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Observations on intravenous administration of lignocaine in patients with myocardial infarction

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SUMMARY Lignocaine was administered intravenously to 36 patients with acute myocardial infarction.

A bolus of 100 mg followed by an infusion of 2 mg/minute failed to maintain plasma levels above 2 μg/ml. A bolus of 100 mg followed by 4 mg/minute also failed to maintain satisfactory plasma concentrations during the first hour of therapy.

A bolus of 75 mg was combined with an infusion of 10 mg/minute for 20 minutes followed by 1·5 mg/minute. Satisfactory plasma concentrations during the first hour were observed in 94 per cent of the estimations. No important adverse side effects occurred during the infusion of 10 mg/minute.

Lignocaine has been found to be relatively ineffective in controlling ventricular arrhythmias occurring immediately after the onset of acute myocardial infarction (Geddes *et al.*, 1972). This may be related in some cases to the presence of sympathetic overactivity in the acute phase of myocardial infarction since the drug has been shown to be more effective when the heart rate is within the normal range (Pantridge *et al.*, 1974). However, failure to achieve adequate plasma concentrations may be an important reason for therapeutic ineffectiveness. It has been said that plasma concentrations of lignocaine of 2 to 5 μg/ml are usually effective (Koch-Weser, 1972). In this study, the plasma concentrations of lignocaine obtained with conventional doses of the drug have been investigated. We have used a theoretical approach to design a regimen that might give therapeutic plasma concentrations, particularly throughout the first hour of therapy.

Patients and methods

Thirty-six patients were studied (Table 1). All received lignocaine because of ventricular arrhythmias complicating acute myocardial infarction. Six had self-terminating ventricular tachycardia. The remainder had ventricular extrasystoles (frequent, consecutive, or R on T). The drug was given to all patients within 48 hours of the onset of symptoms of infarction (median 10 hours). Twenty-six (72%) of the patients had clinical or radiographic evidence of left ventricular failure when treatment was started. None had pulmonary oedema or cardiogenic shock.

The 36 patients were divided into 4 groups. Group 1 (10 patients) received an initial 100 mg injection of lignocaine over 30 seconds. This was followed immediately by a continuous infusion of the drug at a rate of 2 mg/minute. Groups 2 and 3 (each containing 10 patients) also received an initial 100 mg injection but this was followed by a 4 mg/minute infusion for 20 and 45 minutes, respectively. The rate of infusion was then reduced to 2 mg/minute. Group 4 (6 patients) received an initial 75 mg injection of lignocaine given over 30 seconds followed by a 10 mg/minute infusion for 20 minutes. The infusion rate was then reduced to 1·5 mg/minute. The regimen in Group 4 was devised using the method of Wagner (1974). Wagner suggested that a drug might be given intravenously using 2 different infusion rates—an initial rapid rate (Q_1) and a later slower rate (Q_2). Q_2 is calculated from the clearance of the drug and the desired final plasma concentration. A concentration of 3 μg/ml was chosen as this lies near the centre of the therapeutic range (2 to 5 μg/ml). Q_1 is then derived from Q_2 and the half-life of elimination of the drug. Details of the calculation are shown in the Appendix.

Throughout the study, lignocaine was given through an arm vein. Samples were withdrawn through an indwelling cannula from a vein in the

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Table 1 *Details of patients receiving various intravenous doses of lignocaine*

		Age (y)	Sex M	Sex F	Weight kg	Urea (mg* /100 ml)	Site of infarction: Ant	Post	LBBB	SE	Time from onset of symptoms (h)	No. with previous infarction	Total
Single injection with continuous infusion													
Group 1	Mean	57	9	1	72	36	6	4	0	0	13	2	10
	SEM	±2·6			±3·5	±2·6					±4·8		
Group 2	Mean	55	8	2	70	34	6	4	0	0	11	0	10
	SEM	±3·0			±1·8	±3·3					±2·0		
Group 3	Mean	60	8	2	74	41	6	3	0	1	15	1	10
	SEM	±1·9			±2·7	±5·4					±3·3		
Group 4	Mean	50	6	0	79	33	4	2	0	0	19	1	6
	SEM	±4·0			±3·2	±3·1					±5·5		
													36

Ant = anterior; Post = posterior; LBBB = left bundle-branch block; SE = subendocardial; SEM = standard error of mean.
* 1 mg/100 ml ≈ 0 166 mmol/l.

other arm. Blood pressure was measured by sphygmomanometer before and 5 and 15 to 20 minutes after the lignocaine was given. The cardiogram was observed on an oscilloscope throughout the study.

