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REVIEW

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Intravenous amiodarone in intensive care

Time for a reappraisal?

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Abstract Amiodarone is widely used in intensive care units for the treatment of a variety of arrhythmias. It is currently the drug of choice for supraventricular tachyarrhythmias in many units because of its combination of efficacy and safety. This review summarises the current state of knowledge regarding the short-term administration of intravenous amiodarone to control arrhythmias in perioperative, coronary care and intensive care patients. It outlines the electrophysiology, haemodynamics, pharmacokinetics and toxicity of the drug. In particular, it examines the recent concerns regarding acute pulmonary toxicity.

Key words Amiodarone · Intravenous · Critical care · Perioperative · Outcome · Atrial fibrillation · Atrial tachyarrhythmias · Ventricular tachyarrhythmias

Introduction

Amiodarone was originally developed in the 1960s as a coronary vasodilator, though its principal current use is as a broad-spectrum anti-arrhythmic agent. There is a widespread clinical impression of efficacy combined with few short-term serious adverse effects that often make it the agent of first or second choice for treatment of atrial tachyarrhythmias. There is also concern that the side effect profiles of other commonly used anti-arrhythmic agents make them unsuitable for use in critically ill patients. This review article will summarise the current state of knowledge regarding amiodarone, and assess the evidence available concerning its efficacy and safety in different patient populations.

Surprisingly, there are only a few placebo-controlled studies in patients with acute onset atrial fibrillation. Studies comparing amiodarone with other drugs indicate that there is both a broad range of efficacy and that alternatives are available for most situations. These studies assess very different patient populations and utilise varying dosage regimens. Just a handful of trials of anti-arrhythmic therapy have been conducted in critically ill patients in general intensive care units, and these have included only small patient numbers.

Toxicity with prolonged administration is a well-recognised problem. However, there is recent evidence of potentially fatal acute pulmonary toxicity associated with short-term administration in critically ill patients. This may require a re-evaluation of the way in which amiodarone is used in the critically ill.

Methods

The English language literature was searched from 1966–1999 initially using Medline under the headings ‘amiodarone’ and ‘intensive care/critical care’, ‘amiodarone’ and ‘intravenous’, ‘amiodarone’ and ‘coronary care’ and ‘amiodarone’ and ‘ischaemic heart disease’. Papers identified were then searched by hand for relevant references.

Indications

Amiodarone can be used to treat most tachyarrhythmias. These include atrial fibrillation, atrial flutter, supraventricular tachycardias of whatever origin (including those associated with pre-excitation), ventricular tachycardia and ventricular fibrillation. It can be used for both cardioversion and heart rate control.

Dosage and administration

The intravenous dose of amiodarone is 300 mg or 5 mg/kg, infused over 20 –120 min. In an extreme clinical emergency, 150–300 mg in 10 ml of 5 % dextrose can be slowly injected over a minimum of 3 min. This may be followed by an infusion of 1200 mg or 15 mg/kg, in 5 % dextrose, over the next 24 h, although higher doses have been used in a small number of trials. The dose should be adjusted on the basis of clinical response. As a general guideline for most situations, 900 mg on the second day and 600 mg on each day thereafter is a recommended protocol. The daily dose should remain high (600 mg/day) until approximately 15 g have been given (i.e. around 3 weeks). Administration through central veins is preferred because of the risk of venous thrombosis and irritation, but large peripheral veins can be used. If the patient requires long-term administration, the usual dosage schedule is 400 mg p.o. daily for one month, followed by a maintenance dose of 200 mg daily.

Pharmacodynamics

Effects on electrophysiology

The most widely used classification of anti-arrhythmic agents is the Singh, Vaughan and Williams classification, which divides anti-arrhythmic agents into four classes: sodium channel blockers, beta blockers/sympatholytic agents, drugs which delay repolarisation and calcium channel blockers. Amiodarone is unique since it possesses properties belonging to all four of these classes [1, 2, 3, 4, 5].

Given intravenously in man the principal effects are beta blockade, a decrease in anterograde conduction across the A-V node, and an increase in the effective atrioventricular refractory period [6, 7, 8, 9].

