Br. J. Pharmac. (1980), **71**, 597–600

PROPHYLACTIC LIGNOCAINE AND EARLY POST-CORONARY ARTERY OCCLUSION DYSRHYTHMIAS IN ANAESTHETIZED GREYHOUNDS

R.J. MARSHALL[1] & J.R. PARRATT

Departments of Physiology and Pharmacology, University of Strathclyde, and of Surgery, Western Infirmary, University of Glasgow

1 Lignocaine (1 mg kg^{-1} min^{-1} infused intravenously for 30 min) greatly reduced the incidence of ventricular ectopic beats that resulted from acute coronary artery ligation in anaesthetized greyhound dogs. However, the incidence of ventricular fibrillation was only slightly reduced by this treatment which caused significant myocardial depression.

2 There is no good evidence from this study that lignocaine is a particularly effective prophylactic in acute myocardial infarction.

Introduction

Ventricular fibrillation is a major complication of acute mycardial infarction and is responsible for most of the sudden deaths occurring in the early, pre-hospital phase. For example, Gordon & Kannel (1971) found that 61% of electrical deaths (mainly ventricular fibrillation) arising as a result of myocardial infarction in patients younger than 65 years occur within the first hour of onset. These early life-threatening dysrhythmias are seemingly much less sensitive to conventional drug therapy than those occurring several hours after the onset of infarction; there is, for example, a marked contrast between the limited value of lignocaine in the early pre-hospital phase and its well recognized effectiveness in the coronary care unit (Pantridge, Adgey, Geddes & Webb, 1975).

There has been considerable discussion recently concerning the possible prophylactic value of lignocaine early in infarction. It has been variously argued that 'the prophylactic use of lignocaine is unnecessary' (Lancet Editorial, 1979), that 'the prophylactic value of lidocaine (lignocaine) in the very early (< 1 h) acute myocardial infarction period remains to be clarified' (Noneman & Rogers, 1978), that 'the routine administration of (prophylactic) lignocaine to all patients in the coronary care unit seems indicated' (Harrison, 1978) and that the 'routine intramuscular administration (of lignocaine) appears to reduce the risk of ventricular tachyarrhythmias and sudden death over the ensuing 1–1½ hours' (Ribner, Isaacs & Frishman, 1979). It has even been suggested (Sarnoff, 1970, quoted by Borer, Harrison, Kent, Levy, Goldstein & Epstein, 1976) that the drug be offered in an automatic injector for intramuscular self-administration by high risk patients during the pre-hospital phase of acute myocardial infarction.

In the anaesthetized greyhound ventricular dysrhythmias and fibrillation are common following acute coronary artery ligation (reviewed by Marshall & Parratt, 1980) and can be reduced or prevented by the prophylactic administration of creatine phosphate (Marshall & Parratt, 1974), the aminosteroid Org 6001 (Marshall & Parratt, 1975) or disopyramide (Marshall & Parratt, 1979). The purpose of this present study was to examine the possible effectiveness of intravenously infused lignocaine against these early life-threatening, ventricular dysrhythmias.

Methods

Twenty-six greyhounds of either sex and weighing between 19 and 30 kg were anaesthetized with sodium thiopentone (30 mg/kg, i.v.) followed by α-chloralose (85 mg/kg, i.v.). They were intubated and ventilated with 100% O_2. Catheters were then placed under fluoroscopic control in the descending aorta, the lumen of the left ventricle, and in the pulmonary artery, coronary sinus and right atrium, for pressure measurements and blood sampling as previously described (Marshall, Parratt & Ledingham, 1974). Left ventricular (LV) pressure was differentiated (LV

[1] Present address: Department of Pharmacology, Organon Laboratories, Newhouse, Lanarkshire.

0007-1188/80/140597-04 $01.00

dP/dt) and cardiac output was measured by thermodilution. Temperature was measured from the mid-oesophagus with direct recording (Ellab) thermocouples. After a left thoracotomy the pericardium overlying the anterolateral aspect of the heart was incised and the anterior descending branch of the left coronary artery (at a point midway between the tip of the atrium and the apex of the heart) was prepared for ligation with minimal dissection. A major branch of the main vein adjacent to this artery was catheterized by the Seldinger technique (Marshall *et al.*, 1974). After ligation this vein drains blood predominantly from the infarcting area of the left ventricular wall.

