrhythmic agents which prevent  $K^+$  efflux are also capable of decreasing ST elevation produced by experimental coronary occlusion.

## References

- COHEN, D. & KAUFMAN, L.A. (1975). Magnetic determination of the relationship between the ST-segment shift and the injury current produced by coronary artery occlusion. *Circulation Res.*, **36**, 414-424.
- FOZZARD, H.A. & DasGUPTA, D.S. (1976). ST-segment potentials and mapping. *Circulation*, **54**, 533-537.
- KARLSSON, J., TEMPLETON, G.H. & WILLERSON, S.T. (1973). Relationship between epicardial ST segment changes and myocardial metabolism during acute coronary insufficiency. *Circulation Res.*, **32**, 725-730.
- MAROKO, P.R., KJEKSHUS, J.K., SOBEL, B.E., WATANABE, T., COVELL, J.W., ROSS, J. & BRAUNWALD, E. (1971). Factors influencing infarct size following experimental coronary artery occlusions. *Circulation*, **43**, 67-82.
- MARSHALL, R.J. & PARRATT, J.R. (1975). Antiarrhythmic, haemodynamic and metabolic effects of 3 $\alpha$ -amino-5 $\alpha$ -androstane-2 $\beta$ -ol-17-one hydrochloride in greyhounds following acute coronary artery ligation. *Br. J. Pharmac.*, **55**, 359-368.
- MARSHALL, R.J. & PARRATT, J.R. (1977). The haemodynamic and metabolic effects of MG 8926, a prospective antidysrhythmic and antianginal agent. *Br. J. Pharmac.*, **59**, 311-322.
- MARSHALL, R.J., PARRATT, J.R. & LEDINGHAM, I. McA. (1974). Changes in blood flow and oxygen consumption in normal and ischaemic regions of the myocardium following acute coronary artery ligation. *Cardiovasc. Res.*, **8**, 204-215.
- ROBERTS, R., HUSAIN, A., AMBOS, H.D., OLIVER, C., COX, J.R. & SOBEL, B.E. (1975). Relation between infarct size and ventricular arrhythmia. *Br. Heart J.*, **37**, 1169-1175.
- SALAKO, L.A., VAUGHAN WILLIAMS, E.M. & WITTIG, J.H. (1976). Investigations to characterize a new antiarrhythmic drug, ORG 6001, including a simple test for calcium antagonism. *Br. J. Pharmac.*, **57**, 251-262.
- SMITH, H.J., SINGH, B.N., NISBET, HEATHER & NORRIS, R.M. (1975). Effects of verapamil on infarct size following experimental coronary occlusion. *Cardiovasc. Res.*, **9**, 569-578.
- WENDT, R.L., CANAVAN, R.C. & MICHALAK, R.J. (1974). Effects of various agents on regional ischaemic injury: electrocardiographic analysis. *Am. Heart J.*, **87**, 468-482.

(Received June 28, 1977)