Effects on haemodynamics

The net effect of amiodarone results from a complex interplay of simultaneous alterations in preload, afterload, contractility and heart rate (Table 1). Furthermore, coronary blood flow may increase.

Table 1 Key points: haemodynamics (*HR* heart rate, *SVR* systemic vascular resistance, *CO* cardiac output, *LVSWI* left ventricular stroke work index, *MAP* mean arterial pressure)

HR reduced or no change
Contractility reduced
SVR reduced
CO increased or no change
LVSWI increased
MAP no change or mildly reduced

The literature is slightly confusing because of the use of different dosages, rates of infusion and study populations (e.g. human or animal studies, presence or absence of sinus rhythm) [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. In sinus rhythm, either a reduction in heart rate or no change (possibly with an initial increase) have been reported. In any individual patient, this will depend on the balance between the directly induced bradycardia and the sympathetic response to vasodilatation. There are occasional severe bradycardias. In the presence of atrial fibrillation, the heart rate is slowed, though to a rate above the patient's usual baseline.

Contractility is mildly reduced. This is more marked at higher doses and with faster infusion rates and may be related to the drug vehicle. The reduction in contractility is offset by a decrease in the systemic vascular resistance. The combination allows cardiac output to remain the same or even increase. Any improvement in cardiac output is generally more marked in the presence of left ventricular dysfunction, presumably because of the more pronounced afterload dependence of the failing heart. However, one study in patients with impaired left ventricular dysfunction demonstrated a marked increase in left ventricular end diastolic pressure and recommended close observation in this group [12]).

There is a slight reduction or no change in mean arterial pressure. Marked hypotension may happen in the presence of pre-existing diastolic dysfunction, but this is rare. Amiodarone is also a coronary vasodilator.

Pharmacokinetics

There is considerable disparity between authors on many of the pharmacokinetic details (Table 2). The volume of distribution is quoted at between 1.3–65 l/kg. It is probably at the higher end of the range cited (50–5000 l) [2, 6, 23, 24]. The half-life is 16–180 days, giving a mean of 52 days [25]. Elimination half-life after a single intravenous dose is 18–36 h. The reported half-life depends on the length of time the patient has been receiving the drug, and whether amiodarone or the metabolite desethylamiodarone is measured. These factors mainly account for the lack of precision regarding half-life. Oral

Table 2 Key points: pharmacokinetics

Volume of distribution very large (require big loading dose)
Half-life very long (after single i. v. dose up to 20 h)
96 % protein bound
Extensive hepatic metabolism
Negligible renal excretion
Dose adjustments rarely required
Onset intravenously within minutes to hours

Table 3 Key points: efficacy

Excellent heart rate control
Rates of cardioversion similar to other agents
Slower onset of action than some other agents
Spontaneous cardioversion common in supraventricular arrhythmias

bio-availability is 30–50 % and amiodarone is 96 % protein bound.

Elimination occurs through extensive hepatic metabolism. There is negligible renal excretion. The major metabolite is desethylamiodarone. This substance is pharmacologically active with equivalent anti-arrhythmic activity and similar onset and offset times [26]. However, it takes several days of continuous infusion to accumulate even low levels of metabolite [27].

In clinical practice, a large loading dose is required and dosage regimens should not be altered in renal disease. Dosage alteration may be required in severe hepatic dysfunction. Pharmacokinetic properties are also unchanged during short-term administration in the elderly, those with severe left ventricular dysfunction or those with ventricular tachycardia/fibrillaion. Dose adjustment is therefore unnecessary [28, 29].

Amiodarone and its metabolites are extremely lipophilic and these accumulate in the liver, lung, fat skin and other organs [30]. For example, the myocardial concentration is 10–50 times the serum concentration. A total dosage of 15 g is generally sufficient to maximise tissue loading. The onset of action when given intravenously is within several hours, possibly within minutes. If given orally, the delay to maximal effect is between 2 and 21 days.

Drug interactions

In intensive care practice, the most important interactions are with digoxin and warfarin. Warfarin metabolism is slowed and the dose should be reduced. The prothrombin time should be monitored closely. Traditionally, the dose of digoxin is halved since the plasma levels double [31, 32]. However, not all investigators have found this interaction in practice [13]. It is also worth noting that there is a body of opinion that believes that digoxin makes cardioversion from paroxysmal atrial fibrillation less, and not more, likely [33].

