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Intravenous Amiodarone

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Intravenous amiodarone was approved in 1995 for the treatment of malignant and resistant ventricular arrhythmia. Although it is an "old drug," much has been learned recently about this complex drug and its application in a variety of cardiac arrhythmias. The objectives of this review were to summarize what is known about intravenous amiodarone, including its pharmacologic and electrophysiologic effects, to review its efficacy for the treatment of patients with highly malignant ventricular arrhythmia and to provide specific information about its clinical use for this and other indications. The studies that were reviewed were selected on the basis of time published (from 1983 to 1995) and the completeness of information provided regarding patient clinical characteristics, drug dosing and methods of evaluation, efficacy analyses, long-term follow-up and complications. The full data from the three controlled trials that formed the basis of the drug's approval are contained in published reports that were also extensively reviewed. Intravenous amiodarone has demonstrable efficacy for the treatment of frequently recurrent destabilizing ventricular tachycardia and ventricular fibrillation, with suppression rates of 63% to 91% in uncontrolled trials. The three pivotal trials confirmed these findings and demonstrated a dose–response relation, with at least comparable efficacy to bretylium, a drug with a similar indication. The safety profile has also been well described; cardiovascular adverse effects are the most frequent, especially hypotension. Intravenous amiodarone is a useful addition to the drugs available for the treatment of patients with very severe ventricular arrhythmia. Its use in patients with other rhythm disorders appears promising, but final recommendations must await development of definitive data from ongoing clinical trials.

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Amiodarone has emerged as an important drug for the treatment of cardiac arrhythmia (1,2). Its clinical use is increasing as evidence mounts as to its utility for a variety of forms of atrial and ventricular arrhythmias. It can be anticipated that indications for its use may broaden in the next few years as several key clinical trials conclude (3,4). For example, the European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) have been completed and the preliminary results presented (5,6). It would appear that amiodarone has the potential to reduce arrhythmic mortality in patients after myocardial infarction, even though there was no difference in overall survival.

Intravenous amiodarone, like the oral form, has been available in several countries for many years (7,8). It was originally used in the United States under licenses obtained by individual investigators (9). When a U.S. firm obtained marketing rights in the mid-1980s, individual licenses were revoked, and the company began controlled clinical trials that were completed in 1992. The data from those trials were presented to the Food and Drug Administration in 1994, and the drug was approved in August 1995 for the acute suppression of hemodynamically destabilizing ventricular tachycardia (VT) and ventricular fibrillation (VF) refractory to therapy with conventional antiarrhythmic drugs. The purpose of this report is to review intravenous amiodarone, including its pharmacology, efficacy and safety data, dosing recommendations and other relevant information, to provide a framework for its proper clinical use.

Pharmacology

Pharmacokinetics. As with the oral form, intravenous amiodarone has a complex pharmacology that begins with its formulation (10). Because it is not water soluble, the commercial preparation uses a solvent—polysorbate-80—that may contribute to the hypotensive effect of the commercially available compound (11). Polysorbate-80 has also been shown to decrease heart rate, depress atrioventricular (AV) node conduction and increase atrial and ventricular refractory periods (12). Once infused, a large percentage of amiodarone is protein bound predominantly to albumin and also to beta-lipoprotein and alpha-1 acid glycoprotein, an acute-phase reactant (13,14). The drug is metabolized mainly by a P_{450} cytochrome oxidase (CYP3A4)-dependent oxidative deethylation. The principal metabolite is desethylamiodarone, which is

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Abbreviations and Acronyms

AV = atrioventricular
CAMIAT = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
CHF = congestive heart failure
EMIAT = European Myocardial Infarct Amiodarone Trial
VF = ventricular fibrillation
VT = ventricular tachycardia

