Intravenous amiodarone for the pharmacological termination of haemodynamically-tolerated sustained ventricular tachycardia: is bolus dose amiodarone an appropriate first-line treatment?

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Accepted 28 August 2007

ABSTRACT

Objective: To examine the efficacy of bolus dose intravenous amiodarone for the pharmacological termination of haemodynamically-tolerated sustained monomorphic ventricular tachycardia (VT).

Design, setting and participants: Retrospective case series of consecutive emergency admissions with haemodynamically-tolerated sustained monomorphic VT administered bolus dose intravenous amiodarone 300 mg, according to current UK advanced life support practice guidelines.

Main outcome measures: Pharmacological termination rates within 20 min and 1 h and incidence of hypotension requiring emergency direct current cardioversion (DCCV) during this period.

Results: 41 patients (35 men) of mean (SD) age 68 (10) years, the majority (85%) with ischaemic heart disease and impaired left ventricular function (mean (SD) ejection fraction 0.31 (0.11)), were enrolled in the study. The median VT duration was 70 min (range 15–6000), mean heart rate was 174 (34) bpm and systolic and diastolic blood pressures were 112 (22) and 73 (19) mm Hg, respectively. Pharmacological VT termination occurred within 20 min in 6/41 patients (15%; 95% CI 7% to 29%) and within 1 h in 12/41 patients (29%; 95% CI 18% to 45%). Haemodynamic deterioration requiring emergency DCCV occurred in 7/41 patients (17%; 95% CI 8% to 32%).

Conclusions: Although advocated by advanced life support guidelines, bolus dose intravenous amiodarone was relatively ineffective for acutely terminating haemodynamically-tolerated sustained monomorphic VT with a significant incidence of haemodynamic destabilisation requiring emergency DCCV. Previous studies in the identical clinical setting suggest that alternative antiarrhythmic agents, particularly intravenous procainamide and sotalol, may be superior. A prospective randomised trial is required to determine the optimal drug treatment for stable sustained monomorphic VT in the emergency setting.

Haemodynamically-tolerated sustained monomorphic ventricular tachycardia (VT) requires prompt termination due to the risk of haemodynamic decompensation or degeneration to ventricular fibrillation. Although synchronised electrical cardioversion is highly effective, the requirement for general anaesthesia or deep conscious sedation often leads to pharmacological termination being the preferred first-line strategy. Following the publication of advanced cardiac life support guidelines by the Resuscitation Council, UK[1] and the American Heart Association in 2000,[2] bolus intravenous amiodarone replaced lidocaine to become overwhelmingly the commonest agent used for this indication. However, as there is very little direct evidence, this recommendation has been based primarily on expert opinion taking account of the known efficacy of intravenous amiodarone in two related clinical settings: prolonged infusion for suppressing recurrent destabilising ventricular tachyarrhythmias[3–5] and bolus administration for shock-refractory ventricular fibrillation.[6 7] Accordingly, we have undertaken an observational study to examine the efficacy and safety of bolus intravenous amiodarone specifically for terminating sustained stable VT, as stipulated in current emergency care guidelines.

METHODS

Consecutive patients with haemodynamically-tolerated sustained monomorphic VT were retrospectively identified using a database of admissions to the Coronary Care Unit of the John Radcliffe Hospital. The medical records were then reviewed in detail, including all 12-lead ECG tracings and rhythm strips, observation charts and prescription sheets. Inclusion criteria were: (1) patients hospitalised from March 2003 to October 2006; (2) VT duration >15 min; (3) absence of severe haemodynamic compromise resulting in pre-syncope, syncope, pulmonary oedema or cardiac arrest; (4) intravenous amiodarone 300 mg administered according to Resuscitation Council (UK) guidelines. Study end points were: (1) pharmacological VT termination rates within 20 min and 1 h of the start of amiodarone administration and (2) rate of emergency direct current cardioversion (DCCV) within 1 h due to haemodynamic deterioration. The diagnosis of VT was based on standard electrocardiographic criteria[8] and, when administered, the response to intravenous adenosine. The modified Wald method was used to compute the 95% confidence interval of a proportion to permit comparisons between trial data. Statistical analysis was performed using GraphPad Prism 4.01 (GraphPad Software Inc). Unless otherwise stated, data are shown as mean (SD).

