Blood levels of lignocaine after intramuscular administration to patients with proven or suspected acute myocardial infarction

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Lignocaine was given intramuscularly to 31 patients admitted to a coronary care unit with proven or suspected acute myocardial infarction. Seven were given 200 mg as 5 ml 4 per cent solution in the gluteal muscle. Seven received 200 mg as 5 ml 4 per cent and 7 received 200 mg as 2 ml 10 per cent solution in the lateral vastus muscle. Ten patients were given 300 mg 10 per cent solution in the same muscle. Blood levels of lignocaine were studied at different times from 3 to 180 minutes after the injection. The absorption from the gluteus muscle was poorer than from the lateral vastus muscle. An injection of 200 mg lignocaine, though it gave reasonable mean blood levels for some time, was considered insufficient because of the large scatter with several patients below acceptable range (1.2 µg/ml). When using 300 mg 10 per cent solution in the lateral vastus muscle adequate blood levels were reached from between 10 to 15 minutes after the injection up to about 90 minutes. All blood levels were well below the toxic range. Comparisons with results from other studies of intramuscular lignocaine mainly concerning patients without acute myocardial infarction have been made. The possible role of intramuscular lignocaine as a protection against ventricular arrhythmias in the prehospital period of acute myocardial infarction is discussed.

Acute myocardial infarction is associated with death mainly due to arrhythmias, cardiogenic shock, and left heart failure. The commonest of these is ventricular tachyarrhythmias. It has been possible to treat life-threatening arrhythmias and thus to lower the mortality. This has been the major advantage of the coronary care unit, and nowadays very few patients die in primary ventricular arrhythmias while in the unit (Lown, Klein, and Hershberg, 1969). The prehospital mortality is, however, still a large problem (Lown and Wolf, 1971) and different approaches have been suggested to decrease it. One is the use of mobile coronary care units with the intention to reach the patient as soon as possible after onset of symptoms (World Health Organization, 1970). Another approach is arrhythmia prophylaxis during the transport to hospital through the early administration of a drug. This drug could be supplied by a doctor, ambulance personnel, or the patient himself (Scott *et al.*, 1968; Levine, 1969; Lown and Wolf, 1971). Lignocaine has proved to be useful in the treatment of ven-

tricular arrhythmias associated with acute myocardial infarction. The route of administration has been intravenous, usually a bolus injection followed by an intravenous infusion (Bigger and Heissenbuttel, 1969). Interest has been focused on a more practical route to achieve effective therapeutic blood levels for a reasonable time. In the present study varying concentrations and dosages of lignocaine were injected intramuscularly at two different sites in patients with proven or suspected acute myocardial infarction admitted to our coronary care unit.

Materials and methods

Patients admitted to the unit with proven or suspected acute myocardial infarction were included in the study after exclusion of those with the following manifestations: cardiogenic shock, pulmonary oedema, sinus bradycardia (heart rate below 50/minute), atrioventricular block of second or third degree, and ventricular arrhythmias needing treatment. Altogether 31 patients, 7 of whom were female, aged between 42 and 70 years (mean age 60) comprised the material for this study. Of the patients, 21 had proven acute myocardial infarction, 7 had coronary heart disease with severe angina pectoris, 1 had acute

Received 7 February 1972.

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pericarditis, and in 2 the cause of chest pain could not be ascertained. The time interval between the onset of symptoms and start of the trial could be confirmed for 26 patients and varied from 3 to 36 hours (mean 19 hours). Routine treatment as practised in the coronary care unit was given to all (Henning and Holmberg, 1971). The patients were informed about the nature of the investigation and gave their consent. No antiarrhythmic drugs were given except lignocaine (Xylocain¹) and this was given as an intramuscular injection. Seven of the patients were given 200 mg as 5 ml 4 per cent solution in the gluteal muscle. The remaining 24 patients had the injection in the lateral vastus muscle and, of those, 7 received 200 mg as 5 ml 4 per cent solution, 7 200 mg as 2 ml 10 per cent solution, and 10 patients 300 mg as 3 ml 10 per cent solution. The electrocardiogram was continuously monitored and recorded during one minute before and every fifteenth minute for 3 hours after lignocaine injection. Heart rate was determined from the electrocardiographic recordings and brachial artery pressure measured by sphygmomanometer before and every fifteenth minute after the injection. A polyethylene catheter (PE 160) was introduced percutaneously from a brachial vein with the tip positioned in the superior caval vein. Mepivacaine 0.5 per cent (Carbocaine²) which does not interfere with lignocaine determinations was used as a local anaesthetic. Blood samples were taken before and at 3, 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 minutes after injection of lignocaine. In the final series (300 mg) samples at 3, 150, and