The samples for measurement of the plasma concentration of lignocaine were taken 3, 6, 10, 15, 20, 25, 30, 45, 60, 120, and 240 minutes after the initial injection. The rate of infusion was controlled by an IVAC 501 drip counter or a Braun constant infusion pump (Type 871010). Lignocaine hydrochloride BP (the monohydrated form, $C_{14}H_{22}N_2O$, HCl, H_2O molecular weight 288·8) was used throughout the study.

All blood samples were centrifuged and the plasma stored at −20°C. Analysis was subsequently performed using gas liquid chromatography. The plasma was made alkaline and the lignocaine was extracted with ether. After evaporation of the ether and reconstitution with dichloroethane, aliquots were injected into a gas chromatographic column. The column was packed with 2 per cent carbowax 20 M on KOH-treated chromosorb G. Diphenhydramine was used as an internal standard.

Statistical comparisons of mean values were performed using Student's unpaired t test. Comparisons within groups were made using Student's paired t test.

Results

There were no statistically significant differences in age, sex, blood urea, or time from onset of symptoms to administration of the drug among the patients in groups 1 to 4 (Table 1). Patients in group 4 were significantly heavier than those in group 2 ($P < 0·05$).

The mean plasma concentrations achieved are compared in Figs. 1 and 2. When a 4 mg/minute infusion was given after an initial 100 mg injection (groups 2 and 3) the mean concentrations during the first 20 minutes did not differ significantly from those among patients in group 1 (100 mg followed by a 2 mg/minute infusion) (Fig. 1). However, 45 minutes after the initial injection, patients in group 1 had a significantly lower mean plasma concentration than the patients in group 3 ($P < 0·05$). No significant differences occurred between the mean plasma concentrations of patients in groups 2 and 3. One patient in group 2 attained a concentration > 7 μg/ml after 15 minutes. After a small initial fall, the mean plasma concentrations for group 4 patients steadily climbed during the first 20 minutes, in 1 patient reaching 9·3 μg/ml at 20 minutes (Fig. 2). The mean concentrations from 10 minutes to 1 hour after the initial injection for patients in group 4 differed significantly from those in group 1 ($P < 0·05$). At 2 and 4 hours, there were no significant differences between any of the groups (Figs. 1 and 2).

In patients in group 1 47 per cent of the plasma concentrations were less than 2 μg/ml during the first hour of treatment (Table 2). All but 1 of the patients in group 1 had at least 1 plasma concentration < 2 μg/ml during the first hour of treatment. Only 52 per cent of the concentrations were in the

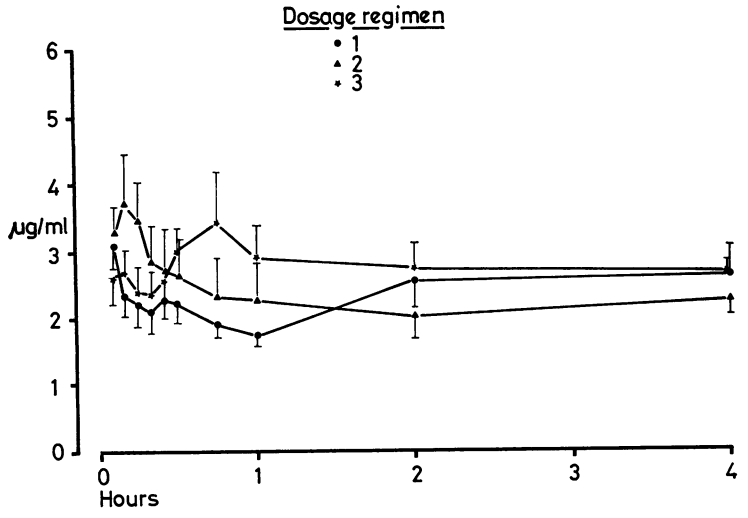

Fig. 1 *Mean (± SEM) plasma concentrations of lignocaine in 3 groups of 10 patients. All patients received an initial 100 mg injection. Those in group 1 received a 2 mg/minute infusion: patients in groups 2 and 3 were given a 4 mg/minute infusion for 20 and 45 minutes, respectively. The infusion was then reduced to 2 mg/minute.*

range 2 to 5 µg/ml. In groups 2 and 3, the percentages within this range were 47 and 65, respectively. In group 4, only 6 per cent of the plasma concentrations were below 2 µg/ml.