RESULTS

During the study period intravenous amiodarone was the only agent used for attempted pharmacological termination of sustained VT in our unit. We

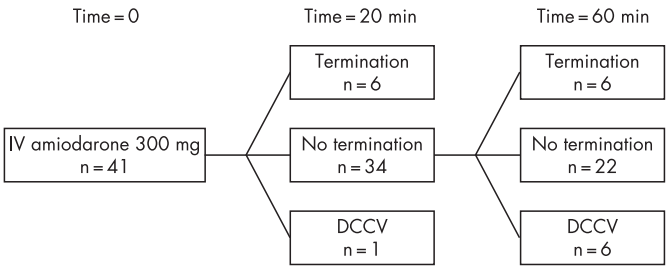

Figure 1 Flow diagram of patient outcomes following intravenous bolus dose amiodarone administration. DCCV, emergency direct current cardioversion.

identified 47 consecutive patients who were treated with bolus dose amiodarone; six received 150 mg and were excluded from the analysis. The final study population therefore comprised 41 patients (35 men, 6 women) of mean (SD) age 68 (10) years and most (85%) with ischaemic heart disease. There were three patients with idiopathic dilated cardiomyopathy (7%) and another three with no structural heart disease (7%). Mean left ventricular ejection fraction was 0.31 (0.11); ejection fraction was <0.40 in 28/41 patients (68%). The mean (SD) plasma potassium level was 4.1 (0.5) mmol/l (range 3.1–5.5) and the median troponin I level was 0.9 (16.9) μg/l (range 0–85.7). Median VT duration was 70 min (range 15–6000) and tachycardia cycle length was 358 (75) ms or 174 (34) bpm. At the time of admission the mean (SD) systolic blood pressure was 112 (22) mm Hg and diastolic blood pressure was 73 (19) mm Hg. Medications on admission included β-blockers in 39% and chronic oral amiodarone in 22%.

Intravenous amiodarone was administered over ⩽30 min in 36 patients and over 30–60 min in 5 patients. The route of administration was via a peripheral intravenous cannula in all patients. VT terminated within 20 min in 6/41 patients (15%; 95% confidence interval (CI) 7% to 29%) and by 1 h in 12/41 patients (29%; 95% CI 18% to 45%; fig 1). When the 9 patients taking chronic oral amiodarone therapy were excluded from the analysis, VT was terminated within 20 min in 6/32 patients (19%; 95% CI 9% to 36%) and by 1 h in 11/32 (34%; 95% CI 20% to 52%), which was not significantly higher than for the total study population.

There we no deaths during amiodarone infusion and no cases of peripheral venous thrombophlebitis. Symptomatic hypotension requiring emergency DCCV occurred in 7/41 patients (17%; 95% CI 8% to 32%); mean (SD) time to emergency DCCV was 42 (16) min. Only one patient developed an early recurrence of VT during the same hospital admission, 1 h after DCCV following unsuccessful pharmacological termination with amiodarone. One late death occurred due to recurrent VT 5 days following admission in a 73-year-old woman with ischaemic cardiomyopathy (ejection fraction 25%). Further bolus intravenous amiodarone 300 mg and DCCV failed to restore a supraventricular rhythm, resulting in haemodynamic collapse.

DISCUSSION

This study shows that intravenous amiodarone—although now recommended and widely adopted as the pharmacological agent of choice for attempted termination of sustained monomorphic VT—is relatively ineffective, converting fewer than 20% of patients within 20 min and only 29% even after 1 h. In addition, its use was associated with haemodynamic deterioration requiring emergency DCCV in 17% of cases. The poor efficacy of intravenous amiodarone is not surprising because sustained monomorphic VT is usually due to macro-reentry[9] and pharmacological termination is therefore dependent upon alteration of the myocardial refractory period. Whereas chronic administration of amiodarone prolongs the action potential duration and refractoriness of ventricular myocardium, bolus intravenous administration exerts predominantly anti-adrenergic effects and is therefore unlikely to interrupt a macro-reentrant arrhythmia.[10] Furthermore, it is well recognised that intravenous amiodarone acutely depresses myocardial contractility and may cause haemodynamic deterioration or even circulatory collapse in patients with VT.[11 12]

Comparison with historical trial data

The efficacy of amiodarone in the present study and another recent report from Marill *et al*[13] was compared with the alternative agents lidocaine,[14] sotalol[15] and procainamide[16] in the identical clinical setting (table 1). Historical data from published reports were identified by a Medline search, and only studies involving attempted pharmacological conversion of spontaneous VT as primary treatment were included; all reported VT termination rates within 15–20 min. We excluded studies in which VT was induced by programmed electrical stimulation. Also excluded were reports of antiarrhythmic drug treatment (usually prolonged amiodarone infusion) to control recurrent or shock-resistant ventricular tachyarrhythmias, as opposed to acute termination of sustained VT specifically.

