

New Zealand Data Sheet

Amiodarone Hydrochloride 50mg/mL

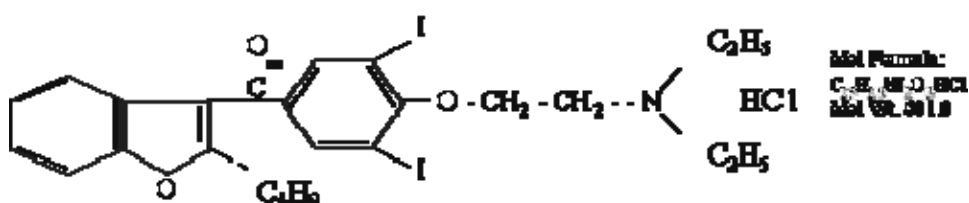
Amiodarone Hydrochloride Concentrated Injection 50mg/mL

Name of the Medicine

Non-proprietary name

Amiodarone hydrochloride

Chemical structure



CAS number

1951-25-3

Description

The active ingredient of Amiodarone Hydrochloride 50mg/mL is amiodarone hydrochloride (2-n-butyl-3-(4-(2-diethylaminoethoxy)-3,5-diiodobenzoyl) benzofuran hydrochloride). Amiodarone hydrochloride is a Class III antiarrhythmic agent.

Amiodarone hydrochloride is a fine white crystalline powder. It is slightly soluble in water and is soluble in alcohol and chloroform. It is an amphiphilic compound and contains iodine in its formulation.

The excipients of Amiodarone Hydrochloride 50mg/mL are polysorbate 80, benzyl alcohol and water for injections, as well as hydrochloric acid and sodium hydroxide for pH adjustment.

Each 3mL ampoule contains 60.6mg of benzyl alcohol and approximately 56mg iodine.

Pharmacology

Actions

Amiodarone is a Class III antiarrhythmic agent prolonging the action potential duration and hence refractory period of atrial, nodal and ventricular tissues, thereby giving a very broad spectrum of activity. An increase in the refractory period of the atrial cells is a major contributing action to the control of atrial tachyarrhythmias.

A reduction in the permeability of the A-V node, both anterograde and retrograde, explains the efficacy of the medicine in nodal tachycardias caused by re-entry through the A-V node.

Its action on ventricular arrhythmias is explained by a number of mechanisms. The effect on the atrium and A-V node results in a reduction in the frequency of stimuli reaching the ventricle thus giving the ventricular cell mass time to repolarise in cases where there has been desynchronisation of the refractory periods. Furthermore, a lengthening of the refractory period of the His-Purkinje system and ventricular contractile fibres reduces or prevents micro re-entry. Amiodarone increases coronary blood flow, decreases cardiac oxygen requirements without producing negative inotropic effects and also suppresses ectopic pacemakers, and this is particularly valuable in arrhythmias associated with ischaemic damage or angina pectoris.

The site and mode of action of amiodarone can be summarised in terms of its effect on myocardial electrophysiology.

Myocardial electrophysiology

Sinus node:

It decreases sinus automaticity by reducing the slow diastolic depolarisation gradient in the nodal cell. This is a direct effect and is not mediated through the sympathetic or parasympathetic system.

Atrio-ventricular (A-V) node:

It reduces the speed of conduction and increases the refractory period of the A-V node.

His-Purkinje system:

It increases the refractory period but does not modify the speed of conduction of the His-Purkinje system.

Contractile fibres:

It increases the action potential but does not alter the rate of depolarisation of the atrial or ventricular myocardial cells; an effect that is more marked in the atria than the ventricles.

Pharmacokinetics

The following information may not necessarily be related to i.v. administration of amiodarone, however is included for reference purposes:

In general, pharmacokinetic data relating to amiodarone are incomplete. Amiodarone is incompletely and erratically absorbed following oral administration. Absolute bioavailability ranges from 22 - 86% but there is extensive inter-subject variation. First-pass metabolism in the gut wall and/or in the liver may be a factor in determining the availability of the medicine.

An HPLC method is available for estimation of amiodarone plasma levels. However, the value of this is limited because the correlation of therapeutic effect and plasma level has not been established. Steady state plasma levels are generally around 1 - 2µg/mL although inter-subject variations are common.