Apart from numbness in the tongue, paraesthesiae, and dizziness after the initial bolus and drowsiness during the continuous infusion, adverse neurological effects were not encountered. Suspected adverse haemodynamic effects caused the drug to be stopped in 4 patients. None of these suspected adverse effects occurred within the first 90 minutes of treatment. Two of these patients (1 from group 1 and 1 from group 2) developed bradycardia and hypotension. One of these developed complete heart block. Both had shown bradycardia before the administration of lignocaine. One patient (from group 4) developed increasing sinus tachycardia and congestive heart failure and in another (from group 1) the systolic blood pressure fell from 85 to 70 mmHg. Since the suspected adverse haemodynamic effects occurred in association with plasma concentrations of lignocaine < 3 µg/ml, they cannot be definitely attributed to the treatment.

In the groups receiving the 4 and 10 mg/minute infusions, a significant mean increase in the mean arterial pressures of 4·8 and 9 mmHg, respectively, was observed after 15 to 20 minutes ($P < 0.05$).

Recurrent arrhythmias were detected in 5 patients. Important ventricular extrasystoles were observed in 3 and ventricular tachycardia in 2. In only 1 of the 5 was the plasma concentration > 2 µg/ml. These arrhythmias occurred more than 2 hours after the onset of therapy.

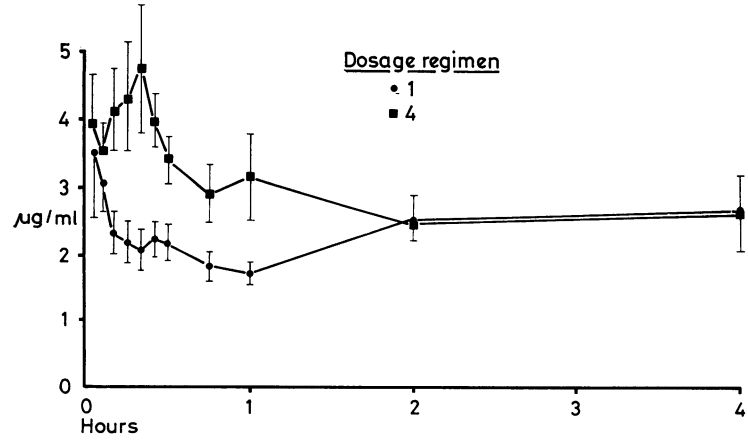

Fig. 2 *Mean (± SEM) plasma concentrations of lignocaine in 16 patients. Group 1 (10 patients) received a 100 mg bolus followed by a 2 mg/minute infusion. Group 4 (6 patients) received a 75 mg bolus and a 10 mg/minute infusion for 20 minutes: the infusion was then reduced to 1·5 mg/minute.*

Table 2 *Distribution of plasma concentrations of lignocaine during first hour of treatment*

Group	% of plasma concentrations		
	< 2 μg/ml	2 to 5 μg/ml	> 5 μg/ml
1	47	52	1
2	35	47	18
3	24·5	65	10·5
4	6	76·5	17·5

Discussion

This study shows that plasma concentrations of lignocaine of < 2 μg/ml are commonly observed during the initial hour of therapy when a bolus injection of 100 mg is combined with a 2 mg/minute infusion. Other workers have observed a fall in plasma concentrations below therapeutic levels when a single bolus injection is followed by an infusion of 2 to 3 mg/minute (Bassan *et al.*, 1974; Greenblatt *et al.*, 1976). Low plasma concentrations of lignocaine may be hazardous. Gamble and Cohn (1972) have indicated that after experimental coronary artery ligation, plasma concentrations of < 2 μg/ml may enhance re-entrant arrhythmias. Geddes *et al.* (1974) described the effects of lignocaine on a re-entrant model where hot and cold lesions were produced on the right ventricular wall of open chest dogs. Re-entry increased as the effect of the intravenous bolus injections of the drug diminished. Geddes *et al.* (1972) described increased frequency of ventricular ectopic activity when 100 mg followed by a 2 mg/minute infusion of lignocaine was given to patients within 4 hours of the onset of acute myocardial infarction.

