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Scientific Update™

Treatment of Acute Ventricular Arrhythmias

Compiled from information presented at the Canadian Cardiovascular Society 1999 and NASPE 2000 Annual Meetings

Reported and discussed by:
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The American Heart Association Guidelines on Adult Advanced Cardiac Life Support (ACLS), published in 1992,[1] made some now widely accepted recommendations for the treatment of serious ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF). The antiarrhythmic drug portion of the ACLS Guidelines listed lidocaine, bretylium, procainamide, and magnesium (in cases of Torsades de Pointes or hypomagnesemia) as medications of "probable benefit" in persistent or recurrent VF/VT. For patients with wide complex tachycardia (WCT) of uncertain type or ventricular tachycardia, and if patients were stable, medications advised included lidocaine, adenosine in the case of WCT of uncertain type, procainamide, and finally bretylium. In the modern era of evidence-based medicine, it is very important that physicians and all caregivers who care for patients with such serious ventricular arrhythmias be familiar with the content and quality of the scientific evidence that supports these recommendations.

Evidence for drug therapy efficacy in the treatment of sustained VT

Lidocaine: There is unfortunately very little evidence to support the use of lidocaine in patients with sustained VT. No placebo-controlled, randomized studies of lidocaine in VT have been performed,and no study has shown that lidocaine is better than any other agent or than no treatment in the acute termination of, the prevention of, or recurrence of sustained monomorphic VT. In one small, randomized comparative study, lidocaine effectively restored sinus rhythm in about 20% of patients with sustained VT, compared to 80% for procainamide.[2] Non-randomized cohort studies of large numbers of patients with hemodynamically stable VT suggest that lidocaine will lead to restoration of sinus rhythm in 10-20% of patients. Since WCT of uncertain origin in adults is most commonly caused by VT rather than supraventricular tachycardia (SVT) with aberrancy,[3] lidocaine is not expected to be very effective in this situation. In any event, if the rhythm is SVT, lidocaine will not be helpful. Thus, despite its long history of use, ease of administration, and relative safety, there is no clear evidence that lidocaine is *effective* in the acute treatment of or the prevention of sustained monomorphic VT.

Procainamide: In the one small, randomized comparative study cited above, as well as in multiple case series and cohort studies, procainamide appears to terminate VT in about 70-80% of patients. This effect is balanced against a 10-20% risk of hypotension, especially if the drug is administered very rapidly (faster than 50-100 mg/min). As for lidocaine, there are no randomized, placebo-controlled studies of procainamide in the treatment of sustained monoform VT.

Bretylium and magnesium: There is virtually no information on the efficacy of either bretylium or magnesium in monomorphic sustained VT. Animal studies and extrapolation from studies of magnesium as prophylaxis for arrhythmias following myocardial infarction (MI) suggest that magnesium is ineffective in the treatment or prevention of monomorphic sustained VT. Importantly, magnesium is very effective, at least in anecdotal case series, in the treatment of a particular form of polymorphic VT known as *torsade de pointes* ventricular tachycardia, which arises in the context of QT prolongation, a typical electrocardiographic pattern of pause-dependent onset of the arrhythmia, and usually in the context of drugs or electrolyte abnormalities which prolong the QT interval, with or without bradycardia. In this latter situation, magnesium is very effective in terminating salvos of non-sustained or sustained polymorphic VT, and preventing their recurrence.

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Although the efficacy of bretylium for sustained monoform VT is unknown, it is well known to cause substantial hypotension in approximately 30-50% of patients with a prior history of VT and structural heart disease,[4] the kinds of patients who are likely to have ongoing sustained VT. As with the other above drugs, bretylium has not been assessed in a randomized, controlled study, nor has its efficacy been well assessed even in cohort studies or case series.