Considerably higher values have been reported, especially subsequent to large single doses. Peak plasma concentrations of $6.9 \pm 4.2\mu\text{g/mL}$ have been recorded following a single dose of 1,600mg and $1.7 \pm 0.3\mu\text{g/mL}$ after a single dose of 800mg. Steady state levels of $1.57 \pm 0.1\mu\text{g/mL}$ and $3.9\mu\text{g/mL}$ have been recorded after daily oral dosing in the range of 800 - 1,800mg.

The half-life of amiodarone is long and with chronic oral dosing can be from 14 – 110 days but is usually in the range 14 - 59 days. The principal metabolite of amiodarone, which has been detected in the plasma and other tissues, is desethylamiodarone. This metabolite is reported to have a longer half-life than amiodarone, i.e. 10 hours after a single dose of amiodarone and 60 - 90 days after chronic dosing with amiodarone. The activity of this metabolite is not known. Amiodarone is highly protein bound and is thought to bind strongly to protein at concentrations of $10\mu\text{g/mL}$. It is believed that most of the medicine is excreted via the liver and gastrointestinal tract by biliary excretion. There may be some hepatic recirculation.

The apparent volume of distribution after oral (200 - 400mg) amiodarone is $6.31 \pm 4.93\text{L/kg}$. Amiodarone appears to accumulate in adipose tissue and in highly perfused organs (lung, bone marrow, adrenals, liver, pancreas, heart, spleen and kidney). The concentration of amiodarone in packed red blood cells is approximately 60% of that in plasma.

Indications

Treatment should be initiated only under hospital or specialist supervision.

Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.

All types of tachyarrhythmias including

- supraventricular, nodal and ventricular tachycardias, atrial flutter and fibrillation;
- ventricular fibrillation;
- when other agents cannot be used.

The injection is to be used when a rapid response is required.

Contraindications

Known hypersensitivity to iodine or amiodarone or to any of the excipients.

Pregnancy and lactation (see Use in Pregnancy and Use in Lactation).

In patients in whom bradycardia or AV block is sufficient to cause syncope, patients with sick sinus syndrome (risk of sinus arrest) or with severe atrioventricular conduction disorders, Amiodarone Hydrochloride 50mg/mL should only be used in conjunction with a pacemaker.

Sinus bradycardia and sino-atrial heart block.

Amiodarone Hydrochloride 50mg/mL is contraindicated in patients with evidence, or a history of thyroid dysfunction.

Combined therapy with medicines which may induce 'torsades de pointes' (see Interactions).

Amiodarone Hydrochloride 50mg/mL is contraindicated in the case of hypotension, severe respiratory failure, cardiomyopathy, heart failure, circulatory collapse and severe arterial hypotension.

Bi- or trifascicular conduction disorders, unless a permanent functioning pacemaker is fitted, or unless the patient is in a special care unit and amiodarone is used under the cover of electrosystolic pacing.

Warnings and Precautions

It is recommended to perform an ECG and serum potassium measurement before treatment initiation.

Caution should be exercised in case of hypotension, severe respiratory failure, uncompensated or severe heart failure.

Intravenous injection is generally not advised because of haemodynamic risks (severe hypotension, circulatory collapse); intravenous infusion is preferable whenever possible. Intravenous injection is to be done only in emergency where alternative therapies have failed and only in an intensive care unit under continuous monitoring (ECG, blood pressure). Intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only one ampoule (possible irreversible collapse). To avoid injection site reactions, amiodarone i.v. should, whenever possible, be administered through a central venous line (see Dosage and Administration).

Thyroid hormone abnormalities

As amiodarone may induce thyroid disorders, particularly in patients with personal or family history of thyroid disorders, clinical and biological monitoring is recommended before starting treatment, ultrasensitive TSH (usTSH) assay, during treatment and for several months following treatment discontinuation. Serum usTSH levels should be measured when thyroid dysfunction is suspected. Severe cases, with clinical presentation of thyrotoxicosis, sometimes fatal, require emergency therapeutic management.

Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, free-T3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment.

Hypothyroidism should be suspected if the following clinical signs, usually slight, occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by a clear increase in serum usTSH. Euthyroidism is usually obtained within 1 – 3 months following the discontinuation of treatment. In life-threatening situations, amiodarone therapy can be continued, in combination with L-thyroxine. The dose of L-thyroxine is adjusted according to TSH levels.

