Prophylaxis of primary ventricular fibrillation in acute myocardial infarction

The case against lignocaine

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Ventricular fibrillation is the most important arrhythmic complication of acute myocardial infarction and accounts for the majority of deaths in the 15-30% of patients with infarction who die in the first hour after the onset of symptoms.¹ In the coronary care unit ventricular fibrillation occurs in 3-10% of patients with myocardial infarction² and would be seen more frequently if the time delay from the onset of symptoms to admission to the coronary care unit were reduced since the incidence of primary ventricular fibrillation falls almost exponentially after the first few hours of infarction.³⁻⁵

The prevention of primary ventricular fibrillation may be viewed as an important goal in the coronary care unit, particularly if the time delay to hospital admission can be reduced. The most widely studied agent in the prophylaxis of this arrhythmia has been lignocaine, but despite numerous reports considerable controversy still surrounds its use. There are two fundamental questions: (a) Is lignocaine effective at preventing primary ventricular fibrillation or its recurrence? (b) Should it be used routinely for these purposes? Although several recent editorials^{6,7} and reviews^{2,8,9} have recommended the use of routine prophylactic lignocaine, its current role in the coronary care unit has evolved in part through emotive argument not always scientifically based. A critical review of the subject appears to be warranted.

Background to the use of lignocaine in the coronary care unit

Early studies with lignocaine showed considerable

efficacy in the treatment of a variety of ventricular arrhythmias with an apparently favourable therapeutic to toxic ratio compared with other antiarrhythmic agents available at the time.¹⁰ Lignocaine found widespread favour in the coronary care unit after a report by Lown *et al*, in which no episodes of ventricular fibrillation occurred in 130 consecutive patients with acute myocardial infarction who received lignocaine for certain patterns of ventricular ectopic activity, termed "warning" arrhythmias.¹¹ Although these observations were uncontrolled and only 61% of the patients were admitted within 12 hours of the onset of symptoms, the concept of warning arrhythmias and their suppression with lignocaine became widely accepted.

Prediction of ventricular fibrillation

Several clinical indices such as infarct site and size, hypokalaemia on hospital admission, and the time from onset of symptoms of myocardial infarction have been related to the incidence of primary ventricular fibrillation, but none of these is sufficiently sensitive or specific to be useful predictive indices. Warning arrhythmias were considered initially to be highly sensitive and specific in predicting ventricular fibrillation but subsequently came under considerable attack. Several studies¹²⁻¹⁴ showed that without computerised monitoring facilities less than 50% of warning extrasystoles are detected by coronary care unit staff, considerably reducing any predictive potential. Furthermore, several workers^{3,15,16} found that these ectopic forms occur in only half of the patients who develop primary ventricular fibrillation and with equal frequency in those who do not. Warning arrhythmias, therefore, cannot be considered to be predictive of subsequent primary ventricular fibrillation.

There is at present no satisfactory method of predicting primary ventricular fibrillation in patients

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Accepted for publication 5 April 1984

Table 1 Percentage (No/total No in study) incidence of failed resuscitation from primary ventricular fibrillation

Study	Deaths (%)
Wyman and Hammersmith (1974) ¹⁹	8 (1/12)
Dhurandhar <i>et al</i> (1971) ²⁰	25 (5/20)
Pentecost and Mayne (1968) ²¹	10 (1/10)
Lawrie <i>et al</i> (1968) ⁴	8 (2/24)
Bennett <i>et al</i> (1970) ²²	22 (5/23)
El-Sherif <i>et al</i> (1976) ¹⁶	0 (0/20)
Darby <i>et al</i> (1972) ²³	29 (2/7)
Lie <i>et al</i> (1974) ⁵	0 (0/18)
Lie <i>et al</i> (1974) ²⁴	11 (1/9)
Carruth and Silverman (1982) ²⁵	0 (0/30)
Campbell <i>et al</i> (1983) ²⁶	6 (1/17)
Campbell <i>et al</i> (1981) ³	0 (0/17)
Total	8.7 (18/207)

with acute infarction. Consequently, any agent thought to be effective in preventing primary ventricular fibrillation would need to be given prophylactically to all patients with suspected myocardial infarction.

Is prophylaxis of primary ventricular fibrillation needed?

The availability of rapid defibrillation by trained coronary care unit staff is one of the most important advances in the management of myocardial infarction. As selective prophylaxis of primary ventricular fibrillation is not possible without specific predictive indices, the alternatives are non-selective administration of a prophylactic agent or the expectant approach, with aggressive management of ventricular fibrillation only when it occurs.

