hospitals,[12] and the encouragement of management of such patients in general hospitals without benefit of scanners or neurosurgeons.[13] We believe that the hazards could be greatly reduced by the adoption of fairly simple measures, both technical and organisational, rather than by stopping transfers. Delay could be minimised by prior agreement between primary surgeons and neurosurgeons about the circumstances that will normally justify transfer, and by ensuring that junior staff at both ends know what has been agreed. All staff dealing with head-injured patients will need standardised and simple methods for describing the patient's state, in particular the consciousness level; the Glasgow coma scale has proved useful for this purpose.[14] Ambulance authorities should be told that some of these interhospital transfers demand a high degree of urgency and should be asked how the urgency is to be made clear as individual cases arise. However, a well-defined policy aimed at encouraging earlier transfer, before drastic deterioration has occurred, should minimise the number of patients that have to be rushed desperately to the neurosurgeon.

To reduce the risk of additional insults to the brain during the transfer also calls for prior arrangements. Experienced personnel should be available on rota in any hospital that admits accidents to advise on the management as and when cases are to be transferred. Those going on this rota could include senior doctors and nurses from the intensive care unit, anaesthetists, and accident and emergency consultants. Advice on management cannot be left on notice boards, and junior staff cannot be left unsupervised in the hope that they will instinctively do the right thing when the time comes. Only an experienced person can weigh the risk of delaying transfer until certain protective measures are taken; can decide whether an oropharyngeal, nasopharyngeal, or endotracheal tube would be most appropriate; can consider who should accompany the patient and ensure that the escort has clear instructions about what to do and the equipment with which to do it. One practical problem in dealing with the comatose patient who vomits or has a fit in the ambulance is how to get adequate access to the head to clear the airways by the use of a portable suction machine. I. Mc.A. Ledingham (personal communication) has proposed how a simple adaptation of normal ambulances would enable them to take a hospital trolley; this modification would make lifting unnecessary and allow access to the patient's head from all angles.

All the evidence shows that attention to matters ensuring the rapid and safe transfer of comatose head-injured patients from primary surgical wards to neurosurgical units would significantly reduce the mortality and morbidity from head injury.

We thank the nursing staff of ward 61 for collecting data for this study.

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Occasional Survey

LIGNOCAINE PROPHYLAXIS IN ACUTE MYOCARDIAL INFARCTION: AN EVALUATION OF RANDOMISED TRIALS

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Summary Although lignocaine has been used in coronary care units for almost two decades, its role in preventing ventricular fibrillation (VF) during acute myocardial infarction (MI) is still debated. Of fifteen randomised trials of lignocaine prophylaxis, most showed no apparent benefit. When the data from all fifteen trials were pooled and a summary relative risk estimate calculated, there was a significant benefit of lignocaine treatment in preventing VF. However, the trials had widely differing treatment schedules, modes of drug administration, and doses of lignocaine; to decrease the clinical heterogenity, minimum criteria for adequacy of treatment were established and the data from six trials which fulfilled these requirements were pooled. The summary relative risk estimate calculated from the pooled data of these six trials also demonstrated a significant prophylactic effect of lignocaine that was even greater when the two trials which treated patients with left ventricular failure and shock were excluded. From these analyses, it is concluded that lignocaine treatment provides prophylaxis against VF in acute MI. The failure of most trials to demonstrate such a prophylactic effect is due to small sample sizes and inadequate treatment protocols.

INTRODUCTION

THE use of lignocaine (lidocaine) to prevent ventricular fibrillation (VF) remains controversial. Lignocaine initially gained acceptance on the basis of a report on an uncontrolled study in patients with acute myocardial infarction (MI) in whom VF was completely prevented by treatment of frequent or complex "warning arrhythmias".[1] Subsequent studies found that VF was preceded by these arrhythmias in only one-half to two-thirds of cases[2–7] and that monitoring by coronary care nurses detected only 7–40% of patients with complex ventricular premature beats (VPB).[8] Consequently, many clinicians gave lignocaine "prophylactically" to all patients

