BRIEF REVIEW

Antiarrhythmic drugs in resuscitation

D A Chamberlain

Drugs play a prominent part in the management of cardiorespiratory arrest, although rigid clinical evidence to demonstrate their value is sparse. Their use depends principally on tradition, on an unproven expectation that antiarrhythmic effects are likely to be beneficial for potentially lethal arrhythmias as well as for less malignant conditions, and on extrapolation from animal experiments. Irrespective of the lack or presence of acceptable evidence, drug administration to counter cardiac arrest has one or more objectives:

- prophylaxis in high risk patients
- countering ventricular fibrillation (VF) either directly or as an adjunct to electrical defibrillation
- eliciting an electrical or mechanical response for patients with asystole or electromechanical dissociation
- preventing recurrent VF
- supporting the circulation during basic life support
- improving the haemodynamic state after coordinated rhythm has been restored.

Antiarrhythmic drugs used for the first four of these indications are discussed here.

Prophylaxis for high risk patients

Simple logic led to the use of antiarrhythmic drugs as prophylaxis against VF in high risk patients, notably after myocardial infarction. Antiarrhythmic drugs can prevent ventricular arrhythmias: VF is a ventricular arrhythmia, thus it is a reasonable expectation that such drugs may prevent VF. Most experience has been gained with lignocaine (lidocaine) because of its favourable pharmacological profile. Lignocaine causes relatively little myocardial depression,¹ has little effect on impulse propagation, does not greatly influence vasomotor tone, is usually excreted rapidly after a few bolus doses, and has little proarrhythmic action.

Two important trials lent support to the efficacy of lignocaine for the prevention of VF.^{2,3} The first by Lie *et al* in 1974 was an in-hospital study²; 212 consecutive patients younger than 70 years were randomly allocated within six hours of acute myocardial infarction to receive either intravenous lignocaine by bolus and infusion or placebo (5% glucose). Nine patients in the placebo group developed VF compared with none in the lignocaine group. This result influenced practice on both sides of the Atlantic and prophylactic lignocaine became commonplace in cardiac care units. The

second important trial based on a major prehospital study in which nearly 6000 patients with suspected myocardial infarction were evaluated, followed in 1985.³ Lignocaine was randomly administered to half of the patients. The intramuscular route was chosen because the drug was given by paramedics (nurses) in ambulances. Earlier observations had shown that 400 mg lignocaine injected into the deltoid muscle achieved therapeutic blood levels within 15 minutes. Thus emphasis centred on the reduction in malignant arrhythmias after this interval. After the initial 15 minutes two patients who received lignocaine developed VF compared with 12 controls. In addition, ventricular tachycardia terminated spontaneously in nine of 21 patients in the lignocaine group compared with one of 11 controls. This evidence supported further the prophylactic use of lignocaine in patients with suspected myocardial infarction.

The effect of lignocaine in reducing the odds of VF after myocardial infarction was also reported in a 1988 review of 14 randomised trials by MacMahon *et al*.⁴ However, the significant result from the meta-analysis depended very heavily on the two trials already discussed.^{2,3} None the less, evidence that lignocaine can prevent considerable VF after suspected myocardial infarction seems secure.

The bottom line in clinical practice must be mortality rather than freedom from VF. Three meta-analyses^{4–6} have clearly shown that prophylactic lignocaine does not reduce mortality. Indeed, data from the eight hospital phase trials⁶ show a significant increase in mortality during treatment, with relative odds of 1.76 (confidence interval 1.04 to 2.98). Lignocaine, therefore, seems to have no clinical value despite its proven antiarrhythmic action. Adverse effects including asystole⁴ and perhaps proarrhythmic and myocardial depressant actions—although minor compared with those of other antiarrhythmic drugs—may counteract some benefits. The more crucial point is that VF can usually be treated—at least under trial conditions—and is therefore not synonymous with death. The mortality data slowly swayed opinion: for routine prophylactic use the notion became widespread, first in Europe and later in the US, that prophylactic lignocaine after myocardial infarction was not helpful and its use was largely abandoned.

The pendulum of opinion, which has swung from enthusiasm for prophylactic lignocaine to disillusion, may not yet have reached a central

25 Woodland Drive,
Hove, East Sussex BN3
6DH, UK
D A Chamberlain

Correspondence to:
Dr Chamberlain.

point that represents the true potential of the drug. Indeed, it will probably never do so because the crucial data cannot be collected. The in-hospital position is clear and well demonstrated in the trial described by Lie *et al.*² Although VF developed only in the placebo group (nine patients), mortality was hardly affected (eight patients who received lignocaine died compared with 10 controls) because recurrent VF was fatal in only one patient. The other deaths occurred as a result of cardiac rupture, cardiogenic shock, or pulmonary oedema. A similar lack of lasting clinical benefit would be expected in an ambulance setting with a defibrillator.