active and has an electrophysiologic effect similar to the parent compound (15). Many other metabolic pathways are known to exist, including glucuronidation, which precedes biliary clearance. A much smaller amount of metabolite is produced when the drug is given intravenously rather than orally unless the drug is infused for several days (16). Amiodarone is widely distributed in the body after intravenous administration, and a three-compartment model best explains its distribution kinetics (17). In addition to a relatively small central compartment, there appears to be both a peripheral and deep compartment. Highest levels of amiodarone and its primary metabolite have been found in the deep compartment, which consists of lymph nodes, liver, lung, and fat and has a steady state partition coefficient relative to plasma of 100 to 1,000 (15). The peripheral compartment is composed of muscle and brain that provide a smaller volume of distribution and a lower solubility coefficient. This model helps to explain the observed phases of plasma elimination after drug discontinuation, including a fairly short initial half-life followed by a much longer elimination period as amiodarone redistributes from deep stores (18). The longer the infusion of intravenous amiodarone, the greater the amount of parent and metabolite that is deposited in the deep compartment. The presence of a large, deep site of distribution accounts for the delay in the onset of antiarrhythmic activity when smaller loading doses are used; a higher dose is necessary to attain a myocardial and plasma concentration during the time that the deep compartment is being filled (19). Elimination is through the biliary system, with essentially no renal component, so that doses need not be adjusted in renal failure (20,21). Amiodarone cannot be removed with dialysis (22). With the possible exception of massive hepatic failure, systemic diseases, including congestive heart failure, do not mandate intravenous amiodarone dose reduction, nor is there any need to use lower doses in the elderly (23).

Drug interactions. Intravenous amiodarone, like the oral form, would be expected to interact with a large number of other drugs, either pharmacokinetically or pharmacodynamically, especially when used for several days (24). Amiodarone inhibits the action of subtypes of the cytochrome P-450 enzyme system. It will increase the levels of several drugs that are thus metabolized, including quinidine, procainamide and warfarin (25,26). The mechanism of the interaction between amiodarone and digoxin is complex, but amiodarone may double steady state digoxin plasma levels when administered concomitantly (27). In addition, drugs such as barbiturates should decrease, and cimetidine may increase, serum amiodarone concentrations. Perhaps more relevant to the use of the intravenous formulation is the pharmacodynamic interactions between amiodarone and a variety of drugs that slow the sinus node and retard conduction through the AV node, including beta-adrenergic and calcium channel blocking agents as well as digitalis (28,29). This is particularly relevant in the treatment of patients with underlying conduction system disease.

Electrophysiologic actions. Intravenous amiodarone has a number of electrophysiologic actions by virtue of its diverse effects on specialized and nonspecialized atrial and ventricular tissue (30,31). It slows intraventricular conduction by blocking the sodium channel; slows the heart rate and impedes AV node conduction by blocking beta-adrenergic receptors and calcium channels; and prolongs atrial and ventricular repolarization by inhibiting potassium channels (32). Sodium channel block probably results from interaction with a number of channel conformations (33,34). The net effect is slowing of conduction that is frequency dependent (exaggerated at higher heart rates). Nanas and Mason (35) have reported a significant correlation between conduction velocity slowing and canine ventricular myocardial concentrations during intracoronary infusion. This early electrophysiologic effect was not accompanied by changes in repolarization. The antisympathetic effect is caused by a noncompetitive alpha- and beta-blockade (36). Although this effect may not be detected by a decrease in heart rate, it may be an important factor in the suppression of acute electrical instability. Depression of sinus rhythm and AV node function in the early phases of treatment is a net result of variable contributions of beta-adrenergic and calcium channel blockade, either or both of which suppress triggered activity and thus may explain the low proarrhythmia potential of amiodarone (37). It may also be that these early electrophysiologic effects may be the most important factor in distinguishing the intravenous from the oral form of the drug. The class III action of the drug may be the least identifiable during the early phases of intravenous therapy. Right ventricular effective refractory periods, prolongation of which is an index of class III effect, are minimally increased during the early phases of intravenous dosing (38,39). A potassium channel blocking action may be more relevant and important during long-term therapy (40). The effects of intravenous amiodarone on pacing and defibrillation thresholds have not been well studied, but a clinically significant increase in defibrillation threshold in animal models or humans has not been shown (41,42).

Hemodynamic effects. The predominant hemodynamic effect of intravenous amiodarone is hypotension caused by a combination of arterial vasodilation and negative inotropy (43). The former may be caused in part by its solvent polysorbate-80 (11). Blood pressure decreases commonly, even in patients without preexisting left ventricular dysfunction, but hypotension may be ameliorated by slowing the rate of infusion. The direct negative inotropic effect of the drug is minimal and transient, may be partially caused by its antisympathetic effect and usually does not lead to a decreased cardiac output. The net hemodynamic effect in patients with antecedent left