The serum levels of quinidine, procainamide, mexilitine and propafenone, will also increase so the doses of these agents should consequently be reduced. When amiodarone is given with drugs that prolong the QT interval there will be an increased risk of torsades de pointes. Examples are Class IA and Class III anti-arrhythmics, antimalarials, antihistamines, antipsychotics, lithium, tricyclic antidepressants and some antimicrobials. Amiodarone also potentiates the hypotensive and anti-chronotropic effects of anaesthetic agents. With beta blockers or calcium antagonists there may be marked depression of sinus or A-V nodal function, as well as enhanced negative inotropism.

Clinical efficacy

Table 3 summarises the important issues surrounding amiodarone and efficacy. The perennial problem for intensive care physicians is how best to interpret the results of studies carried out in patient populations completely unrelated to those seen in most general intensive care units. In this review the patient groups are divided into peri-operative, coronary care and intensive care. The widely varying dosage schedules, results and some population characteristics are shown in Tables 4, 5, 6.

Perioperative

Post cardiac surgery, amiodarone has been compared to propafenone, quinidine and digoxin for the treatment of supraventricular arrhythmias. Di Biasi et al. [34] compared amiodarone with propafenone in 84 patients with atrial fibrillation or flutter after cardiac surgery. They found that conversion rates at 1 h (19.5 % vs 44.7 %) were better with propafenone, but that by 24 h amiodarone was superior (82.6 % vs 68.4 %). Side effects were no different between the groups. These findings were closely reproduced by Larbuisson et al. in 40 patients [35].

Cochrane et al. [36] demonstrated that amiodarone was as safe and at least as effective as digoxin in restoring sinus rhythm and controlling heart rate in 30 patients with atrial fibrillation or flutter after cardiac surgery. Both decreased heart rate equally. At the end of 24 h similar numbers (93 % in the amiodarone group and 80 % in the digoxin group) had cardioverted. McAlister et al. [37] performed a randomised crossover trial of amiodarone with quinidine in 80 patients with atrial fibrillation or flutter after cardiac surgery. There was a higher conversion rate with quindine (64 % vs 41 %)

Table 4 Perioperative studies (*A fib* atrial fibillation, *A flut* atrial flutter, *LVF* left ventricular failure, *SBP* systolic blood pressure)

Study	Dose	No.	Arrhythmia	Outcome (rate of cardioversion)	Comments
Di Biasi [34]	5 mg/kg over 15 min, 15 mg/kg over 24 h	84	A fib, A flut	1 h 19.5 %, 24 h 82.6 % (propafenone 1 h 44.7 %, 24 h 68.4 %)	LVF included except SBP < 90 mmHg
Larbuisson [35]	2.5–5 mg/kg over 10 min, 900 mg over 24 h	40	A fib, A flut	1 h 14 %, 24 h 77 % (propafenone 1 h 41 %, 24 h 67 %)	Mild LVF only
Cochrane [36]	5 mg/kg over 30 min, then 25 mg/h (increased to 40 mg/h if HR > 140 after 6 h) for 24 h	30	A fib, A flut	24 h 93 % (digoxin 24 h 80 %)	No LVF
Mcallister [37]	5 mg/kg over 20 min	80	A fib, A flut	8 h 41 % (quinidine 8 h 64 %)	Including LVF
Installe [38]	2.5–5 mg/kg over 2–4 min then 1200 mg in 24 h	90	Any supra-ventricular arrhythmias	61 % (time of cardioversion not clear)	Included supra-ventricular extrasystoles

at 8 h though the loading dose of 5 mg/kg amiodarone was not followed by an infusion.