Although primary ventricular fibrillation in the early hospital phase of myocardial infarction does not appear to influence the long term prognosis,^{5 17 18} it may not be as benign in its effect on hospital mortality. Pooled results from several studies have shown a mean hospital mortality of 19% in patients with primary ventricular fibrillation compared with 8% in patients without ventricular fibrillation.⁸ Although few of these studies compared matched populations, the results do suggest that the short term mortality may be adversely affected. Furthermore, defibrillation itself is not always successful in these patients who have, by definition, otherwise uncomplicated infarction. In 12 reports reviewed by us (Table 1) unsuccessful defibrillation from primary ventricular fibrillation ranged from 0% to 29% of patients with a pooled failure rate of 8.7%.

These data suggest that successful prophylaxis of primary ventricular fibrillation may have a favourable influence on the overall early mortality from myocardial infarction, particularly in patients seen in the first few hours after the onset of symptoms when the relative incidence of primary ventricular fibrillation is greater.

Is lignocaine effective in preventing primary ventricular fibrillation?

CLINICAL TRIALS

Even before the concept of warning arrhythmias fell into disrepute, clinical trials of routine lignocaine prophylaxis of primary ventricular fibrillation were started. These followed the publication of observational data from one coronary care unit⁴ in which six of 20 patients with primary ventricular fibrillation in a series of 600 patients with myocardial infarction had an episode of ventricular fibrillation in the emergency room or in transit to the coronary care unit, before assessment for the presence of warning extrasystoles was possible.

Over the subsequent decade several centres examined the value of routine lignocaine prophylaxis for preventing primary ventricular fibrillation in the setting of a randomised controlled clinical trial. To date, 16 such trials have been published in the English language literature. Their results have been presented in detail in previous reviews,^{2 8 9} and the overall results are summarised in Table 2, which includes additional data from one study²⁷ updated since publication (1984, personal communication, K O'Brien). Unfortunately, defects in design and methodology in many of these trials make their results extremely difficult to interpret; some of these problems are also outlined in Table 2. Only three of the trials showed statistically significant benefit from lignocaine.^{24 36 39} Five examined the short term (1–4 hours) benefit of a single intramuscular injection of lignocaine (Table 2), although only two were actually conducted in a pre-coronary care setting.^{36 39} One of these³⁹ has suggested benefit for lignocaine, but the final results and statistical analysis are not yet available, and the overall incidence of ventricular fibrillation has been surprisingly low.

Of the trials which used a continuous intravenous infusion of lignocaine for at least 24 hours, only two^{24 27} satisfy the criteria which have been proposed for an acceptable clinical trial of antiarrhythmic prophylaxis.^{9 40} Lie *et al* studied 212 patients and reported a significant ($p < 0.002$) reduction in the incidence of primary ventricular fibrillation but with no influence on total mortality.²⁴ All patients were enrolled within six hours of the onset of symptoms, and those with any degree of left ventricular failure were excluded. In a report presenting observational data on ventricular fibrillation by the same authors in the same year,⁵ however, the incidence of primary ventricular fibrillation was identical during sequential periods with and without the use of lignocaine for warning arrhythmias, and three of the patients who developed primary ventricular fibrillation in the first