Table 1. Selected Clinical Trials

Study (ref no.)	Arrhythmia	No. of Pts	Daily Dose		Acute Efficacy (% of pts)	Adverse Effects (% of pts)	Follow-Up	
			Initial	Infusion (24 h)			Mean Time	Survival Rate
Morady et al. (46)	VT	15	5 mg/kg	600–1,000 mg	80%	AV block (7%)	8 mo	92%
Klein et al. (47)	VT	13	5 mg/kg	10 mg/kg	69%	Shock (8%)	N/A	N/A
Helmy et al. (48)	VT/VF	46	5 mg/kg	1,000 mg	72%	Hypotension/shock (13%)	24 mo	54%
Schmidt et al. (49)	VT/VF	36	300 mg	900–1,200 mg	81%	Hypotension (20%)	10 mo	62%
Ochi et al. (50)	VT/VF	22	240–480 mg	900–1,600 mg	64%	CHF (9%)	22 mo	36%
Schutzenberger et al. (51)	VT/VF	26	5 mg/kg	1,050 mg	73%	Hypotension (19%), bradycardia (4%), proarrhythmia (4%)	N/A	N/A
Williams et al. (52)	CA	14	150–600 mg	N/A	79%	CHF (14%), bradycardia (14%)	14 mo	21%
Mooss et al. (53)	VT/VF	35	5 mg/kg	20–30 mg/kg	63%	Hypotension (23%), bradycardia (14%)	19 mo	34%
Nalos et al. (54)	VT	22	300 mg	1,440 mg	91%	Hypotension (41%), bradycardia (23%)	N/A	86%

AV = atrioventricular; CA = cardiac arrest; CHF = congestive heart failure; N/A = not applicable; Pts = patients; ref = reference; VF = ventricular fibrillation; VT = ventricular tachycardia.

ventricular dysfunction is of particular importance because these patients are the usual treatment targets. This has been addressed in small trials in which such patients have been studied and have had no significant change in hemodynamic profile and no deterioration in functional status (44). Individual cases of hemodynamic collapse have been reported in this impaired population, especially when the drug is infused rapidly (45).

Efficacy

There have been numerous observational studies regarding the efficacy of amiodarone for VT and VF (Table 1) (46–54). There is so much diversity among these studies in terms of patient populations, drug doses and methods of evaluation that it is difficult to derive any firm conclusions about efficacy. Most of these trials included patients in whom previous attempts to control VT or VF, or both, with available drugs had failed. Nevertheless, these studies have value because they indicate that intravenous amiodarone can reduce the frequency of recurrence of VT and VF and can terminate ventricular arrhythmias in very ill patients, including some undergoing resuscitation at the time they received the drug. The studies also provide some guidance as to selection of an effective drug dose and have identified potential adverse effects that helped in designing proper clinical trials.

Three large clinical trials of the relative safety and efficacy of intravenous amiodarone were initiated in the late 1980s and were completed and published within the past year (55–57) (Table 2). The enrollment criterion for all three studies was at least two episodes of hemodynamically destabilizing VT or VF within 24 h of entry despite treatment with lidocaine, procainamide and bretylium (except in the bretylium comparison study). The index arrhythmias were not associated with QT prolongation and were not caused by a drug or electrolyte abnormality. The patient population was similar in the three studies. The average age was 60 years, with a male preponderance. Most of the patients had coronary artery disease and acute or old myocardial infarction. The mean left ventricular ejection fraction was 30%. Approximately 25% of patients were on a ventilator or intraaortic balloon pump before enrollment; 11% were having an acute myocardial infarction; 10% were undergoing cardiopulmonary resuscitation; and >20% could not give informed consent because of altered consciousness.

Because placebo-controlled studies were not deemed feasible and were probably unethical in such ill patients, alternative designs were sought. The first was a randomized, double-blind, dose-ranging study in which a clear difference in response rates among the three dose groups could be considered a surrogate for efficacy (55). This study used doses of 500, 1,000 and 2,000 mg/24 h. Dosing started with 75 to 300 mg administered over 10 min, followed by an infusion of 0.5, 1.0 or 2.0 mg/min for 6 h and then a maintenance infusion of 0.25, 0.5 or 1.0 mg/min for the next 24 h. Differences in event rates and time to first event did not reach statistical significance. Adverse effects occurred with about equal frequency among the three dose groups. Total and cardiac mortality rates were not different among the groups.