One uncontrolled trial [38] used a rapid bolus (2–4 min) and achieved cardioversion in 61 % of supraventricular arrhythmias. However significant hypotension occurred in 18 % of patients. The same group also reported satisfactory efficacy in five cases of ventricular arrhythmias. There is little other reported experience with amiodarone perioperatively for the treatment of ventricular arrhythmias, and no conclusions can be reached on the basis of the small, uncontrolled trials thus far reported. However, the evidence of efficacy in ventricular arrhythmias in other settings (see below) suggest that amiodarone should be a valuable tool. Two trials have shown a reduction in non-sustained ventricular tachyarrhythmias post-cardiac surgery with prophylactic amiodarone [39, 40]. However, as with lignocaine prophylaxis, there was no effect on mortality [41].

Coronary care

Despite the different underlying pathology between coronary care patients and intensive care patients, the majority of work with amiodarone has been carried out in this group. In uncontrolled trials [42, 43, 44, 45] (Table 5) amiodarone cardioverted 61–89 % of various atrial tachyarrhythmias. When compared with other agents, amiodarone's performance is variable. Cowan et al. [46] found amiodarone to be much more successful than digoxin in cardioverting atrial fibrillation (71 % vs 31 %), and controlling heart rate, in the presence of ischaemic heart disease. There was, however, no difference at 24 h. Galve et al. [47], however, found no significant difference in conversion rates between amiodarone plus digoxin (68 %) and digoxin alone (60 %) in 100 patients, only 18 of whom had ischaemic heart disease as the underlying cause. In contrast, Hou et al. [48] directly compared amiodarone with digoxin, observing a higher conversion rate with amiodarone (92 % vs 71 %) and more effective heart rate control but more adverse events, including a death following extreme bradycardia.

When compared with flecainide [49] and placebo, cardioversion at 2 h was more likely to occur with flecainide than with amiodarone or placebo (59 % vs 34 % vs 22 %). At 8 h there was no significant difference between the groups (68 % vs 59 % vs 56 %) while amiodarone had superior heart rate control. Compared to cibenzoline, amiodarone had an identical rate of cardioversion (71 % vs 72 %) and a similar incidence of adverse events [50]. A crossover study with verapamil showed greater cardioversion effect with amiodarone (71 % vs 7 % for verapamil). One episode of hypotension occurred in each group [51].

In summary, when compared with other anti-arrhythmics in this group of patients, amiodarone appears equally efficacious. It may not act as quickly as some agents but it often gives superior heart rate control, even compared to digoxin. The wide variation in reported efficacy may be related both to the different timing of assessment for cardioversion, and the small numbers in some studies. It is noteworthy that four coronary care studies used placebo or digoxin control groups, while one perioperative study used a digoxin control group. Assuming digoxin acts to control heart rate only, these studies can all be regarded as placebo-controlled for the purposes of cardioversion. Amiodarone was no more likely than digoxin/ placebo to produce cardioversion at between 8 and 24 h in four of these five studies.

Table 5 Coronary care studies (*LVF* left ventricular failure, *SBP* systolic blood pressure, *A fib* atrial fibillation, *A flut* atrial flutter, *SVT* supraventricular tachycardia, *AMI* acute myocardial infarction, *EF* ejection fraction, *dig* digoxin)

Study	Dose	No.	Arrhythmia	Outcome	Comments
Vitelli-Ramus [42]	Mean 1400 mg in 24 h	44	SVT 15, A fib 21, A flut 8	24 h SVT 100%, 24 h A fib 85.7%, 24 h A flut 75%	Included LVF but mean EF 60%
Cybulski [43]	Mean 340 mg AF, 220 mg for SVT	142	A fib, SVT	65% A fib at mean 5.5 h, 61% SVT at mean 1.2 h	Included LVF
Strasberg [44]	5 mg/kg over 3–5 min	26	A fib	73% (46% < 30 min, remainder < 8 h)	Included LVF except SBP < 100
Faniel [45]	7 mg/kg over 30 min 1500 mg over 24 h	26	A fib	24 h 80.8%	Included LVF
Kumar (10)	300 mg over 1 h	8	A fib, A flut	1 h 87.5%	Included severe LVF
Cowan [46]	7 mg/kg over 30 min, total 1500 mg over 24 h	34	A fib (in ?AMI)	4 h 72%; 24 h 83% (dig 4 h 31%; 24 h 75%)	No pulmonary oedema or SBP < 100 mmHg
Galve [47]	5 mg/kg over 30 min then 1200 mg in 24 h	100	A fib	With dig 24 h 68% (dig alone 24 h 60%)	Only mild LVF
Hou (48)	5 mg/min for 1 h, 3 mg/min for 3 h, 1 mg/min for 6 h, 0.5 mg/min for 14 h	50	A fib, A flut	24 h 92% (dig 24 h 71%)	Excluded cardiogenic shock or SBP < 80 mmHg
Donovan [49]	7 mg/kg over 30 min	98	A fib	2 h 34%; 8 h 59% (Flecainide 2 h 59%; 8 h 68%, Placebo, 2 h 22%; 8 h 56%)	No significant LVF
Andrivet [50]	5–7.5 mg/kg over 30 min, 10–15 mg/kg over 24 h	46	A fib, A flut, A tachycardia	24 h 71% (cibenzoline 24 h 72%)	No LVF
Noc [51]	5 mg/kg over 3 min	24	A fib	3 h 77% (verapamil 3 h 0%)	No LVF