Adenosine: Although adenosine is mentioned in the management of WCT of unknown origin, it is unlikely to terminate sustained VT, may cause transient hypotension or acceleration of true VT, and may cause dangerous acceleration of ventricular response in WCT associated with ventricular pre-excitation (Wolff–Parkinson-White syndrome) and AF or atrial flutter.[5] The administration of adenosine delays the appropriate treatment of WCT, which in cohort and observational studies is most often due to sustained VT.[3] There are no randomized controlled studies of the usefulness of adenosine in the management of WCT.

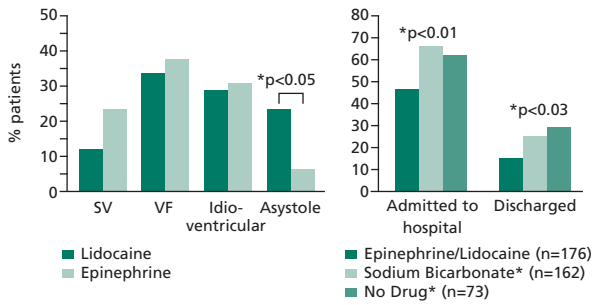
Amiodarone: Since the 1992 ACLS recommendation publication, intravenous amiodarone has become available for the acute treatment of serious ventricular arrhythmias. IV amiodarone was compared in a large, multi-centre trial, in a double-blind, randomized fashion, to bretylium in patients with 'electrical storm,' (ie, frequent recurrences of hemodynamically unstable VT or VF.[4] Some patients in this study were in VT at the time of drug administration. Both amiodarone and bretylium appeared to be effective in the prevention of recurrences of VT in this study, although amiodarone was significantly better tolerated and required significantly fewer premature drug discontinuations due to refractory hypotension or other adverse effects. Multiple cohort series suggest that IV amiodarone is very effective at the prevention of recurrences of sustained monomorphic VT, although there is very little information on the efficacy of amiodarone during ongoing VT. If excessively and rapidly administered, amiodarone, like procainamide, can cause hypotension.

Treatment of ventricular fibrillation

Until recently, there has been very little information to help the clinician choose effective therapy for shock-resistant VF or to prevent recurrences of VF.

Although lidocaine is most often used in this setting, there is unfortunately no corroborative scientific information suggesting that the drug is effective. Two comparative trials with bretylium[6,7] in the cardiac arrest situation suggested no difference in efficacy between lidocaine and bretylium, a result compatible with equal efficacy, equal inefficacy, or equal harm from the two drugs. In a comparative trial between lidocaine and epinephrine, there was no improvement in electrical outcome following lidocaine versus epinephrine, but a statistically significant increased incidence of asystole[8] (Figure 1). In a comprehensive retrospective review

Figure 1: Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. 199 patients with out-of-hospital VF after one failed defibrillation attempt; open randomization (even/odd days) to lidocaine 100 mg IV bolus or epinephrine 0.5 mg IV bolus; drugs repeated if second shock failed.[8]



*historical controls

of antiarrhythmic drug use in in-hospital cardiac arrest, neither the use of lidocaine, nor bretylium, were associated with better outcomes, even when controlling for known prognostic factors.[9] In the animal laboratory, administering lidocaine in acute MI or in an animal model of cardiac arrest does not improve experimental survival, and may decrease survival.[10] Lidocaine consistently increases defibrillation threshold, (ie, the energy required to defibrillate the heart), in experimental models and in humans.[11] When used as primary prevention of VF in acute MI, the setting in which lidocaine has the most plausible basic experimental evidential support, lidocaine does indeed reduce the incidence of VF in a meta-analysis, but very importantly and unfortunately increases total mortality by 62%.[12] Although there is a wide confidence interval about this latter estimate, it seems exceedingly unlikely that lidocaine will *reduce* mortality from VF in acute MI, and by inference lidocaine seems unlikely to reduce mortality from VF when used as secondary prophylaxis (after VF has already occurred).

Procainamide has virtually never been evaluated in the treatment of shock-resistant VF or the treatment of VF, and the requirement for gradual administration precludes the use of this drug in an emergency situation.