But what of patients with suspected infarction who are seen by general practitioners or other health workers without an available defibrillator? Indeed, what might be the value of self administered lignocaine carried by vulnerable patients? The only trial conducted without routine availability of defibrillation was that reported by Valentine *et al* (also published in 1974) involving 233 Australian family physicians.⁷

The results showed a significant reduction in mortality during the first two hours after treatment of patients with suspected acute myocardial infarction. Unfortunately, the apparently promising result after intramuscular injections of 300 mg lignocaine was largely discounted because of unexplained inequalities in randomisation. This type of trial is unlikely to be repeated, but the criticism should not be allowed totally to discount the reduction in mortality. Lignocaine may be of value for prophylactic use in the absence of defibrillation facilities, but we will never have the formal proof needed for a definitive answer to this very important question.

Adjuncts to defibrillation

Evidence relating to antiarrhythmic drugs as adjuncts to defibrillation is also equivocal. The reason for their popularity, especially lignocaine, can hardly depend on evidence from experimental models. For 20 years successive studies have shown that lignocaine increases the defibrillation threshold—that is, defibrillation is more difficult to achieve.^{8–12} The substrate in experimental defibrillation, however, is different from that in ischaemic heart disease. The blocking effect of lignocaine on open and inactivated cardiac Na⁺ channels is greatest on depolarised (ischaemic) tissue.¹ Other factors, notably the use of anaesthetic agents, may also have influenced results in the experimental models. Unfortunately, no reliable placebo controlled human studies are available to guide clinical practice, and small studies do not have the power to give a definitive result.^{13–14} Weaver *et al* in 1990¹⁵ believed, on the basis of a retrospective survey, that lignocaine increased the incidence of asystole, while Herlitz *et al* in 1997¹⁶ also reported that there was no evidence of increased survival after reviewing uncontrolled retrospective observations from the Gothenberg database. Lignocaine is still recommended in the widely used American Heart Association guidelines

for resuscitation.¹⁷ The fact that this recommendation continues despite the persuasive evidence against its value must depend on the lack of definitive clinical studies and the influence of clinical experience. This can seem very convincing if a defibrillating shock is successful after lignocaine has been given for refractory VF. Davey *et al*, however, have shown that the defibrillation threshold is not an absolute figure but rather a dose–response curve: the higher the energy then the greater are the odds of success in percentage terms.¹⁸ Thus a successful shock after treatment with lignocaine when three or four shocks have already failed may be no more than the play of chance rather than a drug effect.

The evidence for most class I agents is no better. Flecainide,¹⁹ mexiletine,²⁰ encainide,²¹ and moricizine,²² increase the defibrillation threshold in experimental animals and human subjects. There may be exceptions to the disappointing conclusion that class I antiarrhythmic drugs are uniformly unhelpful in experimental models. For example, in one study quinidine had no effect on the defibrillation threshold²³ and in another *N*-acetyl procainamide (the principal effect of which is an increase in the duration of action potential) caused the threshold to decrease.²⁴

Amiodarone is (as usual) a special case. It is a complex drug and variations in efficacy as an adjunct to defibrillation may reflect different experimental or clinical circumstances. There was no difference in the defibrillation threshold after oral dosing in a dog model, but a decrease occurred when the drug was administered intravenously.²⁵ Another dog model showed that amiodarone greatly improved the response to defibrillation attempts which had previously been unsuccessful using a series of five shocks with adjunctive lignocaine and adrenaline.²⁶ In human patients, one within-subject study showed an increase in the internal defibrillation threshold after oral administration, which regressed when the drug was discontinued.²⁷ In contrast, there was no evidence of any difference in energy requirements in another small study comparing two series of patients treated with or without amiodarone.²⁸ No definitive trial has yet been reported of the use of intravenous amiodarone during cardiac arrest in human patients. (A report on the recently completed ARREST trial is however, awaited.) In an earlier study, which has attracted considerable attention, amiodarone was given by intravenous bolus, with or without subsequent infusion, to 14 patients with refractory or recurrent ventricular tachycardia or VF.²⁹ The average duration of attempted resuscitation was 75 minutes. Eleven patients regained stable rhythm and eight survived to hospital discharge.