Hyperthyroidism

Hyperthyroidism may occur during amiodarone treatment, or up to several months after discontinuation. Clinical features, usually slight, such as weight loss, onset of arrhythmia, angina, and congestive heart failure should alert the physician. The diagnosis is supported by a clear decrease in serum ultrasensitive TSH (uTSH) level, in which case, amiodarone should be withdrawn. Recovery usually occurs within a few months following withdrawal of treatment; clinical recovery precedes the normalisation of thyroid function tests. Severe and sometimes fatal cases, with clinical presentation of thyrotoxicosis, require emergency therapeutic management. The treatment should be adjusted to each individual case: for example anti-thyroid medicines, corticosteroid therapy, beta-blockers.

Pacemakers/implantable defibrillators

In the context of chronic administration of antiarrhythmic medicines, cases of increase in ventricular defibrillation and/or pacing threshold of pacemakers or implantable cardioverter defibrillator devices have been reported, potentially affecting their efficacy. Therefore, a repeated verification of the functioning of such devices before and during amiodarone treatment is recommended.

Anaesthesia

Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.

Cardiac disorders

Amiodarone Hydrochloride 50mg/mL is not contraindicated in patients with latent or manifest heart failure but caution should be exercised as existing heart failure may occasionally be worsened. In such cases amiodarone should be associated with the usual cardiotoxic and diuretic treatment.

Excessive doses may lead to atropine resistant bradycardia and to conduction disturbances, particularly in elderly patients or during digitalis therapy. Amiodarone, like quinidine and disopyramide, has caused atypical ventricular tachycardia. In patients with previous history of the above condition, amiodarone should be avoided. Use of higher doses of amiodarone is not advisable in persons with a history of atypical ventricular tachycardia previously induced by another antiarrhythmic agent.

Treatment should be discontinued in case of onset of 2nd or 3rd degree AV block, sinoatrial block, bifascicular or trifascicular block.

Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the medicine from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects are more rarely reported with amiodarone than with the other antiarrhythmic agents, and generally occur in the context of medicine interactions and/or electrolytic disorders (see Interactions).

ECG monitoring

Regular ECG monitoring is recommended in patients on long-term therapy with amiodarone. U waves, deformed T waves and QT prolongation (related to prolonged repolarisation) may occur in the ECG because of the fixing of amiodarone in the myocardial tissues and is not an indication for withdrawing amiodarone.

The prolongation of QT interval occurs in almost all patients as this is related to the electrophysiological and antiarrhythmic properties of the medicine. Prolongation of the actual QT above 0.60 seconds rather than QTC or QRS widening, may be an important warning sign that requires modification of therapy. Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm (atypical ventricular tachycardia; 'torsades de pointes') particularly in elderly patients or during digitalis or other antiarrhythmic therapy. In such circumstances amiodarone should be temporarily withdrawn.

Ocular changes

Corneal deposits develop in almost all patients and regular ophthalmological monitoring (e.g. slit lamp biomicroscopy, visual acuity, ophthalmoscopy, etc) is recommended. If blurred or decreased vision occurs, ophthalmological examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness.

Pulmonary disorders

Clinical and radiological evidence of pulmonary fibrosis and/or pneumonitis has been reported, sometimes presenting as unexplained or disproportionate dyspnoea. Regular chest x-ray should be performed routinely in patients undergoing long-term therapy or when diagnosis is suspected. The effect has usually been reversible with corticosteroid therapy and/or reduction or withdrawal of amiodarone therapy.

Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (see Adverse Effects) such as interstitial pneumonitis. Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone. A chest x-ray should be performed, when the diagnosis is suspected in patients developing effort dyspnoea, whether isolated or associated with deterioration of general health status (fatigue, weight loss, fever). Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone (clinical signs usually resolving within 3 - 4 weeks, followed by slower radiological and lung pulmonary function improvement within several months), and corticosteroid therapy should be considered.

Very rare cases of severe respiratory complications, sometimes fatal, have been observed usually in the period immediately following surgery (adult acute respiratory distress syndrome); a possible interaction with a high oxygen concentration may be implicated.

Hepatic dysfunction

Regular monitoring of liver function tests (transaminases) is recommended as soon as amiodarone is started and during treatment.

Elevation of liver enzyme levels (e.g. serum aspartate aminotransferase, serum alanine aminotransferase, glutamyl transpeptidase) occurs quite commonly in patients undergoing treatment with amiodarone and in some cases are asymptomatic. The changes appear to be dose dependent rather than an idiosyncratic type. Hepatotoxicity has occasionally been reported (see Adverse Effects) and close monitoring of hepatic function with liver function tests is recommended as soon as amiodarone is started, and regularly during treatment.