With respect to bretylium, there is likewise very little evidence from prospective, randomized controlled studies of its efficacy. Small, randomized studies do not support its efficacy in the treatment of VF, although one such small study showed improved outcomes in cardiac arrest, considering both asystolic and VF patients.[13] Its use is frequently associated with serious and refractory hypotension as noted above. It has never been evaluated in a randomized, placebo-controlled study for either VF or VT.

Figure 2: The effect of treatment with amiodarone or placebo on the rate of survival to hospital admission in all patients and subgroups of patients. VF denotes ventricular fibrillation, PEA pulseless electrical activity, and ROSC return of spontaneous circulation prior to drug administration with subsequent recurrence of VF. Values above the bars are the percentages of patients who survived to admission.[15]

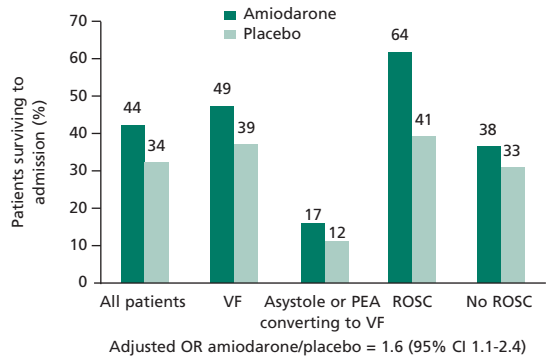
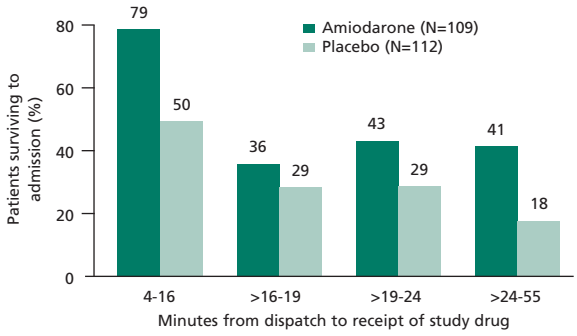


Figure 3: Effect of the length of time to the administration of amiodarone or placebo on the rate of survival to admission to the hospital in patients with witnessed cardiac arrest, according to quartile of time from dispatch. As compared with the placebo group, the amiodarone group had a better outcome at all measured intervals, and the benefit was consistent whether the drug was administered early or late (P=0.008 by the Mantel-Haenszel chi-square test). Values above the bars are the percentages of patients who survived to admission. Note: no interaction between time and amiodarone effect.[15]



In the few studies that have assessed the efficacy of magnesium in the prevention of VF in the post-infarct situation, randomized blinded studies do not show any reduced life-threatening arrhythmias or reduced mortality following magnesium.[14]

Intravenous amiodarone has been the subject of a randomized, placebo-controlled, blinded study in shock-resistant VF. Dr. Peter Kudenchuk and colleagues showed that IV amiodarone was superior to placebo in resuscitation from shock-resistant VF occurring out of hospital.[15] In this study, paramedics administered 300 mg of amiodarone or placebo with the primary endpoint of survival to hospital admission. Overall, 44% of amiodarone and 34% of placebo patients survived to admission to hospital ($p<0.05$) (Figure 2); in the sub-group with transient return of spontaneous circulation (ROSC) during the cardiac arrest, 64% of the IV amiodarone group versus 41% of the placebo group survived to hospital admission (Figure 2). The benefit of amiodarone was independent of the interval from 911 call to the administration of study drug. Although patients treated in less than 16 minutes appeared to serve the greatest absolute benefit (Figure 3).