Table 2 Clinical trials of prophylactic lignocaine

Study	Study period (h)	Dosage*		Double blind	LVF/shock excluded	Crossover from C to L	Plasma concentrations measured (mg/l)	Incidence of PVF	
		Loading (mg) and route	Infusion (mg/min)					Control group	Lignocaine group
Lie <i>et al</i> (1974) ²⁴	48	100 iv	3	Yes	Yes	No	1.5-6.4 at 6 h	11/105	0/107
O'Brien <i>et al</i> (1973) ²⁷	48	75 iv	2.5	Yes	Yes	No	2.4-7.4 at PVF	4/136	4/115†
Mogensen (1970) ²⁸	24	75 iv	2	No	No	Yes	1.0-5.6 at 1 h	1/37	0/42
Bennett <i>et al</i> (1970) ²²	48	60 iv	1 or 0.5	No	Yes	Yes	No	7/125 or 7/125	5/131 or 11/118
Bleifeld <i>et al</i> (1973) ²⁹	120	100 iv	14-42 µg/kg	No	Yes	No	No	2/42	0/41
Church and Biern (1972) ³⁰	48	50-75 iv	2	Single blind	Yes	?	No	3/44	4/42
Darby <i>et al</i> (1972) ²³	48	200 im	2	No	Yes	Yes	No	3/100	4/103
Pitt <i>et al</i> (1971) ³¹	48	75-100 iv (in 50%)	2.5	No	Yes	Yes	No	0/59	0/54‡
Kostuk and Beanlands (1969) ³²	48	—	1	No	Yes	Yes	No	0/31	0/34
Baker <i>et al</i> (1971) ³³	48	—	1.5	Yes	No	Yes	No	0/23	0/21
Chopra <i>et al</i> (1971) ³⁴	24	50 iv (+100)§	1-2	Yes	Yes	Yes	No	0/43	1/39
Lie <i>et al</i> (1978) ³⁵	1	300 im	—	Yes	Yes	No	1.4-1.7 at 1 h	4/153	6/147
Valentine <i>et al</i> (1974) ³⁶	2	300 im	—	Yes	Yes	No	No	8/113	3/156
Singh and Kocot (1976) ³⁷	3	4.5/kg im	—	Yes	Yes	No	1.4 at 1 h	0/27	0/23
Sandler <i>et al</i> (1976) ³⁸	4	200 or 300 im	—	Yes	Yes	No	Peak 1.8 or 1.6	0/46 or 0/44	0/43 or 0/48
Koster and Dunning (1983) ³⁹	1	400 im	—	Yes	Yes	No	1.9 at 1 h	16/906	6/981

LVF, left ventricular failure; C, control; L, lignocaine; PVF, primary ventricular fibrillation; im, intramuscular; iv, intravenous.

*Adequate dose = >75 mg loading and >1.5 mg/min infusion.

†Incidence of all VF in the study population 9/214 (L) and 9/218 (C).

‡Incidence of PVF in overall study population 0/114 (L) and 0/108 (C).

§Only patients with ventricular extrasystoles studied; a further 100 mg lignocaine given if first 50 mg ineffective.

||Sudden deaths rather than PVF; randomisation skewed.

period were receiving lignocaine at the time of the onset of the arrhythmia.

O'Brien *et al* studied over 400 patients and reported no differences between treated or control groups in the incidence of either primary or secondary ventricular fibrillation²⁷; data from patients without pulmonary oedema or shock are available (Table 2; 1984, personal communication, K O'Brien). The incidence of primary ventricular fibrillation in the control population was only 2.9% compared with 10.5% in the study by Lie *et al*.²⁴ Although 50% of patients were entered within four hours of the onset of symptoms, very late enrolment of some patients resulted in a skewed mean time to entry of nine hours; this could have contributed to the lower incidence of primary ventricular fibrillation.

The plasma concentrations of lignocaine at the time of ventricular fibrillation in this study varied from 2.4-7.4 mg/l.²⁷ These figures lie well within or above the range of concentrations which have been found to suppress ventricular extrasystoles and ventricular tachycardia in the first 48 hours after myocardial infarction.⁴¹ While it is not known if these "therapeutic levels"^{10 42} are applicable to ventricular fibrillation in man, concentrations above the upper limit of the

therapeutic range (5.0 mg/l^{10 41}) are more likely to be associated with signs of toxicity.^{10 41}

Thus the two best designed trials of prophylactic lignocaine have reached opposing conclusions regarding its efficacy. Despite the lack of corroborative evidence from controlled studies, however, the results of the trial by Lie *et al*²⁴ have been pivotal in the recommendations put forward in several reviews^{2 8 9} and editorials^{6 7} in favour of the routine use of lignocaine in the coronary care unit. In their review, DeSilva *et al* pooled data from six studies which met predetermined criteria concerning patient number, dose, and route of lignocaine administration.⁹ The apparent benefit found for lignocaine in their pooled data is, however, entirely due to the results of Lie *et al*²⁴; if this study is excluded the number of patients with primary ventricular fibrillation in the treated and control groups of the other five studies are almost identical.

ADDITIONAL DATA

The efficacy of lignocaine in the prevention of primary ventricular fibrillation has not been substantiated by controlled clinical trials. Some additional data on prophylactic lignocaine are available from observa-

tional and experimental studies.