Acute liver disorders (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur with oral and intravenous forms and within the first 24 hours of i.v. amiodarone. Therefore, amiodarone dose should be

reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range.

Use in hepatic disease

Because of the potential risk of hepatotoxicity and/or accumulation, amiodarone should be used with extreme caution in patients with hepatic disease.

Skin reaction

Photosensitivity is quite common and there is a wide spectrum of skin reactions, ranging from an increased propensity to suntan to intense burning and erythema and swelling of the exposed area. The intensity of these reactions could be alleviated by a reduction in dosage or by application of a protective sunscreen. Patients should be instructed to avoid exposure to the sun or use protective measures during therapy.

Some patients have developed skin pigmentation (slate grey/purple colour) of the exposed areas. This pigmentation can be avoided if doses are kept as low as possible. If the pigmentation is cosmetically unsightly, amiodarone should be discontinued if alternative therapy is possible.

Neurological toxicity

Peripheral neuropathy could occur in patients on long-term high dosage (generally over 400mg/day) regime.

Intracellular inclusion bodies, similar to those seen in skin, have been demonstrated in peripheral nerve fibres. Sensorimotor neuropathy, with a glove and stocking distribution, and myopathy have been reported in patients. Histologically, segmental demyelination of the nerve fibres has also been demonstrated. After discontinuation of the medicine, the neurological complication is slowly and incompletely resolved.

Use in renal disease

Renal excretion of the medicine is minimal. This suggests that modification of the dose of amiodarone in patients with renal failure is unnecessary.

Hypotension

Hypotension may occur when amiodarone hydrochloride concentrated injection is given by the intravenous route. In some cases, hypotension may be refractory, resulting in fatal outcomes (see Adverse Effects - Amiodarone hydrochloride concentrated injection).

Use in Pregnancy

Category C

Amiodarone is contraindicated in pregnancy.

No teratogenic effects have been observed in animals. The medicine does cross the placenta.

Because of the long half-life of amiodarone and its major metabolite, and the potential to cause abnormal thyroid function and bradycardia in the foetus, its use is probably best avoided in the three months before and throughout the duration of pregnancy. Where

exposure of the foetus is unavoidable, thyroid function (including TSH) should be assessed promptly in the newborn infant.

The following information may not necessarily be related to i.v. administration of amiodarone, however is included for reference purposes:

In one study a 35 year old woman administered amiodarone in the last weeks of pregnancy, transplacental passage of amiodarone and desethylamiodarone was found to be 10% and 25%, respectively. Changes in maternal thyroid function were similar to those seen in other patients receiving amiodarone therapy, but there was no evidence of clinical hyperthyroidism. The baby's TSH level on day 4 was normal, it had no goitre and was clinically euthyroid. However, the authors caution the use of amiodarone in pregnancy or in those likely to conceive whilst on amiodarone therapy. The long half-life of the medicine requires that the medicine be stopped several months before conception. The possible adverse effects of amiodarone on the foetal thyroid are of concern since administration of iodine (of which there are 75mg in a 200mg dose of amiodarone) during pregnancy may cause foetal goitre, hypothyroidism and mental retardation.

Another patient received 800mg amiodarone for 1 week (maintenance dose thereafter was 400mg daily) in her 34th week of pregnancy. Neonatal levels of amiodarone were 25% of the maternal level. Although the infant's liver and thyroid function tests were normal, it was bradycardic during labour and for the first 48 hours after birth.

Use in Lactation

As amiodarone and its desethyl metabolite are secreted in breast milk, and its safety in the newborn has not been established, it should not be given to nursing mothers. If a situation demands that amiodarone be given to a nursing mother, alternative infant feeding should be instituted.

Paediatric use

The safety and efficacy of amiodarone in paediatric patients have not been established. Therefore its use in paediatric patients is not recommended.

The ampoules of amiodarone injection contain benzyl alcohol (see Description). There have been reports of fatal "gaspings syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing this preservative. Symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardiovascular collapse.

Use in the elderly

In the elderly, heart rate may decrease markedly.

Carcinogenicity

In a carcinogenicity study in rats, amiodarone caused a dose-related increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes. Although mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed but dose dependent thyroid follicular hyperplasia was seen. The relevance of these findings to man is unknown. Clinical experience has indicated that amiodarone can affect thyroid function.