Bretylium tosylate is another complex drug¹ that may have deserved wider interest at least in Europe (it has been used more extensively in the US as an adjunct to defibrillation). The drug has some class III actions but its principal effect may be the release of noradrenaline from nerve endings. The antiadrenergic effect is responsible for pronounced vascular hypoten-

sion. It does not seem to increase the defibrillation threshold.^{9 10 23} Unique among antiarrhythmics, it has a direct antifibrillatory effect, perhaps because it reduces the heterogeneity of repolarisation, an effect that is likely to suppress re-entry.³⁰ Sanna and Arcidiacono³¹ reported spontaneous reversion of VF in six cases, while Bacaner³² observed success with refractory VF. Nowak *et al* also found an increased resuscitation rate.³³ Bretylium has been compared with lignocaine in two studies but these were too small to be definitive. The trend favoured bretylium in one³⁴ and lignocaine in the other.³⁵

To summarise, most class I agents increase the defibrillation threshold at least under experimental conditions. The effects are consistent with lignocaine. Evidence for an adverse effect is, however, equivocal or absent for quinidine, *N*-acetyl procainamide, amiodarone, and bretylium. Short acting β blockers have an attractive pharmacological profile for this indication but have not been tested, and only anecdotal evidence is available for non-specifically used magnesium³⁶ as opposed to its effect in electrolyte deficiency. Clinical experience remains sparse or incomplete.

The value of antiarrhythmic drugs as adjuncts to defibrillation should not be discounted. Some antiarrhythmics may be important. Evidence from experimental VF should be considered with caution as the electrophysiological substrate is different from the substrate in atherosclerotic disease, the most common underlying cause in human patients. The human data may also be flawed because drug requirements after global ischaemia may be appreciably less than in other situations and depend importantly on the route of administration. Experimental evidence for lignocaine supports these notions.³⁷ Even if most patients with refractory VF are not helped by antiarrhythmic agents or indeed are harmed, there may still be a subset who might benefit if they could be identified—a fact that justifies a “last chance” approach of administration by those who remain sceptical of their value. One further point deserves comment. Biphasic defibrillation may respond differently to drugs than does monophasic defibrillation. One study has shown that lignocaine does not increase the defibrillation threshold after biphasic defibrillation.³⁸ If this is true, lignocaine may yet find a place for this indication supported by new experimental data.

Maintenance of coordinated rhythm

Antiarrhythmic drugs are often used to maintain coordinated rhythm after defibrillation, with lignocaine again having pride of place. Extrapolation from the evidence already described shows that lignocaine can prevent initial episodes of VF in vulnerable patients. If initial episodes can be prevented then it is a reasonable expectation that the risk of subsequent episodes can also be reduced. Counter evidence that overall mortality is not influenced favourably may be less relevant for a selected group for whom the risk of fibrillation is extremely high (and any hazards of treatment

are therefore likely to weigh less heavily in a risk benefit equation). There are, however, no reliable trials of antiarrhythmics given after successful defibrillation to confirm whether or not this strategy is effective and safe.

Specific drugs for special situations

POTASSIUM CHLORIDE AND MAGNESIUM SULPHATE

Despite the lack of a formal placebo controlled trial the value of intravenous magnesium sulphate for torsades de pointes is generally agreed. Clinical experience provides such strong evidence that a trial for this potentially lethal indication would hardly be justified.³⁹ Torsades de pointes may be mistaken for VF even by experienced cardiologists,⁴⁰ a fact that may be partly responsible for the impression that magnesium may control recurrent VF. Hypokalaemia predisposes to malignant arrhythmias and is frequently associated with hypomagnesaemia. Both potassium replacement and magnesium replacement should form part of the therapeutic strategy in patients with identified electrolyte deficiency.⁴¹ A similar strategy may be appropriate when electrolyte deficiency is suspected—for example, in those receiving diuretics without adequate electrolyte supplementation.

CALCIUM CHLORIDE

Calcium is less frequently used now than in the early days of resuscitation. The key role of calcium within the contractile elements of the myocardium may be to counteract asystole and electromechanical dissociation. Clinical evidence is sparse. One small study supported administration of calcium chloride in patients with electromechanical dissociation.⁴² Eight of 48 patients treated with calcium chloride in a prehospital setting survived with an effective cardiac output to hospital admission compared with two of 42 patients who were not treated with this drug. An accompanying report from the same authors on the use of calcium for asystole was considered negative.⁴³ Three of 39 patients survived to the emergency department after treatment with calcium chloride compared with one of 34 patients who were not treated with this drug. Whatever the formal statistics, the resemblance of the two sets of figures in percentage terms hardly justifies opposite conclusions based only on an arbitrary *p* value threshold!