The second trial was also a dose-ranging study but used a lower range of doses of 125, 500 and 1,000 mg/day (56). As in the other trials, ~90% of the patients enrolled had VT, and the remaining 10% had VF. There were more events per hour and a shorter time to first event in the low dose group, and the outcome differences among groups were of borderline statistical significance. In addition, provisions had been made in the protocol for supplemental boluses of 150 mg of intravenous amiodarone for recurrent arrhythmias. The number of supplemental doses per hour of study was significantly greater in the patients assigned to the 125-mg dose than in those in the

Table 2. Results From Three Pivotal Trials

Study (ref no.)	Dose Groups (mg/24 h)	Presenting Arrhythmia			No. of Events/ 24 h	Pts Event Free at 24 h (%)	Mean No. of Supplemental Boluses/h	Mortality Rate at 48 h (%)	Cardiovascular Adverse Event Rate (%)				
		VT	IVT	VF					Hypotension	Bradycardia	Asystole	Proarrhythmia	CHF
Levine et al. (55)	500	60	22	6	N/A	30	0.24	20	17	6	6	5	1
	1,000	56	32	4	N/A	40	0.18	21	10	3	3	1	2
	2,000	61	27	5	N/A	38	0.15	22	17	6	4	1	2
Scheinman et al. (56)	125	68	37	12	1.68	37	0.21	21	24	5	5	0	3
	500	62	43	14	0.96	42	0.14	19	27	7	7	2	2
	1,000	64	29	13	0.48	43	0.11	22	26	5	5	1	4
Kowey et al. (57)	125	71	21	7	1.68	38	0.16	13	24	2*	—	1	0
	1,000	64	25	11	0.48	43	0.16	12	27	3	—	0	0
	2,500 (bretylium)	71	18	11	0.96	46	0.22	17	26	4	—	1	5

*Reported as heart block/node rhythm. IVT = incessant ventricular tachycardia, other abbreviations as in Table 1.

1,000-mg dose group (0.21 vs. 0.11, $p < 0.04$), a finding that was a confirmation of dose responsiveness.

The third major efficacy study was a double-blind comparison with bretylium, a drug previously approved for similar indications (58,59). Patients were randomized to receive treatment with conventional doses of bretylium and either 125 or 1,000 mg of intravenous amiodarone (57). The higher dose of amiodarone and bretylium had comparable response rates (using the same end points) in this trial, and patients receiving either of those treatments fared better than those in the low dose amiodarone group (Table 2). The intention to treat analysis was partially confounded by a high rate of crossover from bretylium to open label amiodarone, primarily because of intolerable hypotension that occurred about twice as often with bretylium as with high dose amiodarone. Once again, there was no mortality difference among the three therapies. A post hoc analysis of all three controlled trials was carried out to determine whether there were any clinical characteristics in this patient population that could predict a favorable response both in terms of event and mortality rates (60). Patients with preserved left ventricular function (ejection fraction >35%) who received a dose of 1,000 mg/24 h had a median of 1.0 events/48 h compared with 3.8 events/48 h in patients with an ejection fraction <35%. The difference in mortality between these groups was also statistically significant.

Safety

Observational studies of intravenous amiodarone have provided some data regarding its potential short- and long-term toxicity. Unfortunately, none of these trials were large enough or of sufficient duration to permit definitive conclusions (46–54,61–64). The three large clinical trials were useful because the data were carefully collected and catalogued; some patients received the drug for several weeks; and follow-up information was immediately available. In addition, when the controlled trials were concluded, investigators were permitted to enroll patients in an open label trial. At last analysis, 1,836 patients were in this data set (65). Interpretation of this large body of information is confounded by the fact that there was no placebo group in any of the trials. Thus, in this sick patient population, it is not possible to discern which adverse effects are due to drug or to the underlying disease process.

Cardiovascular adverse effects were most common, and the most frequent of these was hypotension, occurring in 10% to 30% of patients in the controlled trials. It was observed more commonly with rapid rates of infusion, but in the clinical trials there was no significant difference in the incidence of hypotension among the dose groups. Less than 10% of the patients who developed hypotension in the controlled trials had blinded therapy discontinued. The majority responded to adjustment of the rate of infusion, fluid administration or judicious use of a parenteral vasopressor or inotrope. Severe bradycardia and second- and third-degree AV block, both intranode and infranode, have also been reported and were seen in the clinical trials with a frequency of <2% (66,67). However, 10% to 20% of patients who developed this complication required a temporary transvenous pacemaker for rate support if the drug was continued. Although intravenous amiodarone causes QT prolongation, the incidence of torsade de pointes was low (<1%) (37,68). However, identifying worsening arrhythmia in a patient population with such frequent episodes is difficult. The prospective definition of ventricular proarrhythmia for all the clinical trials was torsade de pointes (long QT interval and polymorphous VT initiated with a typical short–long–short cycle length) or the development of VF after drug infusion in patients who only had VT before the drug. Approximately 1.3% of patients in these trials had arrhythmia aggravation using these criteria (65).

