Simple lignocaine regimen for transit to hospital after myocardial infarction

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A simple combined intravenous/intramuscular regimen is described for lignocaine administration in the early vulnerable stage of myocardial infarction. Plasma levels in the therapeutic range are attained. This allows adequate drug protection during transport to hospital when an intravenous regimen may be impractical or impossible.

Lignocaine remains the first line of attack against ventricular arrhythmia after myocardial infarction. Plasma levels required for this purpose are said to lie between 6.4 and 21 $\mu\text{mol/l}$ (1.5 to 5 $\mu\text{g/ml}$) (Harrison and Alderman, 1971; Collinsworth *et al.*, 1974; Koch-Weser, 1975; Aps *et al.*, 1976). There is difficulty in maintaining adequate plasma concentrations in the first two hours of treatment using conventional intravenous dosage (Aps *et al.*, 1976). If such treatment is started in the patient's home, he is likely to be denied protection from arrhythmias at a time when the risk is greatest and surveillance most difficult.

We report our experience using a simple combination of an intravenous bolus and intramuscular injection as a means of overcoming these difficulties.

Methods

Twelve consecutive patients admitted to the Coronary Care Unit, who fulfilled our criteria for lignocaine therapy (Walsh *et al.*, 1972) and who had not received any antiarrhythmic drug outside hospital, received the combined intravenous/intramuscular regimen. Two patients were excluded subsequently because of technical problems relating to the timing of samples for estimation of drug concentration. Of the remaining 10, 8 were men and 2 women, and their ages varied from 28 to 74 years. One patient (case 9) had mitral stenosis and was in heart failure. All the remainder had had a myocardial infarct and one of these (case 8) also had pulmonary venous congestion. Their weights varied from 55.3 to 76.7 kg. The electrocardiograms of these patients were recorded continuously by a

direct-writing electrocardiograph over a 4-hour period and blood pressure was recorded at 15-minute intervals. The recordings were scanned by two observers for changes in heart rate or rhythm.

The patients were given 100 mg lignocaine hydrochloride by intravenous injection over 2 minutes into an arm vein. Five minutes after the beginning of the intravenous injection, 300 mg were given by intramuscular injection into the deltoid muscle. The time of the intramuscular injection was taken as zero time and 10 ml blood samples were taken from a vein in the other arm 2 minutes before zero time and then at 3, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes. The blood was centrifuged and stored at 4°C until plasma concentrations were estimated.

Plasma lignocaine was estimated by a gas chromatographic method. One ml samples of plasma, containing diphenhydramine 5 μg as an internal standard, were made alkaline with 0.5 ml of 2M NaOH. Samples were extracted with 5 ml portions of ether. The ether layer was removed and evaporated to dryness. Samples were reconstituted with 30 μl portions of dichloromethane and 1 μl portions injected into a gas chromatograph (Perkin-Elmer model F11) fitted with a flame-ionisation detector. The column was glass, 6 ft in length and 0.25 in outer diameter and was packed with 2 per cent carbowax 20M on KOH treated chromosorb G. Oven temperature was 200°C and nitrogen carrier gas flow rate was 40 ml/min. The relative retention time of lignocaine to diphenhydramine was 1.4.

Drug half-life ($t_{1/2}$) was estimated from the terminal portion of the plasma curves by least squares regression analysis. The data from 60 to 240 minutes

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was used (45 to 240 minutes for case 8). The area under the plasma concentration/time curve was estimated using the trapezoidal rule, and drug clearance (dose/area) calculated, assuming that all the drug from the intramuscular injection site had been absorbed and therefore that the total systemic dose was 400 mg. The volume of distribution (Vd) was derived from the equation:

$$\text{Clearance} = \text{Vd} \cdot \beta, \text{ where } \beta = \frac{0.693}{t_{1/2}}.$$

Results

No patient developed symptomatic or haemodynamic side effects during the 4-hour period of observation. One patient (case 3) required further lignocaine for recurrent arrhythmia soon after the 4-hour period was over.

The Table and Figure summarise plasma lignocaine concentrations found in the patients. In only one patient did the plasma level fall below 6.4 µmol/l (1.5 µg/ml) in the first 2 hours. At 4 hours, only 4 patients had plasma levels above 6.4 µmol/l (1.5 µg/ml).

The mean drug half-life was 136.2 ± 29.3 minutes with a mean lignocaine clearance of 507 ml/min and volume of distribution of 82 litres. The range of values are shown in the Table.