After a suitable stabilization period lignocaine was infused intravenously in 12 of the dogs in a dose of 1.0 mg kg^{-1} min^{-1}. Ten minutes later the haemodynamic effects were analysed in detail (cardiac output, LV dP/dt_{max}, left ventricular end-diastolic pressure (LVEDP) aortic pressure and mean pulmonary artery pressure) and blood samples taken from the aorta, coronary sinus and pulmonary artery were analysed for O_2 and CO_2 tensions, for O_2 content and for pH as outlined previously (Marshall *et al.*, 1974). Whilst the lignocaine infusion was continued the anterior descending branch of the left coronary artery was ligated in one stage and the resultant ventricular ectopic activity analysed in detail as recently described (Marshall & Parratt, 1980). Twenty minutes after coronary artery ligation the lignocaine infusion was terminated and the cardiovascular and metabolic parameters again measured; these dogs had thus received a total dose of 30 mg/kg. Finally, after a further 10 min (i.e. 30 min post-ligation) blood samples were again taken from the aorta, coronary sinus and local coronary vein (now draining the ischaemic area) and a catheter was inserted into the ligated coronary artery, distal to the point of occlusion. Blood flow within the ischaemic region was then measured with radioactive ^{133}xenon (Marshall *et al.*, 1974). The results obtained were compared with those obtained from the fourteen dogs (control, saline infused) not administered lignocaine. Statistical analysis was carried out by the Student's t test for small samples of paired data.

Results

The intravenous administration of lignocaine (1.0 mg kg^{-1} min^{-1} for 10 min) resulted in a decreased cardiac output (2.72 ± 0.35 l/min pre-lignocaine compared with 2.50 ± 0.32 l/min after 10 min of infusion; $P < 0.05$), and reductions in heart rate (135 ± 8 to 129 ± 8 beats/min; $P < 0.05$), external cardiac work (3.94 ± 0.67 to 3.26 ± 0.53 kgm/min; $P < 0.05$), mean systemic arterial pressure (107 ± 9 to 94 ± 6 mmHg; $P < 0.05$) and in LV dP/dt (from 1700 ± 190 to 1315 ± 200 $mmHgs^{-1}$; $P < 0.005$). This reduction in LV dP/dt_{max} almost certainly reflects a reduced myocardial contractility, despite the reduced afterload, since preload (LVEDP) was significantly increased (from 6 ± 1 mmHg to 8 ± 1 mmHg; $P < 0.05$). There were no significant changes in mean pulmonary artery pressure (9 ± 1 mmHg), peripheral vascular resistance or whole body oxygen consumption. The myocardial extraction of oxygen (coronary sinus sampling) increased (from 56 ± 3 to 61 ± 3%, $P < 0.005$); this probably reflects a reduction in myocardial blood flow. In the two dogs in which myocardial blood flow was measured (electromagnetic flow probe on the circumflex artery) it decreased by 9% and 13% respectively.

The effects of lignocaine on the incidence and severity of ventricular ectopic activity, and on the inci-

Table 1 Total number of ventricular ectopic beats at various times after the acute ligation of the anterior descending branch of the left coronary artery in control (untreated) chloralose-anaesthetized greyhounds and in greyhounds administered lignocaine (1 mg kg^{-1} min^{-1} for 30 min)

	Ectopic count (beats)								
	0–5 min	6–10 min	11–15 min	16–20 min	21–25 min	26–30 min	Total	*VT*	*VF*
Control (n = 14)	22 ± 7	69 ± 14	97 ± 42	120 ± 37	68 ± 30	14 ± 3	344 ± 78	10	5
Lignocaine (30 mg/kg total; n = 12)	12 ± 7	56 ± 31	19 ± 17*	1 ± 1*	6 ± 2*	1 ± 1*	95 ± 53*	4	3

Values are mean counts ± s.e. together with the incidence of ventricular tachycardia (VT) and of fatal ventricular fibrillation (VF).
*$P < 0.05$ compared with controls.

dence of ventricular tachycardia and fibrillation, are given in Table 1. In control dogs the mean ventricular ectopic count over the initial 30 min following acute coronary artery occlusion was 344 ± 78 beats; ectopic activity is rare after this time until 5 h post-ligation. Five of the 14 dogs fibrillated and 10 had runs of ventricular tachycardia. Lignocaine markedly reduced the incidence of ventricular ectopic beats (Table 1) and this was particularly so at the crucial 16 to 20 min post-ligation period. Although only 4 of the 12 animals had ventricular tachycardia 3 dogs died in ventricular fibrillation; this was a similar incidence to that in the control series (25% and 34% respectively). It was of particular interest to analyse the electrocardiograms in the 3 lignocaine-treated dogs that fibrillated. One fibrillated at 6 min with very few 'warning dysrhythmias'; there was however a rather pronounced decrease in systemic arterial pressure in this dog immediately after ligation (of 22 mmHg to a mean pressure of 90 mmHg). The other 2 dogs that fibrillated (at 13 min and 22 min) had many ventricular ectopic beats (168 and 828 respectively) and both had runs of ventricular tachycardia.