Special situations

It is important to recall that not all serious ventricular arrhythmias present as either sustained monomorphic VT or shock-resistant VF. Amongst the many syndromes of serious ventricular arrhythmias, polymorphic VT or VF in the context of an acute ischemic or MI event must be included. Excellent randomized controlled trial evidence suggests that the best acute treatment is IV thrombolytics for MI with ST elevation, aspirin, and intravenous beta-blockers.[16] The clinical and ECG signature of ischemia or infarction related VT/VF needs to be clearly understood for these treatments to be properly applied.

Another syndrome is that of sustained monomorphic VT of right ventricular outflow tract origin in patients with structurally normal hearts, so-called RVOT-VT. This syndrome has its own particular ECG signature, usually arises in younger and otherwise healthy individuals, and responds to beta-blocker therapy. It is seldom life-threatening and does not generally require standard 'antiarrhythmic' therapy.

Torsade de pointes VT, as mentioned above, generally is accompanied by or results from excessive prolongation of repolarization, manifest as QT prolongation on the ECG, and should be treated with IV magnesium, increasing the heart rate with pacing, and removal of offending agents as well as repletion of magnesium or potassium deficiency if present. Standard 'antiarrhythmic' agents are not required and are contraindicated.

'Electrical storm' is a syndrome defined as a frequent recurrence of sustained hemodynamically unstable VT or VF that usually arises in patients with serious structural heart disease, often with heart failure, catecholamine excess, or myocardial ischemia. Since the problem is both stabilization of the poor myocardial substrate and prevention of *recurrence*

Table 1: Recommendations for the management of acute ventricular tachycardia or fibrillation

- **Patients with polymorphic VT and QT prolongation**
  These patients should be treated with intravenous magnesium, temporary pacing, or intravenous isoproterenol.
  (Grade C, Level 4 evidence)
- **Patients with VT or VF complicating acute MI**
  Intravenous beta-blockers are recommended in all patients following acute myocardial infarction unless contraindications exist; this recommendation also applies to patients who develop ventricular tachycardia or ventricular fibrillation during the acute phase.
  (Grade A, Level 1 evidence)
- **Patients with hemodynamically tolerated sustained monomorphic VT**
  Intravenous procainamide is recommended for the treatment of monomorphic sustained ventricular tachycardia with moderate or little hemodynamic compromise.
  (Grade B, Level 2 evidence)
- **Patients with shock-resistant VF**
  Patients with ventricular fibrillation resistant to defibrillation should be treated with intravenous amiodarone.
  (Grade B, Level 2 evidence)
- **Patients with electrical storm**
  Patients with electrical storm (≥ 2 episodes of sustained VT or VF within 24 hours) may be treated with intravenous amiodarone or intravenous bretylium.
  (Grade B, Level 2 evidence)

Grade of recommendation ranges from grade A (strongest) to grade C (with least evidence). Level of evidence ranges from 1 (multiple randomized clinical trials) to 4 (expert consensus but no randomized trial evidence).

of ventricular arrhythmias rather than their initial treatment, the ACLS algorithms do not speak directly to the treatment of this syndrome. With prompt and aggressive treatment, these patients can be effectively stabilized, and will become candidates for long-term antiarrhythmic therapy with drugs or implanted devices.

As discussed above, the preferred antiarrhythmic drug in such patients is IV amiodarone. Sedation, afterload reduction if heart failure is present, beta-blocker therapy unless absolutely contraindicated, and occasionally general anaesthesia or an intra-aortic balloon pump can be useful adjuncts to antiarrhythmic drug therapy.

Conclusion

The treatment of serious ventricular arrhythmias requires consideration of etiologic and exacerbating factors and a knowledge of the risks and benefits of the therapies employed. The Canadian Cardiovascular Society discussed draft guidelines for the acute treatment of ventricular arrhythmias at their annual meeting in October, 1999, and these guidelines will be published this year after ratification. The draft guidelines (as presented) are shown in Table 1.[17] There is no single "recipe" for ventricular arrhythmias; like any good chef, the clinician needs to adapt to the ingredients at hand and the individual needs of the consumer.

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