Noncardiac adverse effects have been reported frequently both in published reports and in the clinical trial experience (69). Many of these were nonspecific and possibly related to the underlying disease process. A variety of pulmonary, hepatic, endocrine and cutaneous complications were reported in the clinical trials, but none appeared to have the typical features of the organ toxicity reported during long-term oral

therapy, and they frequently resolved despite continuation of the drug. Organ toxic side effects, such as transaminase elevation and thyroid abnormalities, did increase in frequency in the patients who were treated with the intravenous preparation for a longer period of time. This observation supports the notion that the duration of therapy is an important factor in the emergence of certain noncardiac adverse effects.

Clinical issues

Dosing. On the basis of the pharmacologic profile of intravenous amiodarone, there appears to be a large interindividual variation in time to response during the initiation of intravenous therapy (70). Consequently, dosing recommendations derived from the clinical trial experience provide a guideline only. Close patient observation and dose adjustments are essential. For example, hypotension and other cardiac adverse effects that may be seen during initial rapid infusion may improve substantially with a decrease in the rate of infusion. In contrast, supplemental boluses are frequently needed for patients who have recurrent arrhythmias during the early phases of dosing. The recommended initial loading dose is 150 mg administered over 10 min, followed by an intermediate infusion of 1 mg/min for 6 h and then 0.5 mg/min thereafter. Supplemental boluses of 150 mg may be given over 10 to 30 min for recurrent arrhythmias, but because hypotension occurs more frequently at daily doses >2,000 mg/day, no more than six to eight supplemental boluses in any 24-h period may be possible. Plasma levels are not routinely used because they are high and uninterpretable in the early phases of therapy and because there is a wide variation in "effective concentrations" of parent and metabolite (16,19,71). In clinical trials with the oral preparation, there has been only a rough correlation between dose and serum level and no correlation between serum level and efficacy or toxicity (56,57). Serum levels of the metabolite are very low in patients dosed for only a few days.

When given intravenously, amiodarone should be mixed in a 5% dextrose solution and should be infused with a volumetric pump. If used in high concentrations (>2 mg/ml), it must be delivered through a central vein because it can cause peripheral phlebitis in <3% of patients. It has been stated that the drug should be placed in glass bottles because it absorbs polyvinyl chloride and that adhesion in plastic tubing is prevented by flow, but those recommendations have been challenged (72,73). Amiodarone does not need light protection but is physically incompatible with a number of drugs such as heparin with which it is frequently used. Although it was thought that amiodarone was physically incompatible with normal saline, Campbell et al. (73) showed that this is a satisfactory admixture.

In the multicenter trials, the median duration of intravenous amiodarone therapy was 4 days, but there was wide variation. Patients who could not take oral medication were treated for >3 to 6 weeks without difficulty. Over 95% of patients in the controlled trials went on to receive oral therapy. The bioavailability of oral versus intravenous amiodarone has varied from 30% to 70% in assorted studies (10,15). Bioavailability also appears to be lower in elderly patients and those with cardiopulmonary disease (74). Recommendations regarding the transition to oral therapy take into account these properties in addition to the fact that there may be a delay of 4 to 5 h between ingestion of the oral drug and an increase in the plasma level. Generally, the longer the patient has been receiving intravenous therapy, the less the need for the customary large oral loading doses.