We also determined the effect of lignocaine on the haemodynamic and metabolic consequences of coronary artery ligation. These effects were in fact similar to those in control (untreated) dogs which have already been described in detail (Marshall *et al.*, 1974). They include a reduction in LV dP/dt_{max} (1100 ± 155 mmHg s^{-1} at 30 min post-ligation from the pre-lignocaine value of 1700 ± 190 mmHg s^{-1}; $P < 0.005$) and in cardiac output (2.26 ± 0.31 l/min from 2.72 ± 0.35 l/min; $P < 0.05$) and an elevation in LVEDP (10 ± 1 from 6 ± 1 mmHg; $P < 0.05$). Changes in local coronary venous Pco_2 and pH at this time (30 min post-ligation) were also similar to those found in dogs not given an antidysrhythmic agent. One hour after ligation the mean blood flow in the developing infarcting region was 22 ± 3 ml 100 g^{-1} min^{-1}; this again is similar to that found at this time after ligation in dogs not administered any antidysrhythmic agent (Marshall *et al.*, 1974). The ST-segment depression in standard limb leads at 20 and 30 min post-ligation (e.g. 1.2 ± 0.3 mV and 1.4 ± 0.2 mV) was also similar in control dogs and in dogs administered lignocaine. We conclude that the haemodynamic and metabolic effects of coronary artery ligation in dogs are similar whether or not lignocaine is administered; there was certainly no evidence that lignocaine reduced the haemodynamic or metabolic consequences of acute myocardial ischaemia.

Discussion

The clinical controversy regarding the effectiveness, or otherwise, of lignocaine in preventing early post-infarction ventricular dysrhythmias and fibrillation (see Introduction) is also reflected in animal studies (reviewed by Borer *et al.*, 1976). For example, Zipes & Troup (1978) quote unpublished data that the incidence of ventricular fibrillation resulting from acute ligation of the anterior descending branch of the left coronary artery in open-chest dogs is not altered by lignocaine (1.0 mg kg^{-1} min^{-1}); the incidence was 13% in saline-treated controls and 15% in those dogs administered lignocaine. This was in contrast to the protection afforded in a similar model by propranolol (0.02 mg kg^{-1} min^{-1}). Borer's study (Borer *et al.*, 1976) in a very severe model (ligation of the anterior descending and septal branches in open-chest pentobarbitone-anaesthetized dogs) showed that the incidence of ventricular fibrillation in dogs receiving either 70 or 100 μg kg^{-1} min^{-1} (after a loading bolus injection of 2.0 mg/kg) was only slightly better (9/15) than that in the untreated controls (14/16). In this particular study, dogs receiving the larger dose (a total of 3 mg/kg lignocaine over a 10 min period) had a greater incidence of fibrillation than those receiving the slightly lower dose (2.7 mg/kg total dose over the 10 min infusion period). Clearly there was no significant protection, despite the fact that the ventricular fibrillation threshold was increased. Some workers have indeed shown that the incidence of fibrillation in this situation is increased by lignocaine, as it is after the administration of its primary analogue, tocainide (Zipes & Troup, 1978).

The present study demonstrates a dissociation between the effect of lignocaine on ventricular ectopic beats (VEBs) and on the incidence of fibrillation (Table 1). Lignocaine clearly and significantly suppressed ventricular ectopic activity and this was particularly evident after 11 min of occlusion (Table 1). Thus the mean total number of VEBs between 11 and 30 min was only 27 beats compared with 299 beats in the non-treated animals. The very early ('immediate') post-ligation ventricular ectopic activity (0 to 10 min) was hardly affected by lignocaine (a total of 68 beats compared with 91 in the untreated dogs). Kaplinsky, Ogawa, Balke & Dreifus (1979) have recently drawn attention to these two quite distinct populations of ventricular dysrhythmias ('immediate', occurring between 2 and 10 min after ligation and 'delayed', occurring between 12 and 30 min). The 'immediate' dysrhythmias are probably due to sub-epicardial re-entry and the 'delayed' dysrhythmias to re-entry pathways located in deep myocardial structures. In contrast to the marked suppression of the delayed VEBs, lignocaine did not dramatically modify the incidence of ventricular fibrillation (3/12 compared to 5/14 in the untreated group) even in doses that caused significant myocardial depression (as evidenced by a decreased LV dP/dt_{max} at elevated left ventricular filling pressures and by a decreased cardiac output).