Interactions

Combined therapy with medicines that may induce 'torsade de pointes' is contraindicated (see Contraindications):

Antiarrhythmic agents, such as

Class IA antiarrhythmic agents including -

Disopyramide - combined treatment of amiodarone and disopyramide causes an increase in the QT interval.

Procainamide - serum level of procainamide increase significantly with co-administration of amiodarone and secondary to this increase cardiac, gastrointestinal and neural toxicity may develop.

Quinidine - atypical ventricular tachycardia with QT prolongation may develop after amiodarone is added to a stable quinidine regimen. This is thought to be due to either a change in the protein or receptor binding of quinidine. Serum levels of quinidine increased significantly with concomitant amiodarone therapy. Careful monitoring of the electrocardiogram for QT interval prolongation and of serum levels of quinidine is indicated when amiodarone is added to quinidine treatment.

Mexiletine - co-administration with amiodarone increases the QT interval.

Sotalol

Bepridil

Non-antiarrhythmic agents, such as

Vincamine, some neuroleptic agents, cisapride, erythromycin i.v. or pentamidine i.v., as there is an increased risk of potentially lethal 'torsades de pointes'.

Combined therapy with the following medicines is not recommended:

Beta adrenergic blocking medicines - amiodarone itself exhibits noncompetitive alpha and beta adrenergic inhibition. It should be used with caution in patients on beta blockers as it may potentiate bradycardia and conduction disorders may occur.

Calcium antagonists - co-administration of amiodarone with medicines of the calcium antagonist type may lead to undue bradycardia and conduction disorders may occur.

MAO inhibitors - co-administration with monoamine oxidase inhibitors is contraindicated on theoretical grounds.

Stimulant laxative agents - their use may cause hypokalaemia and therefore increase the risk of 'torsades de pointes'; other types of laxative agents should be used.

Fluoroquinolones - should be avoided in patients receiving amiodarone.

Caution should be exercised when using the following medicines in combination with Amiodarone Hydrochloride 50mg/mL:

Agents which may induce hypokalaemia - for example, diuretics inducing hypokalaemia, either alone or combined; systemic corticosteroids (gluco-, mineralo-); tetracosactrin; amphotericin B (i.v.).

It is necessary to prevent the onset of hypokalaemia (and to correct hypokalaemia); the QT interval should be monitored and, in case of 'torsades de pointes', antiarrhythmic agents should not be given (ventricular pacing should be initiated; i.v. magnesium may be used).

Digoxin - co-administration of amiodarone to patients already receiving digitalis increases plasma digoxin concentrations by about 70%. This is possibly due to the decrease in digoxin clearance, and therefore precipitates toxicity and could lead to severe bradycardia and conduction disturbances with the appearance of idioventricular rhythm. The mechanism of action is unknown but amiodarone may displace tissue glycoside or interfere with digoxin excretion. ECG and digoxin plasma levels should be monitored and patients should be observed for clinical signs of digoxin toxicity. It may be necessary to adjust dosage of digoxin treatment.

Flecainide - amiodarone increases the concentration of flecainide plasma levels; the dosage of flecainide should be adjusted.

Anaesthesia, oxygen therapy (see Warnings and Precautions) - potentially severe complications have been reported in patients undergoing general anaesthesia, such as bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output.

A few cases of severe respiratory complications, such as adult acute respiratory distress syndrome, resulting sometimes in fatalities, have been observed most often in the period immediately after surgery. A possible interaction with a high oxygen concentration may be implicated.

Phenytoin - amiodarone raises plasma concentrations of phenytoin. The combination of phenytoin and amiodarone may lead to increases in plasma phenytoin levels with signs of overdose (particularly neurological signs); clinical monitoring should be undertaken and phenytoin dosage should be reduced as soon as overdose signs appear; phenytoin plasma levels should be determined.

Warfarin and other anticoagulant agents - amiodarone raises the concentration of warfarin. The combination of warfarin with amiodarone potentiates the effect of the anticoagulant therapy and increases the risk of bleeding. More frequent monitoring of prothrombin level and dosage adjustment of oral anticoagulant during treatment with and after discontinuation of amiodarone therapy is necessary.

Medicines metabolised by cytochrome P450 3A4 - When such medicines are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:

Cyclosporin - dosage should be adjusted.

Fentanyl - combination with amiodarone may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.

