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Clinical Pharmacology of Amiodarone in Infants And Children

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Abstract

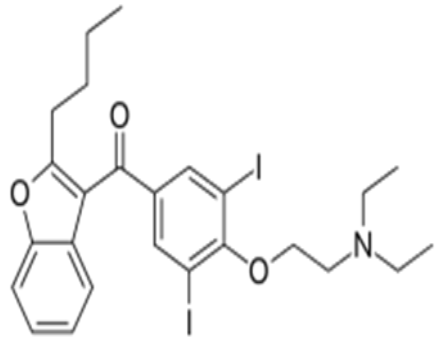
Amiodarone is a class III antiarrhythmic drug and it is used in the treatment of life-threatening or drug-resistant refractory supraventricular, ventricular tachyarrhythmias, and junctional ectopic tachycardia. In infants, the dosing of amiodarone consists in a loading dose of 5 mg/kg followed by a maintenance dose of 10 mg/kg once-daily given by intravenous infusion and in children the intravenous dosing of amiodarone consists in 5 to 10 mg/kg followed by a continuous infusion of 300 µg/kg/hour for the treatment of supraventricular and ventricular arrhythmias and in 5 mg/kg for the treatment of ventricular fibrillation or pulse ventricular tachycardia refractory to defibrillation. Amiodarone has been found efficacy and safety in infants and children but it may induce adverse-effects such as thyroid dysfunction, cardiac collapse, prolongation of QT interval, and toxicity. Amiodarone is metabolized by CYP1A1 by various CYP3A isoenzymes and the major metabolite is desethyl-amiodarone. Amiodarone inhibits various CYPs and P-glycoprotein. The mean elimination half-life of amiodarone is 10.4 hours in infants and young children. Amiodarone interacts with warfarin, β-blocking agents, and with phenytoin. The treatment with amiodarone has been extensively described in infants and children. Amiodarone is poorly transferred across the human placenta and poorly migrates into the breast-milk. The aim of this study is to review the published data on amiodarone dosing, efficacy, safety, adverse-effects, metabolism, CYPs inhibition, pharmacokinetics, interaction with drugs, and treatment in infants and children, and amiodarone transfer across the human placenta and migration into the breast-milk.

Keywords: amiodarone; dosing; efficacy; safety; adverse-effects; metabolism; pharmacokinetics; drug-interactions; treatment; placenta; breast-milk; infants; children

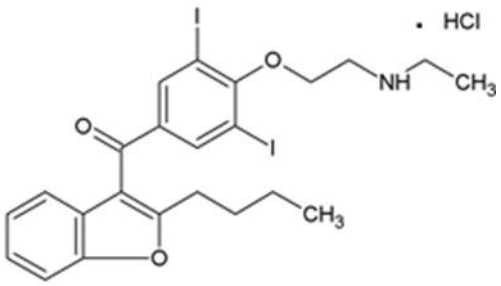
Introduction

Amiodarone exerts a multiplicity of pharmacological effects, none of which is clearly linked to its arrhythmia-suppressing properties. Amiodarone is a structural analogue of thyroid hormone, and some of its antiarrhythmic actions and its toxicity may be attributable to interaction with nuclear thyroid hormone receptors. Amiodarone is highly lipophilic, is concentrate in many body-tissues, and is eliminated slowly; consequently, adverse-effects may resolve very slowly. In the U.S., the drug is indicated for oral therapy in patients with recurrent ventricular tachycardia or ventricular fibrillation resistant to other drugs. In addition, the intravenous form is a first-line drug for the management of ventricular tachycardia or ventricular fibrillation causing cardiac arrest. Trials of oral amiodarone have shown a modest beneficial effect on mortality after acute myocardial infarction. Despite uncertainties about its mechanism of action and the potential for serious toxicity, amiodarone is used widely in the treatment of common arrhythmias such as atrial fibrillation. Studies of acute effects of amiodarone in in-vitro systems are complicated by its insolubility in water, necessitating the use of solvents, such as dimethyl sulfoxide, which can have electrophysiological effects on its own. Amiodarone's effects may be mediated by perturbation of the lipid environment of the ion channels. Amiodarone blocks inactivated Na^+ channels and has a relatively rapid rate of recovery (time constant = 1.6 seconds) from block. It also decreases Ca^{2+} current and transient outward delayed rectifier and inward rectifier K^+ current and exerts a non-competitive adrenergic-blocking effect. Amiodarone potently inhibits abnormal automaticity and, in most tissues, prolongs action potential block by a poorly understood effect on cell-cell coupling that may be especially important in diseased tissues. Prolongation of the PR,