DR GENTLEMAN AND PROFESSOR JENNETT: REFERENCES—*continued*

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with acute MI. However, thirteen of fifteen controlled trials have failed to demonstrate statistically significant prevention of VF.[9-23] The prophylactic use of lignocaine has therefore been challenged.[24-26] The limitations of small trials may be relevant here; they may fail to show statistical significance for a given treatment whereas an effect of the same magnitude could become significant in a larger trial.[27] Bearing in mind this beta, or type-II, error, we first reviewed the fifteen randomised trials with the intent of pooling the results – a valid procedure within limitations.[28,29]

Our second aim was to eliminate trials which used treatment regimens resulting in subtherapeutic concentrations of lignocaine.[30,31] We sought also to evaluate separately those trials which included patients in shock or congestive heart failure (CHF), since patients with CHF or shock have a greater risk of VF and death and are also at greater risk of lignocaine poisoning.[2,7,32-34]

METHODS

A computerised literature search revealed fifteen randomised clinical trials of lignocaine prophylaxis in acute MI.[9-23] We carried out a pooled analysis and then selected a subgroup of six trials which satisfied the following criteria, modified from studies of lignocaine pharmacokinetics.[30,31]

1. Presence of acute MI.

2. Lignocaine loading dose of at least 50 mg intravenously (i.v.).

3. Lignocaine infusion of not less than 1 mg/min, for at least 24 h.

Other relevant variables, including age, time since onset of symptoms, presence of conduction block, shock, or heart failure, were not causes for exclusion from this pooled analysis. We further analysed pooled data from the four trials which satisfied the above criteria and also excluded patients with shock or heart failure.

To analyse the pooled data, relative risk estimates for each trial were combined by calculating a summary relative risk and 95% confidence limits by the method of Mantel and Haenszel.[35] When the upper boundary of the 95% confidence limits does not include or exceed 1·0, the relative risk of VF among lignocaine-treated patients is significantly lower than that for untreated patients.

RESULTS

In seven studies there were fewer than 50 patients in either the treated or the untreated group.[9,10,13-15,17,23] In four trials there were no episodes of VF in the untreated groups.[9,10,13,14] No exclusions were made on the basis of number of patients or absence of VF.

For the pooled data from all fifteen trials (1193 untreated and 1251 lidocaine-treated patients), the summary relative risk was 0·42 with 95% confidence limits of 0·29 to 0·62. Thus, the risk of VF among lignocaine-treated patients was significantly lower than that for untreated patients.

Excluded Trials

After pooling data from all trials, we excluded two trials because they used no loading dose,[9,10] and five because the loading dose was given intramuscularly,[12-14,20,21] which resulted in low serum lignocaine levels.[13,14,20] In another trial,[11] only half the treatment group received a loading dose. In one study there were two treatment groups: the first received a 0·5 mg/min infusion and the second a 1·0 mg/min infusion.[16] Only the second group was included in the pooled study. In one trial[22] only patients with warning arrhythmias were studied.

Included Trials

The stated criteria were satisfied by six trials, of which only one[19] found a statistically significant difference between the treated and untreated groups (see table). That trial and one other[18] (which found no difference between the two groups) were double-blind, one trial was single-blind,[23] and the other three were apparently not blind.[15-17]

In three of the trials, the patients in the untreated group were not given lignocaine for warning arrhythmias.[15,18,19] However, in one trial,[16] 31% of the untreated group developed frequent VPB or ventricular tachycardia (VT) and were given lignocaine boluses and infusions identical to those given to the treated group, but these patients were analysed with the untreated group as if they had not been treated.[15] In another trial, 23% of the untreated group crossed over to the treated group,[23] whereas in the trial reported by Mogensen,[17] only those untreated patients who developed VT (65%) crossed over.

Patients with VT or VF on admission were excluded from five of the six studies.[15,16,18,19,23] Other causes of exclusion were shock,[15-17,19,23] atrioventricular (AV) block,[15-17,19,23] left ventricular (LV) failure,[19,23] or severe LV failure.[15,16] The study by Lie et al.,[19] which showed a favourable effect of treatment excluded patients on all these grounds as well as on the grounds of bradycardia or old age. The study with the least favourable result excluded only patients with VT, VF, or other cardiac arrest.[18]

Toxic effects were generally slight, with transient mild CNS symptoms (shown by drowsiness, dizziness, paraesthesia, and nausea) being noted in four of the five trials, in 7%–39% of patients.[15,17-19] Cardiac toxicity was noted in two studies, with 2 of 7 asystolic deaths being attributed to lignocaine in one study[18] and 21% of patients developing bradycardia or hypotension, possibly lignocaine-related, in the other.[23]