Several coronary care units have recently presented observational data on the incidence of primary ventricular fibrillation in relation to the use of prophylactic lignocaine. Wyman and Hammersmith reported a reduction in the incidence of primary ventricular fibrillation to 0.3% over a period during which routine lignocaine prophylaxis for patients with suspected myocardial infarction was introduced.¹⁹ Pentecost *et al*, however, observed no increase in the incidence of primary ventricular fibrillation in their coronary care unit when the use of prophylactic lignocaine was phased out.⁴³ Carruth and Silverman²⁵ reported a 2.8% incidence in primary ventricular fibrillation in their coronary care unit, where prophylactic lignocaine is not used, and suggested that its use would have been of no potential benefit in 96.8% of their patients. Comparisons between these reports are difficult because of possible differences in the patient populations studied. The conclusions reached are conflicting and could be used to support arguments both for and against the use of prophylactic lignocaine.

Clinical evidence has been presented suggesting that lignocaine may be less effective in the treatment of ventricular arrhythmias in the very early phase of myocardial infarction even in the presence of high blood concentrations,^{44,45} although this has not been confirmed by other workers.⁴⁶ Data from animal studies have, however, also questioned the efficacy of lignocaine very early after infarction. In a study using three antiarrhythmic drugs including lignocaine in 150 dogs, 45 of 57 pooled drug failures occurred within the first hour of infarction.⁴⁷ Gamble and Cohn have presented experimental evidence which suggests that the effects of lignocaine in the early phase of myocardial infarction are critically dose dependent.⁴⁸ Re-entrant arrhythmias predominate in this early phase and may be exacerbated in the experimental animal by low plasma concentrations of lignocaine although abolished by higher concentrations. If this potential arrhythmogenesis is confirmed in man it may mitigate against the use of prophylactic intramuscular lignocaine since the plasma concentrations in this setting rise slowly.

Further clinical work has suggested that R' on T ventricular extrasystoles are more resistant to lignocaine than other ectopic forms.³⁴ The exact role of the R' on T ectopic form in the genesis of primary ventricular fibrillation is still uncertain, but Campbell *et al* found that its incidence closely paralleled that of primary ventricular fibrillation in the first 12 hours of myocardial infarction,³ and in 16 of 17 patients it was the mode of initiation of ventricular fibrillation.

These data from observational and experimental studies together with the results of controlled trials

have not proved the efficacy of lignocaine in the prevention of primary ventricular fibrillation, which must therefore remain in doubt.

Is lignocaine effective in preventing recurrence of primary ventricular fibrillation?

Despite the doubt about the efficacy of lignocaine in preventing primary ventricular fibrillation it is still usually given for 12 to 24 hours after resuscitation from an episode of ventricular fibrillation, even in coronary care units where it is not routinely given on admission to patients with suspected myocardial infarction. Nevertheless, if the drug is indeed ineffective in preventing the initial episode of primary ventricular fibrillation, why should it prevent a recurrence, which most often occurs soon after the initial event?

Surprisingly few data are available on the prophylaxis of recurrence of primary ventricular fibrillation, which has been reported to vary from 8–67% (Table 3). In all of these studies many of the patients were receiving antiarrhythmic treatment at the time of recurrence, and in many cases this was with lignocaine. Lie *et al* reported recurrences in 12 of 18 patients with primary ventricular fibrillation in their coronary care unit,⁵ where the use of lignocaine after the initial episode is routine practice. In six of these patients, multiple recurrences of ventricular fibrillation were resistant to several antiarrhythmic agents and could be managed only by repeated defibrillation.

To our knowledge, no data on the true natural history of recurrence of primary ventricular fibrillation in myocardial infarction have been published to date, and it is therefore difficult to claim efficacy for lignocaine in this setting. Further research is required, although this may well be hampered by difficulties in obtaining the approval of ethics committees.

Problems of lignocaine prophylaxis

Despite doubts about its efficacy the routine use of lignocaine in preventing primary ventricular fibrilla-

Table 3 Percentage (No/total No in study) of recurrences of primary ventricular fibrillation

Study	Recurrences (%)
Pentecost and Mayne (1968) ²¹	30 (3/10)
Lawrie <i>et al</i> (1968) ⁴	8 (2/24)
Dhurandhar <i>et al</i> (1971) ²⁰	20 (4/20)
Lie <i>et al</i> (1974) ⁵	67 (12/18)
El-Sherif <i>et al</i> (1976) ¹⁶	30 (6/20)
Lie <i>et al</i> (1977) ⁴⁹	22 (8/36)
Logan <i>et al</i> (1981) ⁵⁰	16 (12/73)
Logan <i>et al</i> (1981) ⁵¹	20 (19/94)

tion based on the possibility of hitherto unconfirmed efficacy would seem reasonable if such a policy could be implemented easily and with absolute safety. In a series of 950 patients with myocardial infarction receiving lignocaine according to an individualised treatment plan, Wyman and Hammersmith reported no adverse haemodynamic effects and only minor dose related central nervous system effects, although three patients had convulsions caused by a "runaway" infusion.¹⁹