QRS, and QT intervals and sinus bradycardia are frequent during chronic therapy. Amiodarone prolongs refractoriness in all cardiac tissues; Na^+ channel block, delayed repolarization owing to K^+ channel block, and inhibiting of cell-cell coupling all may contribute to this effect. Amiodarone's oral bioavailability is about 30%, presumably due to poor absorption. This incomplete bioavailability is important in calculating equivalent dosing regimens when converting from intravenous to oral therapy. The drug distributes into lipids; heart tissue-to-plasma concentration ratios of greater than 20:1 and lipid-to-plasma ratios of greater than 300:1 have been reported. After the initiation therapy, amiodarone increases refractoriness, a marker of pharmacological effect, and requires several weeks to develop. Amiodarone undergoes hepatic metabolism by CYP3A4 to desethyl-amiodarone, a metabolite with pharmacological effects similar to those of the parent drug. When amiodarone therapy is withdrawn from a patient who have been received therapy for several years, plasma concentrations decline with a half-life of weeks to months. The mechanisms of amiodarone and desethyl-amiodarone elimination are not well established. A therapeutic plasma amiodarone concentration range from 0.5 to 2 µg/ml has been proposed. However, efficacy apparently depends as much on duration of therapy as on plasma concentration, and elevated plasma concentrations do not predict toxicity. Because of amiodarone's slow accumulations in tissues, a high-dose oral loading regimen (e.g., 800 to 1,600 mg daily) usually is administered for several weeks before maintenance therapy is started. The maintenance dose is adjusted based on adverse-effects on the arrhythmias being started. If the presenting arrhythmia is life-threating, dosages of more than 300 mg daily normally are used unless toxicity occurs. On the other hand, maintenance doses of 200 mg daily or less are used if recurrence of an arrhythmia would be tolerated as in patients with atrial fibrillation, because amiodarone slows the ventricular rate during atrial fibrillation. Dosage adjustments are not required in hepatic, renal, or cardiac dysfunction. Amiodarone potently inhibits the hepatic metabolism or renal elimination of many compounds. Mechanisms identified to date include inhibition of CYP3A4, CYP2C9, and P-glycoprotein. Dosages of warfarin, other antiarrhythmics (e.g., flecainide, procainamide, and quinidine), or digoxin usually require reduction dosing amiodarone therapy [1].



Amiodarone molecular structure (molecular weight = 645.31 grams/mole)



Desethyl-amiodarone hydrochloride (molecular weight = 653.7 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "amiodarone dosing infants, children", amiodarone efficacy, safety infants, children", amiodarone adverse-effects infants, children", "amiodarone metabolism", "enzyme inhibition by amiodarone", "amiodarone pharmacokinetics infants, children", "amiodarone drug interactions", "amiodarone treatment infants, children", "amiodarone placental transfer", and "amiodarone migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] were consulted.

Results

Administration schedules of amiodarone to infants and children

Administration to infants [2]

Resuscitation

In the management of "shockable" cardiopulmonary arrest (ventricular fibrillation or pulseless ventricular tachycardia) in children, amiodarone 5 mg/kg is administered after the third DC shock whilst cardiopulmonary resuscitation is continued. Repeat the dose after the fifth shock if still in ventricular fibrillation or pulseless ventricular tachycardia. If defibrillation was initially successful but ventricular fibrillation or pulseless ventricular tachycardia recurs, amiodarone may be repeated (unless two doses have already been given) and continuous infusion started.

Intravenous treatment

Only give this drug intravenously in an intensive care setting, and when a rapid response is essential. Give 5 mg/kg over 30 min and a second similar dose if the first is ineffective. Watch for bradycardia and hypotension. The hypotension that occurs with intravenous amiodarone is related to the rate of delivery and perhaps also to the solvent (polysorbate 80 and benzyl alcohol), which causes histamine release, than the drug itself. Further 5 mg/kg maintenance dose can be given intravenously twice-daily or once-daily if necessary. Change to oral administration as soon as possible.

Intravenous infusion

As before, give this drug by intravenous infusion only in an intensive care setting, and when a rapid response is essential. Give a loading dose of 5 mg/kg over 30 min followed by 19 mg/kg daily maintenance infusion.

