Regular Review

Amiodarone: the experience of the past decade

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Amiodarone is an effective agent for treating troublesome supraventricular and some serious ventricular arrhythmias. It is particularly effective for paroxysmal atrial fibrillation, supraventricular arrhythmias associated with the Wolff-Parkinson-White syndrome, and in the suppression of ventricular arrhythmias complicating hypertrophic cardiomyopathy.[1 2] Its place in the treatment of arrhythmias during acute myocardial infarction is still uncertain but it was effective in several American series of patients with refractory ventricular tachycardia or fibrillation.[3–6]

With the increased use of amiodarone side effects are being reported increasingly often, particularly in the United States and Britain,[4–7] and both the place of the drug and measures to prevent these unwanted effects need reassessment.

Pharmacokinetics

Many of the pharmacological data come from Holt *et al.*[8] Amiodarone has a variable bioavailability (20-80%) and a huge volume of distribution (5000 litres). Desethylamiodarone is the sole metabolite detected to date, but neither its electrophysiological nor possible antiarrhythmic actions have yet been studied. The drug is highly lipid soluble, and tissue studies suggest that much of the unmetabolised compound is stored in fat. The highest concentration of desethylamiodarone is found in the liver, with progressively lower concentrations in reticuloendothelial, lung, myocardial, skin, and brain tissues. Apart from the stores in fat the concentration of the metabolite always exceeds that of the parent compound. Only trace amounts of amiodarone or desethylamiodarone are detectable in the urine,[9] and elimination seems to occur through the biliary and gastrointestinal tracts. Plasma concentrations of both compounds fall by half in the first three to 10 days; the terminal elimination half life is usually 35-40 days,[8] though we have observed it to be as long as 104 days in an obese patient.

Clinical experience has shown that a loading dose is necessary, varying from 0·6 to 2 g daily for one to eight weeks. A high daily dose might be expected to give a more rapid onset of efficacy, but this may be so only within certain dose ranges. Furthermore, side effects, particularly gastrointestinal and neurological, are seen more often with higher loading doses; the elderly are particularly susceptible. Non-life threatening supraventricular and ventricular arrhythmias are usually suppressed by a loading dose of 600 to 1200 mg daily for one week. The ideal loading regimen depends, however, on the response of the individual patient, and control may be seen within a wide range, from three days to as much as several weeks.

Life threatening arrhythmias should initially be treated in hospital, where resuscitation facilities are available. The place of intravenous infusion in achieving a more rapid onset of efficacy is under investigation.[10] Further studies will need to show positive results to overcome the disadvantages of intravenous infusion—the need for a central line to avoid phlebitis and for careful monitoring of blood pressure because of the risk of severe hypotension.[11]

Guidelines for maintenance treatment have also developed from clinical experience. The common dose for the treatment of supraventricular arrhythmias associated with the Wolff-Parkinson-White syndrome or for paroxysmal atrial fibrillation is 200 mg daily. In idiopathic supraventricular or ventricular arrhythmias, or those associated with hypertrophic or dilated cardiomyopathy, 300 to 400 mg daily is usually appropriate. For recurrent ventricular tachycardia or fibrillation associated with ischaemic heart disease up to 800 mg daily has been used.

This experience should not, however, necessarily be the model for future treatment. Many of the side effects associated with amiodarone are dose dependent,[7] and each patient should receive the minimum effective maintenance dose; in patients with non-life threatening arrhythmias not only should such a minimum dose be determined but the question of the need for treatment should also periodically be reassessed.

Unwanted effects

The unwanted effects of amiodarone are sometimes idiosyncratic but are more often related to the dose and duration of treatment.[7] Patients with disorders of the thyroid, lung, or liver are at particular risk. Skin reactions are common, and photosensitivity may be particularly troublesome.[12] With other drugs this indicates sensitivity to ultraviolet light; amiodarone is unusual in its capacity to cause photosensitivity from solar radiation in the visible as well as the ultraviolet light range (J Ferguson, personal communication). Since radiation in the visible range penetrates glass and is not blocked by most commercial barrier creams, patients needing protection will require creams containing opaque pigments, such as titanium dioxide and zinc oxide. Severe photosensitivity may result in erythematous swelling and prickly heat after quite brief exposure. This is uncommon, affecting less than 5% of patients, but it may persist for a long time after the drug has been stopped. Rarely patients may develop an otherwise asymptomatic blue grey discoloration on exposed areas. This is usually related to earlier photosensitivity and to prolonged high dosage (600 to 800 mg daily).[7] After stopping treatment we have observed that the discoloration resolves slowly if at all despite a considerable decline in skin concentrations of amiodarone and desethylamiodarone, but other workers have seen improvement.