Transition to oral therapy and follow-up testing. Over 90% of the patients who received intravenous amiodarone in controlled clinical trials went on to receive oral therapy. This conversion rate was high because the patients had severe arrhythmias that were not due to an easily reversible cause (75). When the drug is used in clinical situations in which the underlying condition can be remedied, such as in patients with acute myocardial infarction and successful revascularization, the rate of conversion to oral therapy will probably diminish. Patients who have been receiving intravenous therapy for >2 to 3 weeks can be started safely on maintenance doses of oral amiodarone (300 to 400 mg/day). Those treated for <1 week should probably receive the usual oral loading regimen of 800 to 1,400 mg/day, whereas an intermediate dose of 400 to 800 mg/day might be suitable for patients who fall in between these time frames. If there is any concern about gastrointestinal function, oral and intravenous therapy should both be maintained for a few days. These recommendations are empiric, based on the usual target total drug dose for in-hospital loading and are not based on careful pharmacologic trials.

A situation may arise in which a patient who is receiving long-term therapy temporarily cannot take oral medication. Because amiodarone is slowly eliminated, cessation of therapy for a few days is probably of little consequence, but patients should have electrocardiographic monitoring within 5 to 7 days because of the drug's biphasic elimination profile. If oral therapy cannot be started after that time, and if there is doubt about adequate gastrointestinal absorption, intravenous therapy can be substituted. A loading dose is not necessary; based on the known range of its bioavailability, infusion of 30% to 70% of the patient's daily oral dose will suffice.

Intravenous amiodarone has been used for treatment of patients who have received long-term oral therapy and have had recurrent arrhythmias. Under these circumstances, it should be assumed that the patient has insufficient myocardial tissue concentrations, especially if the QT interval is not prolonged (76). It is customary in these situations to use the recommended loading and maintenance doses of the intravenous formulation until the arrhythmia is suppressed and then to prescribe oral therapy, as previously described.

After a patient has received loading doses of either the oral or intravenous preparation, the question may arise as to the need for an evaluation to confirm clinical efficacy before patient discharge because suppression of arrhythmia with an intravenous antiarrhythmic drug does not necessarily predict efficacy of its oral formulation. Furthermore, the sporadic

nature of recurrent VT/VF often makes short-term suppression of clinical arrhythmia difficult to interpret. The options are either to monitor the patient to determine whether repetitive forms, especially nonsustained VT, have been suppressed or to carry out electrophysiologic testing. Although proof of ambient arrhythmia suppression is frequently obtained before discharge, there are no definitive data to prove the value of either method. Two small studies that have attempted to examine the role of predischarge electrophysiologic testing arrived at contradictory conclusions (77,78). It is our custom to perform electrophysiologic testing and to consider implantation of an arrhythmia control device in those cases in which the arrhythmia can be induced and causes hemodynamic instability despite treatment with intravenous and then oral amiodarone. Such testing is generally done after the patient is clinically stable and has received the equivalent of 6 to 10 g of oral amiodarone, a dose that has been shown to produce a variable but reasonable plasma concentration and to suppress spontaneous ventricular ectopic beats (10,15,79).

Other indications. Most of the information available about intravenous amiodarone relates to ventricular arrhythmias. Because it has some effect on atrial myocardium, the sinus and AV nodes and accessory pathways, some investigators have explored the efficacy of the drug for supraventricular indications (31,80–82). In patients with accessory pathway-related tachycardias, including AV reentry tachycardia and anterograde conduction during atrial fibrillation/flutter, the drug may slow conduction or terminate the arrhythmia (38). It may work synergistically with other negatively dromotropic drugs to slow the ventricular response rate during atrial arrhythmias. However, the rate of conversion of atrial fibrillation or flutter to normal sinus rhythm within 24 h of administration is lower than that reported with class Ic or even some other class III agents (83,84). Nevertheless, because of its safety in patients with poor left ventricular function and the relatively low incidence of ventricular proarrhythmia, it is occasionally used in the urgent treatment of atrial fibrillation with rapid conduction that causes hemodynamic embarrassment (85–87). In a recently reported study, Galve et al. (88) confirmed that patients treated with intravenous amiodarone whose rhythm did not convert to sinus rhythm had a significantly slower heart rate response than those treated with digoxin alone. The reported experience with the drug in patients after coronary artery bypass graft surgery is similar (83,85,87–89). It is less effective than class Ic drugs for conversion but is useful for rate control and may prevent recurrence of atrial fibrillation in those with electrical conversion to sinus rhythm after drug loading. Intravenous amiodarone may prevent postoperative atrial fibrillation when given prophylactically either before or immediately after operation, but this question requires more detailed investigation (90).