Uncontrolled trials treating ventricular tachycardias and ventricular fibrillation resistant to conventional therapy [52, 53, 54] have demonstrated successful arrhythmia control in 40.3–100% of cases. When low and high dose amiodarone were compared with bretylium, there was no difference in mortality between groups. There were fewer arrhythmic events in the bretylium and high dose amiodarone groups [55].

Intensive care

Atrial tachyarrhythmias are common in patients who are critically ill. These are associated with increased pulmonary artery wedge pressure, decreased cardiac output, a deterioration in respiratory function [56] and increased mortality [57]. Although successful treatment of these arrhyhthmias has never been shown to improve mortality, the published evidence available for the efficacy of amiodarone in achieving cardioversion and heart rate control in these patients is sparse. Only four small studies have been undertaken in patient populations similar to those encountered in a general intensive care unit.

Kumar [10] and Holt [13] both demonstrated efficacy (cardioversion in 7/8 and 9/10 respectively) and, importantly, haemodynamic stability in critically ill patients. Kumar's eight patients had severe left ventricular dysfunction (left ventricular ejection fraction < 15%) while Holt's patients all had severe sepsis requiring inotropic therapy to maintain blood pressure. Amiodarone was infused slowly and produced no untoward haemodynamic effects. Indeed, haemodynamically there was, in general, a marked improvement. This cardio-stability in critically ill patients was confirmed by Leak (150 mg over 5 min, then 600 mg in 24 h) and Benditt (900–1600 mg/24 h) when treating life-threatening refractory arrhythmias [53, 54].

Chapman et al. [58] compared procainamide to amiodarone in 24 patients with atrial tachyarrhythmias after precipitating factors (hypoxia, hypokalaemia, hypomagnesaemia and hypophosphataemia) had been corrected as far as possible. They found an almost identical conversion rates of 70% and 71%. Neither group had significant haemodynamic deterioration, despite the need for adrenaline to treat the underlying condition in five of the procainamide group and three of the amiodarone group. Moran et al. [59] found magnesium to be

Table 6 Intensive care studies (*LVF* left ventricular failure, *SBP* systolic blood pressure, *A fib* atrial fibillation, *A flut* atrial flutter, *SVT* supraventricular tachycardia, *AMI* acute myocardial infarction)

Study	Dose	No.	Arrhythmia	Outcome	Comments
Chapman [58]	3 mg/kg over 15, 10 mg/kg over 24 h, further 3 mg/kg at 1 h if no response	24	Atrial tachy-arrhythmias	12 h 70 % (procainamide 12 h 71 %)	Included all patients except SBP < 80 mmHg
Holt [13]	Mean 4.3 mg/kg over 2 h, mean 13.6 mg/kg over 24 h	10	A fib, A flut, A tachy-arrhythmias	12 h 80 %, 24 h 90 %	Including severe LVF
Moran [59]	5 mg/kg over 15 min, 10 mg/kg over 24 h	42	A fib, A flut, other SVTs	1 h 12 %; 2 h 38 %, 4 h 44 %; 12 h 50 %, 24 h 50 % (magnesium 1 h 22 %; 2 h 39 %, 4 h 61 %; 12 h 72 %, 24 h 78 %)	Included all patients except SBP < 80 mmHg
Clemo [60]	Mean 242 mg over 1 h, mean 1137 mg over 24 h	38	A fib, A flut	29/38 at 24 h; 18 with amiodarone only, 11 with DC shock (cardioversion not primary end point of study)	Retrospective but included patients with LVF