None of these studies used the exact dosages recommended by Harrison[31] (a 3 mg/min drip after a loading dose of 200 mg i.v. over 10–20 min) which were designed to prevent an early period with subtherapeutic levels of lignocaine corresponding to the distribution phase. These studies used loading doses of 100 mg or less, and infusions of less than 3 mg/min were given in all studies but one.[19] Nevertheless, lignocaine levels were generally within the therapeutic range, as determined by efficacy against other ventricular arrhythmias, in the three studies that measured them.[17-19] These levels and the development of some toxic reactions despite relatively low doses of lignocaine probably reflect the inclusion of some older patients and patients with mild or moderate CHF.

Pooling the six studies gave an untreated group of 505 patients, 29 of whom (5·7%) had VF, compared to 16 of 517 (3·1%) treated patients. The summary relative risk was 0·53 with 95% confidence limits from 0·28 to 0·98. This result indicates a significant treatment benefit of lignocaine.

When we pooled only the four studies which excluded patients with shock or severe LV failure,[15,16,19,23] VF occurred in 23 of 322 untreated patients compared with 9 of 321 lignocaine-treated patients. The summary relative risk is 0·22 with confidence limits from 0·09 to 0·55, indicating a highly significant treatment benefit.

SIX RANDOMISED TRIALS OF PROPHYLACTIC USE OF ADEQUATE LIGNOCAINE DOSAGE TO PREVENT VENTRICULAR FIBRILLATION IN ACUTE MYOCARDIAL INFARCTION

—	Bleifield[15] (1973)	Bennett[16] (1970)	Mogenson[17] (1970)	O'Brien[18] (1973)	Lie[19] (1974)	Church[23] (1972)
Exclusions	AV block Shock VT, VF Severe LV failure	AV block VT, VF Shock HR<50 Severe LV failure	Shock AV block	VT, VF Other cardiac arrest	AV block Shock VT, VF HR<50 Age >70 LV failure	LV failure Arrhythmias AV block Shock
% older than 70 yrs *(untreated, lignocaine)*	Not stated	8·2 *(8·0, 8·4)*	27 *(24, 29)*	Not stated	0	Not stated
Mean age, *(untreated, lignocaine)*	60·1 *(61·0, 59·0)*	57·0 *(56·8, 57·2)*	63·7 *(63, 64·3)*	Not stated	58·5 *(59·0, 58·1)*	Not stated
Blinded	Not stated	No	Not stated	Double	Double	Single
Onset–admission interval	<5h–34% <24h–63% <48h–82% (unknown–18%)	⩽3h–36% ⩽12h–72% ⩽24h–100%	⩽6h–58% ⩽12h–72% >12h–28%	Not stated	<2h–47% <6h–100%	<4h 64% lignocaine 68% untreated
Bolus — Infusion	100 mg i.v. — 14–42 mg/kg/min	60 mg i.v. — 1 mg/min	75 mg i.v. — 2 mg/min	75 mg i.v. — 2·5 mg/min	100 mg i.v. — 3 mg/min	50·75 mg i.v. — 2 mg/min
Duration	120h	48h	24h	48h	48h	48h
Cross-overs	No	Yes–31%	Yes–65%	No	No	Yes–23%
Toxic effects	7% slight CNS; more 2nd degree AVB on days 2 and 3 in lignocaine group	None	39% slight CNS	CNS: 36% asystole (duration unstated) in 7 lignocaine patients and 2 untreated	15% slight CNS	21% bradycardia or hypotension
Lignocaine level (mg/ml)	Not determined	Not determined	1·0–5·6 at 1 h	4·0 at 24h 5·5 at 48h	1·5–6·4	Not stated
VF incidence in untreated group	2/48 (4·2%)	7/125 (5·6%)	1/37 (2·7%)	5/146 (3·4%)	11/105 (10·5%) Transient VF–2 patients	3/44 (6·8%)
VF incidence in lignocaine group	0/41 (0%)	5/131 (3·8%)	0/42 (0%)	7/154 (4·5%)	0/107 (0%)	4/42 (9·5%)
Statistical significance	NS	NS	NS	Not stated	p<0·03	Not stated

HR = heart rate; NS = not significant.