There are no data to support the use of intravenous amiodarone for primary prophylaxis against ventricular arrhythmias in any clinical situation. Likewise, there have been no studies that have directly compared the efficacy of the oral and intravenous preparations for the suppression of VT or VF. One recent study by Russo et al. (91) found that doses of 1,200 to 1,400 mg/day of the oral form might be beneficial in a cohort that was similar to the patients in the clinical trials (91). Nine of the 12 patients entered into that study survived to hospital discharge. Because that study was uncontrolled and had a small number of patients, adequate conclusions about the role of oral therapy are not possible. However, because of the vagaries of bioavailability, oral loading in patients with highly malignant arrhythmia should be implemented with caution.

Although time to effect may be shortened by administration of intravenous rather than oral amiodarone, giving clinically stable patients loading doses of the intravenous formulation provides little potential benefit. The total daily dose that can be delivered safely may be higher with the oral formulation because hypotension is usually not seen, even with oral doses of up to 3 g/day (gastrointestinal side effects at these doses are more common) (92). In addition, the cost of the intravenous formulation should be a consideration in this strategy. Not only does the drug itself cost more, but its administration obligates extended observation periods in an intensive care setting, with a higher level of nursing care than that required for oral loading. The concept of combining oral and intravenous doses to truncate the loading period has not been studied adequately.

Special patient groups. There is some reported experience with intravenous amiodarone in infants, children and adolescents (93,94). A recent study from Figa et al. (95) and earlier smaller published reports have indicated that the drug, when used in proportionate per kilogram doses, has efficacy similar to that reported for adults. The principal adverse effect was symptomatic bradycardia requiring a temporary pacemaker in a small percentage of children. Recently, Perry et al. (96) published the results of a small multicenter protocol in which intravenous amiodarone was administered to critically ill pediatric patients. They concluded that the intravenous form is safe and effective in young patients with critical tachycardias, including supraventricular arrhythmias.

Intravenous amiodarone is toxic to embryos in selected animal species (97). In humans, amiodarone and desethylamiodarone cross the placenta and reach levels in the fetus of up to 50% of maternal serum levels (98). The principal toxicity that has been seen in such fetuses has been hyperthyroidism, hypothyroidism and congenital goiter (99). A recent report by Ovadia et al. (100) described one major and two minor congenital anomalies in which amiodarone was administered throughout the embryonic period. Amiodarone has no effect on the duration of gestation or labor in rats, but inadequate data are available in humans. Amiodarone and desethylamiodarone have been found in breast milk in humans, and nursing offspring of rats fed amiodarone have reduced body weight gain and life expectancy (101). For all these reasons, pregnant woman should receive the drug only if other options have been exhausted. Breastfeeding is contraindicated for women taking amiodarone.

Guidelines for clinical use. How might intravenous amiodarone fit into an algorithm for the treatment of patients with recurrent, hemodynamically destabilizing VT or VF? Intrave-

nous lidocaine should and will remain first-line therapy for this patient group. Although it has a low efficacy rate, it is very familiar to practitioners and is relatively safe when used in proper doses (102). Its short half-life after rapid loading makes interactions with successive drugs less likely. For patients who do not respond to lidocaine, procainamide is frequently chosen. The evidence of procainamide's efficacy comes mainly from studies in which it was used to terminate or prevent the reinduction of monomorphic VT (103). Bretylium is generally considered a third-line drug primarily because of its tendency to cause severe hypotension (104,105). Data from the recent clinical trials provide reassurance that bretylium is beneficial in this clinical situation, although hypotension occurs frequently and can be sustained over several days (57). Intravenous beta-blockers should also be considered on the basis of results of small series in which such agents have been effective (106). Their principal liability is myocardial depression, which is a particularly important problem in this patient population.

According to the controlled clinical trials, intravenous amiodarone can be considered effective therapy for patients in whom conventional therapy fails. Although a myocardial depressant, intravenous amiodarone does not appear to cause congestive heart failure as frequently as intravenous beta-blockers, possibly because of its vasodilator properties. For patients who continue to have frequent arrhythmias despite the use of supplemental boluses of intravenous amiodarone, other parenteral agents may be added. Although there is scant experience with parenteral antiarrhythmic drug combinations, procainamide, quinidine and propafenone have been added to oral amiodarone with evidence of supplemental efficacy (107,108). The mortality rate for patients with incessant ventricular arrhythmias that do not respond to such aggressive pharmacologic therapy is high despite emergent surgical or catheter ablation (109,110).

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