180 minutes were omitted and in the gluteus series no samples were taken at 5 minutes. The blood was frozen at -16°C and sent to the ASTRA laboratories, Södertälje, Sweden, for lignocaine determinations according to Svinhufvud, Örtengren, and Jacobsson (1965) with some modifications: to 2.0 ml of the blood samples 0.5 ml 10 per cent sodium carbonate solution and 1.0 ml carbon disulphide were added. The mixture was shaken mechanically for 10 minutes and centrifuged. Four µl of the carbon disulphide phase was injected on the column (2% XF 1112, nitrile-silicone on Chromosorb G, 80-100 mesh) in a Perkin-Elmer chromatograph equipped with a flame ionization detector. The chromatographic conditions were: injection port temperature 250°C and carrier gas flow 40 ml/minute (B. Örtengren, 1971, personal communication). The lignocaine levels were expressed as lignocaine HCl (anhydrous) µg/ml of whole blood. Altogether 8 blood samples were lost during the handling and they can be identified in the Table as well as in the Figures. Blood samples were taken for determination of SGOT, SGPT, LDH-isoenzymes, serum-bilirubin, and alkaline phosphatase, as well as arterial blood for pH and gas analyses.

Results

The 4 groups of patients receiving different amounts and concentrations of lignocaine did not differ significantly concerning age, weight, length, ratio between proven and suspected acute myocardial infarction, time interval between onset of symptoms and start of study,

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TABLE Blood levels after intramuscular lignocaine injections

			Blood lignocaine (HCl µg/ml)										
			Time after injection (min)										
			3	5	10	15	30	45	60	90	120	150	180
Site of injection	Gluteus	Mean	0.54	—	1.90*	1.46	1.34†	1.08	1.04	0.72	0.58	0.46	0.40
Amount of lignocaine	200 mg	SD	0.48	—	1.01	0.81	0.75	0.37	0.33	0.08	0.15	0.16	0.13
Concentration of lignocaine	4%	SEM	0.18	—	0.51	0.31	0.28	0.14	0.12	0.03	0.06	0.06	0.05
No. of patients	7												
Site of injection	Vastus lateral	Mean	0.24	0.80‡	1.55‡	1.61	1.87	1.69	1.49	1.21	0.96	0.70	0.43
Amount of lignocaine	200 mg	SD	0.08	0.26	0.99	0.74	0.60	0.86	0.41	0.39	0.41	0.12	0.33
Concentration of lignocaine	4%	SEM	0.03	0.10	0.49	0.28	0.23	0.33	0.15	0.15	0.15	0.04	0.12
No. of patients	7												
Site of injection	Vastus lateral	Mean	0.17	0.59	1.11	1.45	1.57	1.29	1.23	0.80	0.67	0.50	0.39
Amount of lignocaine	200 mg	SD	0.15	0.31	0.75	0.77	0.54	0.48	0.39	0.37	0.24	0.21	0.20
Concentration of lignocaine	10%	SEM	0.06	0.12	0.28	0.29	0.21	0.18	0.15	0.14	0.09	0.08	0.08
No. of patients	7												
Site of injection	Vastus lateral	Mean	—	0.56	1.09	1.42	1.71	1.73	1.58	1.25	1.07	—	—
Amount of lignocaine	300 mg	SD	—	0.40	0.35	0.48	0.37	0.29	0.15	0.21	0.30	—	—
Concentration of lignocaine	10%	SEM	—	0.13	0.11	0.15	0.12	0.09	0.05	0.07	0.09	—	—
No. of patients	10												

SD, standard deviation; SEM, standard error of the mean.