DISCUSSION

These results suggest that lignocaine in adequate dosage may indeed prevent VF in the setting of acute MI, especially in the absence of severe LV failure or shock. The preponderance of negative studies may be explained by the small numbers of patients in most of these trials and by inadequate dosage in others. Pooling of those with small numbers of patients, after excluding those giving inadequate doses, demonstrates a statistically significant benefit of treatment. This benefit seems even greater for patients without shock or severe LV failure. More favourable results might have been obtained if all the trials had been as stringent as that of Lie et al.[19] This trial had the shortest interval between onset of symptoms and admission, was double-blind, allowed no cross-overs from the untreated group, and made some attempt to tailor the dose to the individual patient (to the extent of halving the infusion rate in toxic patients).

It should be noted, however, that the results of the pooled analysis are not as reliable as those of single trials of this size or those of multi-centre cooperative trials. Trials should be combined only if the populations studied and the treatment regimens used are reasonably similar: the age, diagnosis, disease severity, and associated diseases of the populations should be similar, as should the dosage amounts, duration of treatment, associated therapies, and definition of outcome or endpoint. Studies which differ widely suggest that there may be important differences between the groups and that they should not be pooled: investigation of such differences may be productive.

In the present pooled study there was a moderate degree of variation among the trials in patient population, treatment regimens, and outcome. If only primary VF is studied, the degree of variation is smaller.

Clinical Implications

Assuming that the six trials which satisfied the minimum criteria of adequate treatment are sufficiently similar to be pooled, there remains a second key assumption—i.e., that it is important to prevent VF. In a poorly staffed general ward, or one without monitoring, the value is obvious. In the coronary care unit (CCU) it is assumed that VF is better prevented than treated, since some patients cannot be successfully resuscitated. The question then is whether more patients die from VF which could have been prevented, than die because

of the toxic effects of lignocaine. This question cannot be answered from the six CCU trials pooled here, since mortality data were incomplete; however, it appeared that there were very few deaths due either to VF or to lignocaine toxicity. The case control study of Horwitz and Feinstein[36] showed a favourable outcome of lignocaine treatment using mortality rather than VF to judge its effect.

Some further indirect evidence on this point has been discussed by Ribner et al.[34] Reviewing disparate trials, they collected data on in-hospital mortality of patients with haemodynamically uncomplicated MI. In these studies, mortality was generally higher in patients with VF (mean 19%; range 0–50%) than without (mean 8%; range 3–13%).

Furthermore, if prevention can be justified by analogy to successful resuscitation, it should be noted that long-term prognosis after resuscitation from VF, in the setting of acute MI without shock or CHF, equals that of patients without VF.[32,37] (This should not be confused with the much poorer prognosis of patients who experience VF without acute MI.[37] The term "primary VF", having been applied to these patients as well as to patients with VF who have an acute uncomplicated MI, [33,40] can be misleading.)

In other words, VF is perhaps best seen not as an inevitable development for certain predisposed individuals but as an electrical accident, which, if not always predictable, is at least largely preventable.[38]

These results should not be extrapolated uncritically to all patients with MI. For example, in elderly patients the risk of VF appears to be less,[5,7] but that of lignocaine toxicity greater.[19,39]. In those patients with CHF, shock, conduction disease, acidosis, or hyperkalaemia, the risk of both VF and lignocaine toxicity are unusually high even with careful dose adjustment.[2,7,12,32,33,41,42] Perhaps most important of all is the time from onset of MI symptoms, since most epidodes of VF occur in the first hour, with the risk in the first 4 h being 15 times that between 4 and 12 h.[5,43,44] These observations are consistent with the greater protective effect of lignocaine found from the pooled data of the four trials which excluded patients with severe CHF and shock. This large treatment benefit was also found in the single trial[19] which in addition enrolled all patients within 6 h of MI and excluded patients with any degree of CHF and those aged over 70.

Thus, it is possible that the benefits of lignocaine shown by the present study were restricted to patients without CHF, to the younger patients, to those enrolled early, or some combination of all three. Until subsets of older patients or those with complicated MI can be studied separately,[45] the benefits of lignocaine prophylaxis in such patients should probably be considered unproven.

The work was supported in part by a research grant (HL-07776) from the National Heart, Lung and Blood Institute. C H H. is a recipient of a research career development award (HL-00286) from the National Heart, Lung and Blood Institute.

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