Several studies have confirmed the poor efficacy of intravenous lidocaine which only terminates VT in around 20% of cases. However, VT termination rates achieved with sotalol (69%) and procainamide (80%) were significantly higher than with intravenous amiodarone in the present study. With regard to adverse effects, the rate of hypotension requiring emergency DC cardioversion in the present series was higher at 17% (95% CI 8% to 32%) than the 6% (95% CI 1% to 20%) observed by Marill *et al*[13]; notably, all but two of their patients received amiodarone 150 mg. Following intravenous sotalol in the study by Ho *et al*,[15] hypotension requiring DCCV occurred in 10% (95% CI 3% to 26%) of patients. Gorgels *et al*[16] did not report this specific end-point, but the study protocol was terminated in 13% (95% CI 2% to 39%) of patients administered procainamide because of hypotension and/or VT acceleration.

Taken together, these results suggest that bolus intravenous amiodarone is probably no more effective for terminating sustained VT than lidocaine, the agent which it replaced in clinical practice largely because of concerns about the latter's lack of efficacy. The greater efficacy of both intravenous sotalol and procainamide may be attributed to their more immediate effect on ventricular refractoriness.[17]

Study limitations

The data on amiodarone were generated from retrospective case series, whereas sotalol and procainamide were assessed in randomised controlled trials. It is possible that predefined entry criteria for those prospective studies may have selectively excluded sicker patients who were less likely to respond to treatment, thus exaggerating the efficacy of sotalol and procainamide for terminating sustained VT. However, the baseline clinical characteristics—including patient demographics, left ventricular function, VT duration and haemodynamic parameters—were similar in all the studies. Furthermore, the lidocaine control groups of the randomised trials would also

Table 1 Studies of pharmacological agents for the termination of haemodynamically-tolerated sustained monomorphic ventricular tachycardia (VT)

Author	Study type	Patients (n)	Age (years)	IHD (%)	LVEF (%)	SBP (mm Hg)	Drug	VT termination within 15–20 min*
Armengol *et al*[14]	Retrospective case series	20	64	85	NR	NR	Lidocaine	19% (95% CI 9% to 37%)
Marill *et al*[18]	Retrospective case series	35	NR	60	NR	110	Lidocaine	29% (95% CI 15% to 47%)
Ho *et al*[15]	RCT	33	64	91	35	110	Sotalol	69% (95% CI 44% to 86%)
							Lidocaine	18% (95% CI 5% to 42%)
Gorgels *et al*[16]	RCT	29	61	79	30	115	Procainamide	80% (95% CI 54% to 94%)
							Lidocaine	21% (95% CI 7% to 48%)
Marill *et al*[13]	Retrospective case series	33	67	66	34	111	Amiodarone	29% (95% CI 13% to 49%)
Present study	Retrospective case series	41	68	85	31	112	Amiodarone	15% (95% CI 7% to 29%)

IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; NR, data not reported.
*VT termination rate within 15 min was the only time point assessed in the retrospective case series of lidocaine and historical randomised controlled trials (RCT), whereas the pharmacological VT termination rate at 20 min is shown for both case series of intravenous amiodarone.

have been subject to any such selection bias but reported similar termination rates (around 20%) to observational studies.

The numbers of patients involved in all of these studies are small, considering that sustained VT is a reasonably common medical emergency, with correspondingly wide confidence intervals. In addition, because of the retrospective nature of the study, the incidence of hypotension may have been underestimated as only instances that precipitated the need for immediate DCCV were included in the analysis.