* Four samples.

† Six samples.

‡ Five samples.

FIG. 1 Blood level of lignocaine HCl (anhydrous) after 200 mg 4 per cent solution in gluteus muscle. In this and the other Figures solid circles represent individual levels, open squares mean level of the group, and dashed line the lowest effective plasma level according to Gianelly et al. (1967) and Harrison et al. (1970).

size of the infarction as judged from SGOT maximum, and degree of haemodynamic disturbance as judged by clinical examination and noninvasive techniques. Blood levels of lignocaine are presented in Fig. 1-4 and the Table. The Figures present individual values of all patients and the group means, and the Table shows mean values, standard deviation, and standard error of the mean. Hepatic function as judged from laboratory data was normal in all patients except 3 who showed

FIG. 2 Blood level of lignocaine HCl (anhydrous) after 200 mg 4 per cent solution in lateral vastus muscle.

FIG. 3 Blood level of lignocaine HCl (anhydrous) after 200 mg 10 per cent solution in lateral vastus muscle.

minor alterations. These 3 patients had lignocaine levels corresponding well to the other members of their groups. There was no correlation between body weight and peak lignocaine blood level. No difference could be found between mean peak lignocaine levels in patients with proven acute myocardial infarction (mean 1.8, SD 0.63 µg/ml) and patients without infarction (mean 1.8, SD 0.65 µg/ml). When comparing the lignocaine levels after injecting 200 mg 4 per cent solution in the gluteus and the lateral vastus muscle the gluteal injection resulted in significantly lower values at 60 ($P < 0.05$), 90 ($P < 0.02$), and 150

FIG. 4 Blood level of lignocaine HCl (anhydrous) after 300 mg 10 per cent solution in lateral vastus muscle.

minutes ($P < 0.01$). There was no significant difference in lignocaine levels between the 10 per cent and 4 per cent solution when injecting 200 mg into the vastus muscle.

No side effects were observed after the lignocaine injections. No patient spontaneously or on questioning complained of dizziness, vertigo, or paresthesias. None of the patients showed any sign of local irritation or experienced discomfort at the site of injection. No significant changes in heart rate or blood pressure were observed. The electrocardiographic recordings showed no change in PQ interval or QRS configuration. During the continuous electrocardiographic monitoring none of the patients showed ventricular arrhythmias needing therapy.

Discussion

About 60 per cent of the deaths due to acute myocardial infarction occur soon after the onset of symptoms and before the patients have time to reach hospital (McNeilly and Pemberton, 1968; Fodor, 1969; Fulton, Julian, and Oliver, 1969; Kuller, 1969). The dominant cause of this high death rate in the very early phase of acute myocardial infarction is ventricular fibrillation (Pantridge and Geddes, 1967; Scott, 1970). One way of approaching the challenge of prehospital mortality due to acute myocardial infarction is the early administration of an antiarrhythmic agent.

In most coronary care units lignocaine has become the drug of choice for treating ventricular arrhythmias (Jewitt, Kishon, and Thomas, 1968; Lown and Vassaux, 1968; Spracklen *et al.*, 1968). A lignocaine plasma level of 1.2 µg/ml has been considered to be the lowest effective therapeutic level (Gianelly *et al.*, 1967; Harrison, Stenson, and Constantino, 1970) usually reached by infusion rates above 1.5–2.0 mg/minute intravenously (Gianelly *et al.*, 1967; Jewitt *et al.*, 1968). It has also been shown that lignocaine in the same dosages has a prophylactic antiarrhythmic effect when given to patients with acute myocardial infarction in coronary care units (Mogensen, 1970; Pitt, Lipp, and Anderson, 1971). The intravenous administration of lignocaine is not convenient outside hospital, requiring trained personnel, and, with a bolus injection, resulting in only a transient effect (Boyes *et al.*, 1971; Hayes, 1971). Oral and rectal lignocaine is not feasible due to the very low absorption (Boyes *et al.*, 1971; L. Ehn, 1971, personal communication). Intramuscular injection thus seems to be the most practical way to give this drug outside hospital.