Table 7 Key points: toxicity

Possible severe pulmonary toxicity with short-term use
Definite pulmonary toxicity with long-term use
Occasional extreme bradycardias
Occasional hypotension

superior to amiodarone in cardioverting atrial tachyarrhythmias in 42 patients in a multidisciplinary intensive treatment unit (Table 6). Both drugs were cardiostable in this group of patients, who had mean APACHE II scores of 22. Magnesium concentrations in both groups were similar and within normal limits. Although serum magnesium levels are no guide to cellular levels, the authors make a good case for magnesium as an anti-arrhythmic in its own right. However, 17 potentially arrhythmogenic infusions (i.e. adrenaline, dobutamine, salbutamol or aminophylline) were running in the amiodarone group (number eventually included = 16) compared to ten in the magnesium group ($n = 18$). Further work comparing these two agents would be of great value and interest.

Finally, Clemo et al. [60] used amiodarone successfully in 38 critically ill patients for heart rate control after failure of other therapy (digoxin, esmolol or diltiazem). Eighteen of the patients required inotropes or vasopressors, six had an intra-aortic balloon pump and one had a left ventricular assist device. Improvements were noted in systolic blood pressure, pulmonary artery wedge pressure and cardiac output.

We were unable to find any paper demonstrating an effect, or otherwise, of amiodarone on ventricular tachyarrhythmias in critically ill, ventilated patients.

Toxicity

Prolonged administration of amiodarone is associated with side effects in up to 80 % of patients (Table 7). Withdrawal of therapy is necessary in 10–15 % of patients [23]. These side effects are multi-system, serious but generally not life-threatening. There is recent evidence, however, associating amiodarone with potentially fatal acute pulmonary toxicity. This is a cause for genuine concern.

Clinically important acute changes take place in only the respiratory and cardiovascular systems [23, 61, 62].

Pulmonary toxicity

Amiodarone-induced pulmonary toxicity (APT) is a well recognised but poorly understood complication of amiodarone therapy. The reported frequency of APT ranges from 0–61 % [61, 63], but a figure of 5–10 % may be more realistic. A delayed pulmonary reaction (i.e. several months or years after the start of treatment) is the more common form of APT. It commonly presents insidiously with non-specific features such as cough, fatigue, low-grade fever and dyspnoea or, rarely, with acute respiratory failure.

An acute form (i.e. occurring within the first few weeks of therapy) presents with fever, pleuritic chest pain and a cough. Examination reveals crepitations and, occasionally, a pleural rub. There is a raised erythrocyte sedimentation rate (ESR) in 47–100 % of patients, a raised white cell count and elevated LDH levels. The diagnosis outwith the intensive care unit is made using clinical symptoms and confirmed by reduced diffusing lung capacity for carbon monoxide (DLco) and bilateral reticulonodular infiltrates on chest X-ray. Gallium scans, bronchoalveolar lavage or lung biopsy are used in non-specific or atypical cases. Positive gallium

scans, foamy alveolar macrophages on biopsy or lavage, and improvement of chest X-ray appearances on withdrawal of amiodarone or institution of steroid therapy all support the diagnosis. Conversely, a normal DLco and a lack of foamy alveolar macrophages on lavage or biopsy make the diagnosis less likely. In the critically ill patient, some of these symptoms cannot be described and some investigations cannot be performed. Diagnosis is thus made using a combination of clinical history, chest X-ray appearances and bronchoalveolar lavage.

Treatment is essentially supportive. Amiodarone therapy should clearly be withdrawn. Its prolonged half-life means there may be no immediate improvement. Some authors have suggested the addition of corticosteroids [64].