Neurological side effects are also common. On questioning, about a third of patients will admit disturbance of sleep, taking the form of early morning waking, vivid dreams, or nightmares.[13] With maintenance doses of up to 400 mg daily about one third of patients will complain of a fine resting tremor[13]; this is dose related and clears rapidly (within two or three days) after stopping amiodarone, suggesting that circulating drug concentrations are more important than deposition in tissue.[14] In most patients the tremor may be controlled by reducing the dose of amiodarone or by giving a small dose of propranolol. Peripheral neuropathy is rare and is most often related to high doses (2 g daily); it resolves slowly after the drug is stopped.

Both hypothyroidism and thyrotoxicosis have been reported to complicate treatment and every patient's thyroid function should therefore be checked before treatment is started. Amiodarone contains roughly 75 mg of iodine in each 200 mg tablet, and, though the rate of deiodination is comparatively low, the amount of iodide released is roughly 100 times the average needed for hormone formation.[7] Amiodarone is passed from mother to fetus, and the drug is therefore contraindicated during pregnancy and should be used only with great care in women of childbearing age.[15] Excessive iodide will inhibit organification in the thyroid, though normal glands will usually show escape from this phenomenon.[16] The susceptibility of the elderly to hypothyroidism while receiving amiodarone may reflect decreased glandular reserve with advancing age.

Excess iodide may also induce hyperthyroidism in patients with glands deficient in iodide; whether it occurs in patients with normal glands remains controversial.[16] In practice fewer than 2% of patients receiving amiodarone develop overt thyroid disease despite the heavy iodide load.[7] Clinical hyperthyroidism seems to occur predominantly in patients with goitre or active autoimmune thyroid disease.[7 16] Routine thyroid function tests may identify patients whose arrhythmia results from thyrotoxicosis; once amiodarone is being taken their interpretation is complicated.[16] Amiodarone inhibits the peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) in favour of reverse T3: thus most patients receiving long term treatment will show an increase in T4, a normal or low T3 value, and an increased reverse T3 concentration.[17 18] In addition, the flat thyroid stimulating hormone response to thyrotrophin releasing hormone seen in thyrotoxicosis also occurs in patients taking amiodarone. The serum concentration of T3 (or ideally of free T3) is the most helpful test in confirming the diagnosis of hyperthyroidism.

The clinical diagnosis of thyrotoxicosis may be difficult in patients taking amiodarone as the drug masks many of the signs of hyperthyroidism. Ophthalmic signs of Graves' disease and a goitre are uncommon, and the drug blurs the symptoms because of its adrenergic antagonist properties.[19] The most useful pointers to hyperthyroidism in patients taking amiodarone are loss of weight, asthenia, restlessness, and recurrence of arrhythmias; low grade fever, a rapid erythrocyte sedimentation rate, and shortening of the QT interval may also be seen.

Amiodarone has been associated with radiological evidence of interstitial pulmonary changes, and in some patients this progresses to an alveolitis with patchy consolidation.[4 20–22] These changes are usually but not invariably associated with high doses (over 600 mg daily)[7 22]; patients with pre-existing abnormalities of diffusing capacity may be particularly susceptible.[23] Chronic obstructive pulmonary disease does not, however, appear to confer particular risk. Progressive or fatal pulmonary alveolitis is rare,[4 20] and the alveolitis usually resolves with treatment with steroids or discontinuation of amiodarone or both.[24] A striking difference has been seen in the incidence of pulmonary alveolitis in American series, with up to 10% of patients affected[4 20–22] whereas such patients have been very rare in Europe.[7] We cannot explain this discrepancy, but it may be related to the higher maintenance doses of amiodarone used for refractory ventricular tachycardia and fibrillation in the American series.