Some studies indicate (Scott *et al.*, 1968; Bellet *et al.*, 1971; Meyer and Zelechowski, 1971) that 200 to 300 mg intramuscular lignocaine is sufficient to give plasma levels above 1.2 µg/ml from about 15 up to about 90 minutes. Most of these patients did not have acute myocardial infarction. The circulatory state of patients suffering an acute myocardial infarction might, however, influence the absorption and redistribution of intramuscular lignocaine.

In the present study 200 mg 4 per cent lignocaine in the gluteus and lateral vastus muscle gave satisfactory mean blood levels for some time as well as 200 mg 10 per cent lignocaine in the vastus. However, the blood levels for several patients never reached 1.2 µg/ml (Fig. 1, 2, and 3). After 300 mg 10 per cent lignocaine the mean level of lignocaine reached 1.2 µg/ml between 10 to 15 minutes after the injection and was maintained up to about 120 minutes. No patient showed toxic levels which are above 6 µg/ml according to Gianelly *et al.* (1967) and most values were above or at the 1.2 µg/ml level from 15 to 90 minutes (Fig. 4). The values achieved in the study are lower than those reported by Scott *et al.* (1968). Our analyses are done on whole blood, which means that transformed to plasma levels the values will be higher. However, as the lignocaine concentration ratio in plasma/erythrocytes was found to be 1.34 by Eriksson (1966) this factor cannot be the single explanation. The present results correspond more with those of Bellet *et al.* (1971) and Meyer and Zelechowski (1971). Thus it seems that there are not very large differences in the absorption of lignocaine between patients with suspected or proven acute myocardial infarction in a relatively good circulatory condition and healthy volunteers or patients with other types of cardiac disease. This is further supported by our observation of no differences in peak lignocaine levels in patients with proven and not proven acute myocardial infarction.

Cohen *et al.* (1970) stated that more diluted lignocaine solutions were better absorbed than a 10 per cent solution. When injecting intramuscularly in dogs, R. N. Boyes (1970, personal communication) found that different concentrations (2–64%) did not influence the blood levels of lignocaine. The same result was reached by Jebson (1971) when using 2 and 10 per cent solutions in healthy humans. In addition, in the present series there was no difference between the 4 and 10 per cent solution. Thus, the 10 per cent solution is to be preferred to lower concentrations because the amount injected is conveniently small.

The vastus lateralis muscle is recommended as the site of injection because the absorption from the gluteus muscle was poorer, thereby confirming the observation made by Cohen *et al.* (1970). This may be due to slow muscle circulation as the patients were lying on their backs. The relatively high mean blood level 10 minutes after the gluteal injection (Fig. 1; Table) is probably influenced by a high level reached in one patient. Though more rapid and higher peak levels have been reported after injections into the deltoid muscle (Cohen *et al.*, 1970; Meyer and Zelechowski, 1971), we do not think it is a convenient and practical place for injection especially if in the future autoinjections or injections are to be given by medically unqualified persons. As blood levels of more than 1.2 µg/ml were reached within 15 minutes after injection even in the lateral vastus muscle, the absorption rate appears to be satisfactory for prophylactic purposes.

So far only the prophylactic use of intramuscular lignocaine has been discussed. There may, however, be other advantages with this route. When using intravenous infusions given as drips the control of drip rate is rather time-consuming. Intravenous infusion of lignocaine has also been found to increase the incidence of thrombophlebitis (Nordell *et al.*, 1971). Thus, the intramuscular use of lignocaine may be an easily performed and safe mode of maintenance therapy even in coronary care units.

In conclusion, we think that 300 mg lignocaine of a 10 per cent solution given into the lateral vastus muscle should be investigated for its clinical effect.

The authors wish to thank Dr. Börje Örtengren, ASTRA Laboratories, Södertälje, Sweden, who performed the lignocaine determinations.

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