A much higher incidence of clinically important adverse reactions in the treated groups was, however, found in many of the 16 clinical trials of prophylactic lignocaine. Central nervous system disturbances ranged from 7–39%, and, although these were usually of a mild nature, convulsions and syncope occurred in 2% of treated patients in one study.³¹ Bleifeld *et al* noted a 10% incidence of high grade atrioventricular block in the treated group compared with 5% in the control group.²⁹ In the trial by O'Brien *et al*, 38% of patients reported side effects including eight episodes of syncope²⁷; total deaths were twice as common in the lignocaine group, and two deaths in asystole were attributed to the drug itself.

The risks of lignocaine toxicity are increased in patients with myocardial infarction complicated by heart failure,^{41 42} in whom the dosage must be reduced. Surprisingly high plasma concentrations and elimination half life of lignocaine have, however, been found even in patients with myocardial infarction not complicated by heart failure compared with healthy subjects.⁵² Furthermore, a policy of routine lignocaine prophylaxis would of necessity initially include patients with suspected myocardial infarction, some of whom would subsequently have this diagnosis disproved but still be exposed to the risks of toxicity. One clinical trial has highlighted the frequency of adverse reactions in this subgroup of patients.²⁸

Apart from the concerns regarding the safety of routine lignocaine administration to large numbers of patients, the financial constraints of such a policy have also been emphasised.²⁵ Accurate control of prolonged intravenous drug administration is best achieved with the use of infusion pumps; the numbers required would add substantially to coronary care unit costs as would the required quantity of the drug itself.

Thus considerations of safety and cost in the setting of doubtful efficacy represent a poor foundation on which to base the recommendation of routine lignocaine prophylaxis. At present, such a policy cannot be recommended. Although the efficacy of lignocaine in preventing recurrences of primary ventricular fibrillation must also be considered unproved, the number of patients involved, the risks of toxicity, and the costs are far lower, and until further information

is available the use of lignocaine in this setting remains reasonable.

Alternatives to prophylactic lignocaine

The prophylaxis of primary ventricular fibrillation has been studied using several other antiarrhythmic agents apart from lignocaine. Trials in which reduction of primary ventricular fibrillation was a major endpoint have been conducted using disopyramide,^{53–55} tocainide,²⁶ and metoprolol.⁵⁶ An apparent reduction in the incidence of primary ventricular fibrillation by oral disopyramide in patients with myocardial infarction managed in an open ward⁵³ was not confirmed in two other studies using the same drug,^{54 55} and a recent well designed study of the lignocaine congener tocainide showed no clinically important benefit in the prophylaxis of primary ventricular fibrillation.²⁶ Thus none of the Vaughan-Williams class I antiarrhythmic agents studied to date have been proved effective in preventing primary ventricular fibrillation.

A recent study of the beta adrenergic blocking drug metoprolol, however, reported a significant reduction in the incidence of ventricular fibrillation in the treated group.⁵⁶ Interestingly, this has been only the first study of a class II agent reported to date in which sufficient patient numbers were investigated to allow examination of the effects on ventricular fibrillation as a major endpoint, and confirmation of the findings are awaited.

Nevertheless, it is likely that any currently available antiarrhythmic agent given to large numbers of patients early in acute myocardial infarction would carry an important incidence of adverse reactions, and beta adrenergic blocking drugs are no exception. As routine prophylaxis of primary ventricular fibrillation in the coronary care unit necessarily requires large numbers of patients to be treated in order to potentially benefit only a few, any antiarrhythmic agent which has confirmed clinically important efficacy in preventing primary ventricular fibrillation must have a minimum incidence of adverse reactions before its routine use can be recommended. The potential value of prophylactic antiarrhythmic agents would, however, be considerably accentuated if they could be used selectively. Therefore, the thrust of future research must also be directed towards a further understanding of the mechanisms of primary ventricular fibrillation and its prediction.

We thank Drs RWF Campbell and S Saltissi for reviewing the manuscript.

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