Gastrointestinal complaints—constipation, nausea, and vomiting—are uncommon and seldom a problem; they occur particularly during the loading period and respond to a reduction in the dose. Abnormalities in liver function values, with an increase in aminotransferase activity (two to three times normal), are observed in about 15% of patients and often resolve spontaneously without the dose being decreased.[7]

The unwanted effect that has received the greatest attention is the least important. Corneal microdeposits are related to the dose and duration of treatment and eventually occur in 98% of patients.[25] These rarely produce symptoms: blurred or halo vision occurs in 1-2% of cases and improves with reduction of the dose. Decreased visual acuity attributable to amiodarone has not been reported. In terms of effects on the eyes amiodarone appears to be safe and ophthalmological supervision does not seem to be required.[25]

No unifying explanation can be advanced for the side effects of amiodarone. Electron microscopy and x ray dispersion analysis show lipophilic lamellar deposits which are thought to lie within the lysosomes of tissue macrophages.[26] Similar findings have been observed in the cornea, peripheral nerves, lung, and skin,[20 27–29] but their relevance to the clinical side effects is uncertain. Another aspect is the geographical variation in the incidence of side effects, particularly photosensitivity, pulmonary changes, and sleep disturbance. This may reflect differences in dosage, racial predisposition, the amount of exposure to sun, or differences in reporting. In addition to at least seven different licensed producers world wide there are several unofficial manufacturers whose formulations may not be identical.

Drug interactions

Amiodarone may interact with several other drugs used for heart disease. It has an additive effect with beta blockers and some calcium antagonists (verapamil and diltiazem) in depressing the function of both the sinoatrial and atrioventricular nodes, so caution is required in patients with disorders of the sinus node or the conduction system. Amiodarone increases the plasma concentration of digoxin, perhaps because of displacement of tissue bound glycoside or by interference with digoxin excretion.[30] Constitutional symptoms of digoxin toxicity (but not arrhythmic complications) have been seen and may usually be avoided by halving the dose of digoxin. Potentiation of warfarin may be secondary to inhibition of hepatic microsomal enzyme systems rather than to protein displacement[31] and causes difficulty in maintaining anticoagulant control during the loading period; the dose of warfarin needs to be reduced by about half. Pharmacological interactions with disopyramide, quinidine, propafenon, and mexiletine have also been reported.[32]

Assessment of efficacy

If ventricular arrhythmias can be induced by programmed electrical stimulation in a patient having treatment with conventional antiarrhythmic agents the treatment is likely to

fail. This predictive test may not, however, be valid for amiodarone. Ventricular tachycardia may often be induced during electrophysiological tests in patients who have had or who subsequently have a good clinical response.[4] Non-invasive markers of therapeutic effect have therefore been sought. In a selected small group of patients it has been shown that the increase in the QT interval correlates strongly with drug concentrations and myocardial tissue concentrations, suggesting that QT prolongation may be a marker of myocardial impregnation.[33] In practice it is difficult to measure the QT interval reproducibly in patients having amiodarone and the assessment is also complicated by the frequent presence of U waves. Furthermore, the drug may be effective in the absence of QT changes. Prolongation of the QT interval during antiarrhythmic treatment, especially when considerable, may paradoxically be arrhythmogenic, and isolated but well documented cases have been reported of patients who develop torsades de pointes in association with other recognised causes of this arrhythmia[34 35] as well as in their absence.[35] The suggested correlation of plasma reverse T3 concentrations with clinical efficacy[36] may not be very useful because it is influenced by stress and concurrent illness.

Evidence is growing of the value of assays of plasma concentrations of amiodarone and desethylamiodarone. At present there is a rough "therapeutic range" of 0·5 to 1·5 mg/l, which corresponds in most patients with efficacy in the absence of any substantial side effects.[37] Plasma drug concentrations may also help identify patients with decreased bioavailability who have low plasma concentrations and may require an increased dose. The ratio of amiodarone to the desethyl metabolite may help to identify those patients who are not complying with treatment. Plasma concentrations are, however, most useful in determining the minimum effective maintenance dose when coupled with the information from clinical evaluation or ambulatory electrocardiographic monitoring or both. The drug may be being given for a serious or life threatening arrhythmia but that should not blind the physician to the fact that higher doses than are warranted carry an increased morbidity.

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