The data in this study indicate that when the bolus was followed by a 4 mg/minute infusion, the infusion rate had to be maintained for 45 minutes to give a mean plasma concentration significantly higher than that obtained with a 2 mg/minute infusion. Furthermore, with this regimen nearly one-quarter (24·5%) of the plasma concentrations during the first hour of treatment were potentially ineffective (< 2 μg/ml). To overcome this problem the approach suggested by Wagner in 1974 was adopted. Using this regimen, only 6 per cent of the concentrations during the first hour were < 2 μg/ml. During the first hour of therapy, the mean plasma concentrations were either greater than or approximated to 3 μg/ml. However, 17·5 per cent of the plasma concentrations during the first hour of treatment were > 5 μg/ml and in 1 patient a concentration of 9·3 μg/ml was obtained during the 10 mg/minute infusion. After the infusion rate was reduced to 1·5 mg/minute at 20 minutes, the plasma concentration fell rapidly.

Despite the high plasma concentrations, no important adverse reactions occurred during high infusion rates. However, with infusion rates of 4 and 10 mg/minute, a significant increase in mean arterial pressure was observed. Such increases have been described in previous reports and have been attributed to an increased sensitivity to circulating catecholamines (Grossman *et al.*, 1969).

Since there is considerable variation in kinetics observed in patients with acute myocardial infarction and as low plasma clearances were used for calculation of the regimen from Wagner's (1974) theoretical approach, it is not surprising that concentrations after 1 hour fell during the 1·5 mg/minute infusion. In all 6 patients in group 4, the mean 4-hour plasma concentration was 54 per cent of the peak concentration after 20 minutes. This suggests that a higher infusion rate than 1·5 mg/minute should have been given 20 minutes after the initiation of treatment.

Other regimens have been suggested to maintain effective plasma concentrations during the early hours of treatment with lignocaine. Collinsworth *et al.* (1974) suggested that an initial small bolus injection (0·75 mg/kg) might be given and a similar dose administered 15 minutes later. However, using this approach, the fall in plasma concentrations after the first injection may not be prevented (Greenblatt *et al.*, 1976) and very high plasma concentrations may occur after the second injection. Aps *et al.* (1976) suggested an initial bolus of 75 to 100 mg intravenously followed by a 4 mg/minute infusion for 30 minutes, 2 mg/minute for 2 hours, and 1 mg/minute thereafter. They found that the mean plasma concentration 'within a few minutes' of the initial injection was approximately 1·8 μg/ml. More recently, Levy *et al.* (1977) have reported a regimen without an initial bolus in which 200, 250, or 300 mg lignocaine was infused at 25 mg/minute. This was followed by a slower rate of infusion. Plasma concentrations were not determined during the 8 to 12 minutes of rapid infusion. Because of the absence of an initial bolus injection, this method is less suitable for the immediate correction of rhythm disturbances. Sheridan *et al.* (1977) have reported the use of the combination of single intravenous and intramuscular injections of lignocaine. Plasma concentrations of 2 μg/ml or greater were obtained in all patients throughout the first hour of treatment. Nevertheless, the intramuscular route has the disadvantage that the rate of absorption varies with the injection site and the blood flow at the site (Schwartz *et al.*, 1974; Evans *et al.*, 1975). Furthermore, should complications such as atrioventricular block develop, a large depot of lignocaine might be hazardous.

Appendix

Calculations of therapeutic regimen for group 4

Wagner (1974) in designing an intravenous dosage regimen suggested that a constant rate infusion (Q_1) can be given over a short period of time (T hours = 0·25 − 3 hours). The infusion rate is then abruptly reduced to a second speed (Q_2) which is maintained as long as required. Q_2 is calculated from the clearance and the desired plasma concentration. The ratio Q_1/Q_2 is estimated using the relation $Q_1/Q_2 = 0{\cdot}5 + 1{\cdot}443\ (t_{\frac{1}{2}}/T)$ where $t_{\frac{1}{2}}$ = the plasma elimination half-life and T = the time over which an infusion rate of Q_1 is to be given. The longest half-life and the lowest plasma clearance cited by Prescott and Nimmo (1971) in patients after myocardial infarction were 4·4 hours and 280 ml/minute respectively. From these figures Q_2 approximated to 1·5 mg/minute. During the present study, a plasma concentration of 3 μg/ml was considered desirable. 0·33 hours was selected as a suitable value for T. Using these data, a value of 16·5 mg/minute for Q_1 was calculated, that is 330 mg to be administered over the first 20 minutes. To reduce the risk of toxicity, this dose was reduced to a 75 mg bolus followed by a 10 mg/minute infusion for 20 minutes (total dose 275 mg).

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