Statins metabolised by CYP 3A4 - the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 when given with amiodarone.

Other - lignocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine.

Medicines metabolised by cytochrome P450 2D6 and 2C9 - amiodarone has been reported to interact with flecainide, a CYP 2D6 substrate, and phenytoin and warfarin

which are CYP 2C9 substrates; as such amiodarone may interact with other 2D6 and 2C9 substrates.

Other - consideration should be given to the possibility that amiodarone may alter the plasma concentration of other medicines, particularly those which are highly protein bound.

Effect on laboratory tests

Thyroid function tests

Amiodarone contains 2 atoms of iodine and bears a structural resemblance to the molecule of thyroxine. A 300mg maintenance dose of amiodarone has been reported to yield 9mg/day of iodine at steady state, well in excess of the highest normal dietary intake.

As a consequence of taking the medicine and in the absence of any clinical thyroid dysfunction, changes in tests of thyroid function may occur, variable in number and degree. Typically, the PBI, iodine uptake, serum thyroxine (T4), reverse triiodothyronine (rT3) and free thyroxine index (FTI) rise, and serum triiodothyronine (T3) falls.

Abnormalities, either multiple or single, may occur in approximately 12% of patients. In particular, a low T3 syndrome has been described, as with other medicines such as dexamethasone.

General

It has been shown that there is a physical incompatibility of heparin and aminophylline with amiodarone when mixed in an infusion administration set. It is recommended that amiodarone for infusion not be mixed with other medicines.

Adverse Effects

Amiodarone has been reported to cause frequent and potentially serious toxicity. The incidence, variety and severity of the effects varies from study to study. Most of the adverse effects are also related to dosage and duration of amiodarone, concurrent use of other antiarrhythmic agents, severity of underlying disease state, and individual variation in pharmacokinetic profile of the medicine.

Amiodarone hydrochloride concentrated injection

Amiodarone hydrochloride concentrated injection may cause moderate and transient reduction in blood pressure, and circulatory collapse may be precipitated by too rapid administration or overdosage. Atropine has been successfully used in such patients presenting with bradycardia. Temporary hot flushes, sweating, and nausea have also been reported with amiodarone hydrochloride concentrated injection.

Local

Possible inflammation of veins following intravenous infusion that may be avoided by the use of a central venous catheter. Injection site reactions such as pain, erythema, urticaria, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes.

Systemic

Hot flushes and sweating have been reported rarely.

Common reports of decrease in blood pressure, usually moderate and transient have been received. Cases of severe hypotension or collapse have been reported following overdosage or a too rapid injection.

Moderate bradycardia - in some cases, and especially in patients with sinus node dysfunction and/or elderly patients, marked bradycardia, or more exceptionally sinus arrest, requires the discontinuation of therapy.

Occurrence of arrhythmia, or aggravation of the pre-existing trouble, followed in some cases by cardiac arrest, have been reported. In view of current knowledge, it is not possible to differentiate what may be due to the medicine from what may be related to the underlying cardiac condition, or what may be the result of a lack of efficacy of therapy. These effects are more rarely reported than with most of the other antiarrhythmic agents, and they occur in general in case of certain medicine interactions or electrolyte disorders.

Isolated elevation of serum transaminases, which are usually moderate (1.5 - 3 times normal) have been reported at the beginning of therapy. They may regress with dose reduction or even spontaneously.

Very rare cases of acute liver disorders with elevated serum transaminases and/or jaundice, which included hepatic failure, some fatal, have also been reported. Treatment should be discontinued and monitoring of liver function tests is therefore recommended.

Very rare cases of interstitial pneumonitis have been reported with intravenous amiodarone. When the diagnosis is suspected, chest x-ray should be performed. Amiodarone therapy should be re-evaluated since interstitial pneumonitis is generally reversible following early withdrawal of amiodarone, and corticosteroid therapy should be considered.

Very rare cases of severe respiratory complications, sometimes resulting in death, have been observed usually in the period immediately following surgery (acute adult respiratory distress syndrome): a possible interaction with high oxygen concentrations may be implicated. Bronchospasm and/or apnoea in the case of pre-existing severe respiratory failure and especially in asthmatic patients have also been reported.

A few isolated cases of anaphylactic shock and benign intra-cranial hypertension (pseudotumor cerebri) have been reported.

Nausea and headache have been reported very rarely. Isolated cases of angioneurotic oedema (Quincke's oedema) have been reported.