Discussion

In myocardial infarction the commonest cause of death is ventricular arrhythmia occurring in the early phase of the attack (Pantridge and Geddes, 1967). The generally accepted first line drug to counter this is lignocaine and there is some clinical evidence that its early use may lower mortality (Morgensen, 1970; Valentine *et al.*, 1974).

The usual lignocaine regimen is an intravenous

Fig. Mean plasma lignocaine concentrations after the administration of lignocaine 100 mg intravenously at -3 minutes and 300 mg intramuscularly at time 0. Results are mean of 10 patients $\pm$ SEM.

bolus of 1 to 2 mg/kg, followed by constant infusion of 1 to 4 mg/min. Aps *et al.* (1976) have emphasised that this is associated with a period of about 2 hours when the plasma concentration is subtherapeutic and have recommended a more complex regimen involving different and reducing rates of infusion. We have found that meticulous control of intravenous infusion flow rates is very difficult during travel in an ambulance and an alternative seemed desirable. The combination of an intravenous bolus and intramuscular injection was a possible answer, and we were pleased to find that in all our patients therapeutic levels were maintained long enough to allow transport from home to hospital. The mean plasma concentrations in the first two hours of treatment were similar to those re-

Table Plasma lignocaine concentrations and pharmacokinetic measurements after intravenous/intramuscular lignocaine

	Plasma lignocaine concentration ($\mu\text{mol/l}$)													$t_{\frac{1}{2}}$ (min)	β (min^{-1})	Clearance (ml/min)	Vd (l)
	-2 (min)	3	5	10	20	30	45	60	90	120	150	180	240 (min)				
1	29.0	17.5	18.8	22.2	17.9	22.6	17.5	21.8	18.3	15.8	16.2	10.7	6.8	114.5	0.0062	669	108
2	11.5	16.6	10.2	17.9	20.1	18.3	15.8	17.9	19.2	11.9	7.3	4.3	4.3	71.7	0.0096	540	56
3	25.2	—	26.5	23.9	22.6	16.2	12.8	16.6	11.9	9.4	6.8	5.5	3.8	86.0	0.008	553	69
4	46.5	—	19.2	—	25.6	16.6	23.0	22.2	13.7	—	10.2	6.4	5.1	88.5	0.0078	440	56
5	29.0	13.2	18.3	15.8	19.2	14.9	12.8	11.9	15.8	14.1	11.9	11.9	8.5	177.1	0.0039	511	80
6	19.2	42.7	—	—	40.5	32.9	27.3	23.0	17.1	14.5	16.6	10.7	10.7	177.1	0.0039	334	60
7	5.5	16.6	13.7	13.2	24.3	23.0	17.9	18.8	15.8	11.9	5.5	5.1	4.3	75.3	0.0092	537	58
8	47.8	12.8	21.8	25.3	20.1	24.7	11.9	—	0.8	7.3	5.5	5.1	—	103.8	0.0066	591	90
9	4.3	18.8	25.6	18.8	15.4	11.1	12.8	7.7	6.0	5.1	3.0	2.6	2.1	91.2	0.0075	733	98
10	2.1	9.8	13.7	12.8	13.2	11.5	13.2	11.5	9.4	9.0	9.8	8.5	7.7	376.3	0.0018	257	142
Mean	22.0	18.5	18.6	18.7	21.9	19.2	16.5	16.8	13.7	11.0	9.3	7.1	5.9	136.2	0.0064	507	82
SEM	5.2	3.6	1.8	1.7	2.4	2.1	1.6	1.8	1.4	1.2	1.4	1.0	0.9	29.3	0.0008	51	9

Conversion: SI to traditional units—lignocaine: 1 µmol/l $\approx$ 0.23 µg/ml.

ported by Aps *et al.* (1976) using his more complicated regimen. Most lethal arrhythmias occur in the first few hours after the onset of myocardial infarction, so that in many patients no further anti-arrhythmic drug may be needed after receiving the combined intravenous/intramuscular lignocaine. However, the main practical advantage of the combination is that it ensures adequate plasma concentration in the early vulnerable phase while the patient is being transported to hospital, whether by specially equipped ambulance or not.

We cannot say if the doses we have used would be appropriate in patients with severe shock or heart failure who may handle the drug differently, but these complications rarely occur during the very early phase of the attack. Certainly, the estimates of half-life, clearance, and volume of distribution of lignocaine obtained in this present study appear to lie somewhere between those previously found after constant intravenous infusion in normal volunteers (Boyes *et al.*, 1971) and in patients after myocardial infarction (Prescott and Nimmo, 1971).

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