Implications for advanced life support guidelines

The emergence of intravenous amiodarone as the main agent used for pharmacological termination of stable VT in clinical practice undoubtedly reflects the powerful influence of advanced cardiac life support guidelines, both in North America and Europe, which have recommended it as a first-line treatment for this indication. The International Liaison Committee on Resuscitation (ILCOR) in 2005 reiterated the viewpoint that "amiodarone is effective in terminating stable sustained VT",[19] and current Resuscitation Council (UK) guidelines still recommend using intravenous bolus dose amiodarone 300 mg.[20] In their review of the scientific evidence, ILCOR cited only one small report that specifically addressed the efficacy of intravenous amiodarone as a primary treatment for terminating sustained VT; Schutzenberger *et al*[21] administered amiodarone 5 mg/kg followed by continuous infusion and converted 8/19 patients (42%) within 1 h (mean 31 min), only slightly higher than the 29% termination rate by 1 hour in the present study.

In the absence of direct evidence, expert opinion has relied on the known antiarrhythmic efficacy of intravenous amiodarone in related but different clinical settings. In particular, several studies have shown that prolonged amiodarone infusion is effective for suppressing recurrent haemodynamically-destabilising ventricular tachyarrhythmias over a time course of several hours to days.[3 4 12 22] However, early recurrence of VT is relatively uncommon (only 1/41 patients in this series) and continuous amiodarone infusion is not required routinely after termination of the initial episode. A second source of indirect evidence has been two randomised trials which demonstrated that bolus intravenous amiodarone improves immediate survival in cardiac arrest due to ventricular fibrillation or pulseless VT.[6 7] Finally, promising results were reported with a new aqueous formulation of intravenous amiodarone in 18 patients with incessant shock-resistant VT, terminating 67% within 1 h.[23]

Perhaps mindful of the shortcomings in the evidence base, the recent AHA/ACC/ESC 2006 practice guidelines have preferentially recommended intravenous procainamide for termination of stable VT and downgraded the role of amiodarone to patients with haemodynamically unstable VT, or VT resistant to shock therapy or recurring despite the use of other antiarrhythmic agents.[24] Intravenous procainamide is licensed in the UK but rarely used, even in specialist units, in contrast to North American practice. Nevertheless, only a direct comparison of these agents in larger scale randomised trials could definitively establish their relative merits.

CONCLUSIONS

Although recommended by current UK advanced life support guidelines, intravenous bolus dose amiodarone is relatively ineffective for the pharmacological termination of stable sustained monomorphic VT. This regime results in haemodynamic deterioration in a significant proportion of cases and may be less effective than other established agents, particularly procainamide and sotalol. A prospective randomised trial is therefore required to establish the optimal pharmacological agent for termination of haemodynamically-tolerated sustained VT in the emergency setting.

Funding: None.
Competing interests: None.

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Images in emergency medicine

A persistently painful hand

The CT scan shows non-union of a fracture through the tip of the hook of the hamate, previously missed by the radiologist on plain radiographs.

Fractures of the hook of hamate are missed on plain radiographs in 50% of cases; CT scanning is now seen as the gold standard investigation for identifying such injuries. They are common in athletes, most often resulting from a heavy golf or tennis swing, but may follow a fall.

Theoretically, non-displaced fractures can heal with immobilisation in a Colle's plaster for 6 weeks. However, the origins of flexor digiti minimi brevis and opponens digiti minimi may cause a failure of a hamate fracture to heal; approximately 46% heal with plaster of Paris immobilisation only. Displaced fractures can be treated with open reduction and internal fixation, but fibrous or non-unions may result from avascular changes in the hook. These generally heal after hamate fragment excision and have been shown to have excellent results.

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Emerg Med J 2008;**25**:18.
doi:10.1136/emj.2007.046516

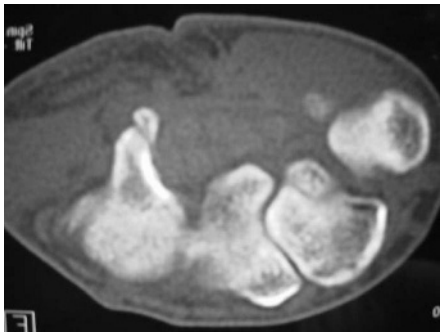

Figure 1 CT scan of left wrist.

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Emerg Med J 2008 25: 15-18
doi: 10.1136/emj.2007.051086