Dosage and Administration

Amiodarone Hydrochloride 50mg/mL should only be used when facilities exist for cardiac monitoring and defibrillation, should the need arise. Intravenous injection is generally not advised because of haemodynamic risks (severe hypotension, circulatory collapse). Intravenous infusion should be preferred whenever it is possible.

Infusion

The standard recommended dose is 5mg/kg body weight given by intravenous infusion over a period of 20 minutes to 2 hours. This should be administered as a dilute solution in 250mL 5% glucose. AMIODARONE HYDROCHLORIDE 50MG/ML IS INCOMPATIBLE WITH SALINE AND SHOULD BE ADMINISTERED SOLELY IN 5% GLUCOSE SOLUTION.

This may be followed by repeat infusions up to a maximum of 1,200mg/day (approximately 15mg/kg body weight) in up to 500mL 5% glucose per 24 hours, the rate of infusion being adjusted on the basis of clinical response.

When given by infusion, Amiodarone Hydrochloride 50mg/mL may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

Repeated or continuous infusion via the peripheral veins may lead to local discomfort and inflammation. When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

Injection

In extreme clinical emergency Amiodarone Hydrochloride 50mg/mL may, at the discretion of the clinician, be given as a slow injection of 150 - 300mg in 10 - 20mL 5% glucose over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way must be closely monitored, e.g. in an intensive care unit.

Changeover from i.v. to oral therapy

Oral therapy should be initiated concomitantly at the usual loading dose i.e. 200mg 3 times a day as soon as possible after an adequate response has been obtained using Amiodarone Hydrochloride 50mg/mL, which should then be phased out gradually, and an overlap of oral and intravenous medication of up to two days is recommended to prevent plasma levels falling and efficacy being lost.

Instructions for Handling

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Experience has shown that amiodarone can be absorbed into PVC infusion bags and administration sets possibly because of the presence of plasticisers in PVC plastic. It is important to prepare the infusion solution immediately prior to use in either glass or rigid PVC bottles containing no plasticisers.

The use of medical equipment or devices containing plasticiser such as DEHP (di-2-ethylhexyl phthalate) in the presence of amiodarone injection may result in leaching out of DEHP. In order to minimise patient exposure to DEHP, the final amiodarone dilution for infusion should preferably be administered through non-DEHP containing sets.

Incompatibilities

Amiodarone Hydrochloride 50mg/mL is incompatible with saline and should be administered solely in 5% glucose solution.

Do not mix amiodarone with other preparations in the same syringe or infusion solution.

Solutions containing less than 2 ampoules Amiodarone Hydrochloride 50mg/mL in 500mL 5% glucose are unstable and should not be used.

Use in the elderly

As with all patients it is important the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is used. Particular attention should be paid to monitoring of thyroid function.

Overdose

Overdosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances amiodarone should be temporarily withdrawn and if necessary beta adrenostimulants or glucagon given. In the event of ingestion of a toxic dose, gastric lavage should be employed to reduce absorption and in addition general supportive measures should be applied.

The following information may not necessarily be related to i.v. administration of amiodarone, however is included for reference purposes:

A case of attempted suicide with 2,600mg amiodarone is reported in the literature. No clinical symptoms, changes in heart rate or blood pressure were reported. The ECG revealed considerable lengthening of the QT interval and T wave inversion in the precordial leads with transient disappearance of R wave in leads V1 to V4, simulating an antero-septal infarction.

In another case of attempted suicide with 8 g amiodarone, the only symptoms reported were profuse perspiration. No signs of cyanosis, dyspnoea or decreased sensitivity were found. No clinical side effects were documented over the monitored period of 3 months.

Presentation and Storage Conditions

Amiodarone Hydrochloride 50mg/mL is a clear, pale yellow solution for intravenous administration.

Each 3mL ampoule contains 150mg amiodarone hydrochloride. The ampoules are packed in units of 10 on a tray contained in a cardboard carton.

Shelf-Life

Packaged for sale: 2 years

Following dilution: After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 36 hours at 25°C when exposed to light.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C unless dilution has taken place in controlled and validated aseptic conditions.

For single use only. Discard any unused solution.

Special Precautions for Storage

Store below 30°C. Do not refrigerate. Protect from light.

Sponsor Details

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Medicine Schedule

Prescription Only Medicine

Date of Preparation

03 March 2011