The reasons for the failure of lignocaine to prevent ventricular fibrillation are unclear. Presumably the precipitation of ventricular fibrillation is multifactorial and may involve sympathetic overdrive. However, we have found no evidence (Marshall & Parratt, 1980) for a significantly increased release of noradrenaline, either from the normal or ischaemic regions of the left ventricle wall during the initial 30 min following coronary artery ligation (at times when ventricular fibrillation occurs in this model). In addition we have demonstrated that antiarrhythmic drugs like Org 6001 and disopyramide, which do not possess any sympatholytic properties, are capable of preventing ventricular fibrillation (Marshall & Parratt, 1975; 1979).

It is more probable that the ineffectiveness of prophylactic lignocaine in preventing ventricular fibrillation is related to its complex electrophysiological effects. Studies on human ventricular muscle (Kane, 1980) have shown that lignocaine differs from Org 6001 (and quinidine) in its actions on absolute refractory period. However until the genesis of ventricular fibrillation is better understood, the relevance of these subtle differences in the electrophysiological profile of Class I antiarrhythmic drugs remains unclear.

We conclude from the present experiments that there is no good evidence that even large doses (30 mg/kg total dose) of lignocaine dramatically increase early survival from myocardial infarction; this is in general agreement with our previous studies on single bolus injections of the drug (Marshall & Parratt, 1974). As a recent *Lancet* editorial (1979) has also pointed out, there is also no good clinical evidence that prophylactic lignocaine reduces mortality. From our experience with the greyhound model (Marshall & Parratt, 1975; 1979) we would suggest that it would be more worthwhile to examine the effects of the aminosteroid, Org 6001, or disopyramide in the acute clinical situation. Both abolish, or greatly reduce, the incidence of early ventricular fibrillation; of the two, the aminosteroid has the distinct advantage of being virtually devoid of myocardial depressant activity.

Reprint requests to J.R.P. at the University of Strathclyde, please.

References

BORER, J.S., HARRISON, L.A., KENT, K.M., LEVY, R., GOLDSTEIN, R.E. & EPSTEIN, S.E. (1976). Beneficial effect of lidocaine on ventricular electrical stability and spontaneous ventricular fibrillation during experimental myocardial infarction. *Am. J. Cardiol.*, **37**, 860–863.

EDITORIAL (1979). Anti-dysrhythmic treatment in acute myocardial infarction. *Lancet*, **i**, 193–194.

GORDON, T. & KANNEL, W.B. (1971). Premature mortality from coronary heart disease. *J.A.M.A.*, **215**, 1617–1625.

HARRISON, D.C. (1978). Should lidocaine be administered routinely to all patients after acute myocardial infarction? *Circulation*, **58**, 581–584.

KANE, K.A. (1980). Comparative electrophysiological effects of Org 6001, a new orally active antidysrhythmic agent, and lignocaine on human ventricular muscle. *Br. J. Pharmac.*, **68**, 25–31.

KAPLINSKY, E., OGAWA, S., BALKE, C.W. & DREIFUS, L.S. (1979). Two periods of early ventricular arrhythmia in the canine acute myocardial infarction model. *Circulation*, **60**, 397–403.

MARSHALL, R.J. & PARRATT, J.R. (1974). Reduction in ventricular arrhythmias following acute coronary artery ligation in the dog after the administration of creatine phosphate. *Naunyn-Schmiedebergs Arch. Pharmac.*, **281**, 437–441.

MARSHALL, R.J. & PARRATT, J.R. (1975). Antiarrhythmic, haemodynamic and metabolic effects of 3α-amino-5α-androstan-2β-ol-17-one hydrochloride in greyhounds following acute coronary artery ligation. *Br. J. Pharmac.*, **55**, 359–368.

MARSHALL, R.J. & PARRATT, J.R. (1979). The effects of disopyramide phosphate on early post-coronary artery ligation dysrhythmias and on epicardial ST-segment elevation in anaesthetised dogs. *Br. J. Pharmac.*, **66**, 241–250.

MARSHALL, R.J. & PARRATT, J.R. (1980). The early consequences of myocardial ischaemia and their modification. *J. Physiol. (Paris)* (in press).

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.

NONEMAN, J.W. & ROGERS, J.F. (1978). Lidocaine prophylaxis in acute myocardial infarction. *Medicine*, **57**, 501–515.

PANTRIDGE, J.F., ADGEY, A.A.J., GEDDES, J.S. & WEBB, S.W. (1975). *The Acute Coronary Attack*. London: Pitman.

RIBNER, H.S., ISAACS, E.S. & FRISHMAN, W.H. (1979). Lidocaine prophylaxis against ventricular fibrillation in acute myocardial infarction. *Prog. Cardiovasc. Diseases*, **21**, 287–313.

ZIPES, D.P. & TROUP, P.J. (1978). New antiarrhythmic agents. *Am. J. Cardiol.*, **41**, 1005–1024.

(Received March 20, 1980. Revised May 13, 1980.)