Other factors have led to a reduction in the use of calcium. The most important has been the perceived value of calcium channel blocking agents as drugs beneficial to the cardiovascular system. Administration of calcium thus became counter intuitive. Evidence was also adduced that calcium levels were normal during attempted resuscitation, so supplements may not have an important role. Subsequent studies have shown, however, that ionised calcium is low during resuscitation in experimental models⁴⁴ and in humans after out-of-hospital cardiac arrest,⁴⁵ perhaps because it binds to lactate. This at least raises the possibility that use of calcium chloride during resuscitation may have an underlying theoretic

cal basis. Further work with calcium seems to be highly desirable. A major definitive study is unlikely to be supported by industry because of little commercial interest.

The role of antiarrhythmic drugs in resuscitation remains ill defined—a fact that reflects little credit on all of us who have taken an interest in the subject for 30 years or more. Definitive studies in what is admittedly a difficult area for research can be performed only on a cooperative basis. Such studies are long overdue.

- Hardman JG, Limbird LE, Molinoff PB, et al, eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 9th ed. New York: McGraw-Hill, 1996.
- Lie KI, Wellens HJ, van Capelle FJ, et al. Lidocaine to prevent death in early phase of acute infarction. *N Engl J Med* 1974;25:1324–6.
- Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985;313:1105–10.
- MacMahon S, Collins R, Peto R, et al. Effects of prophylactic lidocaine in suspected acute myocardial infarction. *JAMA* 1988;260:1910–16.
- Lau J, Antman EM, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992;327:248–54.
- Hine LK, Laird NL, Hewitt P, et al. Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. *Arch Intern Med* 1989;149:2694–8.
- Valentine PA, Frew JL, Mashford ML, et al. Lidocaine to prevent death in early phase of acute infarction. *N Engl J Med* 1974;291:1327–31.
- Babbs CF, Yim GKW, Tacker WA, et al. Elevation of ventricular defibrillation threshold in dogs by antiarrhythmic drugs. *Am Heart J* 1979;98:345–50.
- Chow MSS, Kluger J, Lawrence R, et al. The effect of lidocaine and bretylium on the defibrillation threshold during cardiac arrest and cardiopulmonary resuscitation. *Proc Soc Exp Biol Med* 1986;182:63–7.
- Kerber RE, Pandian NG, Jensen SR, et al. The effect of lidocaine and bretylium on energy requirements for trans-thoracic defibrillation: experimental studies. *J Am Coll Cardiol* 1986;7:397–405.
- Dorian P, Fain ES, Davey J-M, et al. Lidocaine causes a reversible, concentration-dependent increase in defibrillation energy requirements. *J Am Coll Cardiol* 1986;8:327–32.
- Topham SL, Cha Y-M, Peters BB, et al. Effects of lidocaine on relation between defibrillation threshold and upper limit of vulnerability in open-chest dogs. *Circulation* 1992;85:1146–51.
- Kerber RE, Jensen SR, Gascho JA, et al. Determinants of defibrillation: prospective analysis of 183 patients. *Am J Cardiol* 1983;52:739–45.
- Harrison EE. Lidocaine in prehospital countershock refractory ventricular fibrillation. *Ann Emerg Med* 1981;10:420–3.
- Weaver WD, Fahnenbruch CE, Johnson DD, et al. Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. *Circulation* 1990;82:2027–34.
- Herlitz J, Ekström L, Wennerblom B, et al. Lidocaine in out-of-hospital ventricular fibrillation. Does it improve survival? *Resuscitation* 1997;33:199–205.
- Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. *JAMA* 1992;268:2171–295.
- Davy J-M, Fain ES, Dorian P, et al. The relationship between successful defibrillation and delivered energy in open-chested dogs: reappraisal of the “defibrillation threshold” concept. *Am Heart J* 1987;113:77–84.
- Hernandez R, Mann DE, Breckinridge S, et al. Effects of flecainide on defibrillation thresholds in the anesthetized dog. *J Am Coll Cardiol* 1989;14:777–81.
- Marinchak RA, Friehling TD, Kline RA, et al. Effect of antiarrhythmic drugs on defibrillation threshold: case report of an adverse effect of mexiletine and review of the literature. *PACE* 1988;11:7–12.