Of more relevance to intensive care physicians, there is recent evidence from four centres that acute administration of amiodarone can cause the rapid development of pulmonary toxicity. Laprinsky et al. noted the development of pulmonary phospholipidosis 6 days after commencing therapy [65]. Donaldson et al. in a retrospective analysis of post mortem data noted three cases of acute APT in patients receiving greater than 48 h of amiodarone [66]. They also commented on the possible association of APT with patients receiving a high FIO_2. It is suggested that some of the damage caused by amiodarone may be mediated by toxic oxygen free radicals. Acute APT has also been noted following thoracic surgery; 3 of 11 patients receiving amiodarone prophylaxis for only 2–3 days developed ARDS after pneumonectomy. In contrast, 0 of 21 patients receiving placebo or verapamil developed this problem [67]. A further case report demonstrated acute toxicity in an infant after only 8 days of amiodarone therapy [68].

A high index of suspicion is required to identify this rare cause of deteriorating oxygenation and worsening pulmonary infiltrates in patients with a high risk of new or progressive acute lung injury (including ventilator-induced lung injury).

Cardiovascular toxicity

The incidence of arrhythmia is very low and probably amongst the lowest of all anti-arrhythmic agents. Torsades de pointes almost always occurs when amiodarone is administered with another QT prolonging drug (especially class 1A anti-arrhythmics) or in the presence of hypokalaemia [69, 70, 71, 72].

Although left ventricular failure is a theoretical possibility because of the negative inotropic effect of amiodarone [12], it is rarely seen in practice. Hypotension may occur, especially when amiodarone is given by bolus or at fast infusion rates. Bradycardias are possible, and may occasionally be both severe and life-threatening [48]. Sinus bradycardia is common and atrioventricular node conduction abnormalities, including complete heart block, may occur when co-administered with verapamil or general anaesthetic agents.

Other forms of toxicity

Besides the important cardiovascular and respiratory effects outlined above, there are other side effects that occur only after prolonged administration. These include disturbances of thyroid function, corneal microdeposits, gastro-intestinal problems and photosensitivity. These are not relevant to acute intravenous administration in intensive care.

Current place in therapy

There are no guidelines concerning the use of amiodarone in intensive care units. The present policy for treatment of atrial tachyarrhythmias in our intensive care unit is to optimise oxygenation and fluid balance, correct electrolyte abnormalities (especially potassium and magnesium), minimise myocardial ischaemia and reduce, where possible, arrhythmogenic infusions. If cardioversion is considered possible and an anti-arrhythmic agent is needed, first line therapy is magnesium sulphate (8 mmol bolus, followed by 64 mmol over 24 h) irrespective of serum magnesium levels. The evidence available for the efficacy of magnesium in various settings has been recently comprehensively reviewed [73]. This strategy may require to be updated if assessment of magnesium status becomes easier and more accurate. If this is unsuccessful, amiodarone is used as the second line agent. Amiodarone therapy is limited to 48 h of therapy unless absolutely necessary. For ventricular tachyarrhythmias, if DC shock is ineffective or inappropriate, amiodarone remains our drug of choice.

Summary

In critically ill patients, amiodarone is indicated for a wide range of arrhythmias. It is haemodynamically stable and frequently very effective at controlling ventricular rate. In many patients, however, there are alternatives available for treatment of tachyarrhythmias. These may be equally effective, be less expensive, have fewer interactions with other drugs, and may have less risk of serious long-term and short-term adverse effects. Furthermore, atrial arrhythmias often cardiovert spontaneously.

In addition, there are an increasing number of reports in critically ill patients highlighting occasional serious acute pulmonary toxicity. It is the authors' view that

there is now enough evidence to urge a degree of caution in the use of amiodarone in the critically ill, especially in the presence of a high FIO_2 requirement. It is now our policy to restrict the duration of therapy to 24–48 h, except when absolutely necessary. Patients receiving intravenous amiodarone who develop new or progressive pulmonary infiltrates or worsening pulmonary disease should be considered for bronchoalveolar lavage. The presence of foamy alveolar macrophages in the lavage fluid confirms the diagnosis of APT. Further evaluation, including both efficacy and safety, of the currently available anti-arrhythmics is required for the rational treatment of tachyarrhythmias in the critically ill patient.

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