- Fain ES, Dorian P, Davy J-M, et al. Effects of encainide and its metabolites on energy requirements for defibrillation. *Circulation* 1986;73:1334–41.
- Avitall B, Hare J, Zander G, et al. Cardioversion, defibrillation, and overdrive pacing of ventricular arrhythmias: the effect of moricizine in dogs with sustained monomorphic ventricular tachycardia. *PACE* 1993;16:2092–7.
- Dorian P, Fain ES, Davy J-M, et al. Effect of quinidine and bretylium on defibrillation energy requirements. *Am Heart J* 1986;112:19–25.
- Echt DS, Black JN, Barbey JT, et al. Evaluation of antiarrhythmic drugs on defibrillation energy requirements in dogs. Sodium channel block and action potential prolongation. *Circulation* 1989;79:1106–17.
- Fain ES, Lee JT, Winkle RA. Effects of acute intravenous and chronic oral amiodarone on defibrillation energy requirements. *Am Heart J* 1987;114:8–17.
- Anastasiou-Nana MI, Nanas JN, Nanas SN, et al. Effects of amiodarone on refractory ventricular fibrillation in acute myocardial infarction: experimental study. *J Am Coll Cardiol* 1994;23:253–8.
- Jung W, Manz M, Pizzulli L, et al. Effects of chronic amiodarone therapy on defibrillation threshold. *Am J Cardiol* 1992;70:1023–7.
- Huang SKS, Tan de Guzman WL, Chenarides JG, et al. Effects of long-term amiodarone therapy on the defibrillation threshold and the rate of shocks of the implantable cardioverter-defibrillator. *Am Heart J* 1991;122:720–7.
- Williams ML, Woelfel A, Cascio WE, et al. Intravenous amiodarone during prolonged resuscitation from cardiac arrest. *Ann Intern Med* 1989;110:839–42.
- Cardinal R, Sasyniuk BI. Electrophysiological effects of bretylium tosylate on subendocardial Purkinje fibers from infarcted canine hearts. *J Pharmacol Exp Ther* 1978;204:159–74.
- Sanna G, Arcidiacono R. Chemical ventricular defibrillation of the human heart with bretylium tosylate. *Am J Cardiol* 1973;32:982–7.
- Bacaner MB. Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate. *Am J Cardiol* 1968;21:530–43.
- Nowak RM, Bodnar TJ, Dronen S, et al. Bretylium tosylate as initial treatment for cardiopulmonary arrest: randomized comparison with placebo. *Ann Emerg Med* 1981;10:404–7.
- Haynes RE, Chinn TL, Copass MK, et al. Comparison of bretylium tosylate and lidocaine in management of out of hospital ventricular fibrillation: a randomized clinical trial. *Am J Cardiol* 1981;48:353–6.
- Olson DW, Thompson BM, Darin JC, et al. A randomized comparison of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. *Ann Emerg Med* 1984;13:807–61.
- Tobey RC, Birnbaum GA, Allegra JR, et al. Successful resuscitation and neurologic recovery from refractory ventricular fibrillation after magnesium sulphate administration. *Ann Emerg Med* 1992;21:92–6.
- Lindner KH, Ahnefeld FW, Dirks B, et al. Lidocainkonzentrationen im plasma nach peripher- bzw. zentralvenöser applikation während der kardiopulmonalen reanimation. Ergebnisse einer tierexperimentellen studie. *Anaesthesist* 1989;38:604–9.
- Ujhelyi MR, Schur M, Frede T, et al. Differential effects of lidocaine on defibrillation threshold with monophasic versus biphasic shock waveforms. *Circulation* 1995;92:1644–50.
- Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulphate. *Circulation* 1988;77:392–7.
- Clayton RH, Murray A, Higham PD, et al. Self-terminating ventricular tachyarrhythmias—a diagnostic dilemma? *Lancet* 1993;341:93–5.
- Chamberlain D. Peri-arrest arrhythmias. *Br J Anaesth* 1997;79:198–202.
- Steuen HA, Thompson B, Aprahamian C, et al. The effectiveness of calcium chloride in refractory electromechanical dissociation. *Ann Emerg Med* 1985;14:626–9.
- Steuen HA, Thompson B, Aprahamian C, et al. Lack of effectiveness of calcium chloride in refractory asystole. *Ann Emerg Med* 1985;14:630–2.
- Cairns CB, Niemann JT, Pelikan PCD, et al. Ionized hypocalcemia during prolonged cardiac arrest and closed-chest CPR in a canine model. *Ann Emerg Med* 1991;20:1178–82.
- Urban P, Scheidegger D, Buchmann B, et al. Cardiac arrest and blood ionized calcium levels. *Ann Intern Med* 1988;109:110–13.