Oral administration

Give 15 mg/kg loading dose (unless the infant has already had intravenous treatment) and then a maintenance dose of between 5 and 10 mg/kg once-daily depending on the response achieved.
Amiodarone is a class III antiarrhythmic dug and it is used in the treatment of life-threating or drug-resistant refractory supraventricular, ventricular tachyarrhythmias, and preoperative junctional ectopic tachycardia. Monitor electrocardiogram and blood pressure for intravenous administration. Follow aspartate aminotransferase, alanine aminotransferase, T3, T4, and thyroid-stimulating hormone. Observe intravenous site for extravasation. Amiodarone and desethyl-amiodarone inhibit CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP2A6, CYP2B6, CYP2C8 and the transporter P-glycoprotein. Amiodarone prevents the elimination of digoxin resulting high digoxin levels [3].
Treatment of children with amiodarone hydrochloride [4]
Oral treatment of supraventricular and ventricular arrhythmias (initiated in hospital or under specialist supervision)
Children aged 1 month to 11 years. Give initially 5 to 10 mg/kg twice-daily (maximum per dose = 200 mg) for 7 to 10 days, and then reduce the dose to 5 to 10 mg/kg once-daily (maximum dose = 200 mg daily).
Children aged 12 to 17 years. Give 200 mg thrice-daily for 1 week, and then 200 mg twice-daily for 1 week, and then the usual dose is 200 mg daily adjusted according to the response.
Intravenous treatment of supraventricular and ventricular arrhythmias (initiated in hospital or under specialist supervision)
Children. Give initially 5 to 10 mg/kg, the dose should be given over 20 min to 2 hours, and then (by continuous intravenous infusion) 300 µg/kg/hour, adjust the dose according to the response (by continuous intravenous infusion) increase the dose if necessary up to 1.5 mg/kg/hour (maximum dose = 1.2 grams daily).
Intravenous administration of ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation (for cardiopulmonary resuscitation)
Children. Give 5 mg/kg (maximum per dose = 300 mg), the dose should be given over at least 3 min.

Efficacy and safety of amiodarone in infants and children

Intravenous amiodarone alone, or in combination with digoxin, is found safe and effective in controlling refractory and life-threatening supraventricular tachyarrhythmia in neonates and small infants [5]. Orally administered amiodarone is a safe and effective treatment for drug-refractory foetal tachycardia, specifically re-entrant supraventricular tachycardia, and junctional ectopic, or ventricular tachycardia, even when accompanied by hydrops foetalis or ventricular dysfunction [6]. Intravenous amiodarone is found efficacy and safe in infants with incessant tachycardia [7]. Amiodarone is an effective and safe therapy for the control of tachycardia in infancy [8]. Prophylactic amiodarone is safe and effective in preventing early junctional ectopic tachycardia in children after open heart surgery [9]. Intravenous amiodarone is efficacy and safe in infants and children with tachyarrhythmias [10]. Early treatment of postoperative tachyarrhythmia with amiodarone is safe and has beneficial effects on the control of arrhythmia in paediatric cardiac intensive care unit stay [11]. Intravenous amiodarone is found an effective and safe antiarrhythmic agent for children with acute life-threatening, chronic tachyarrhythmias and depressed left ventricular systolic functions [12]. Intravenous amiodarone is an effective and safe antiarrhythmic drug for short-term treatment of supraventricular tachycardia in children [13]. Intravenous amiodarone is an effective and safe antiarrhythmic drug for short-term treatment of supraventricular tachycardia in children [14].

Adverse-effects caused by amiodarone in infants and children

Neonates and infants receiving amiodarone have more thyroid dysfunction with greater degrees of thyroid-stimulating hormone elevation than older children [15]. Given the potential adverse developmental consequences associated with hypothyroidism during infancy and early childhood, thyroid function tests should be carefully monitored in any infant treated with amiodarone [16]. One of five children (20.0%) develops thyroid dysfunction caused by amiodarone treatment [17]. Paediatric and young-adult subjects develop thyroid dysfunction caused by amiodarone treatment [18]. Amiodarone-induced thyroid dysfunction is usually atypical; therefore, monitoring of thyroid status before, during, and after amiodarone is demanded [19]. An association between amiodarone administered intravenously and the risk of developing cardiovascular collapse is observed in children [20]. A child with supraventricular tachycardia post repair of transposition of the great vessels develops amiodarone toxicity [21]. A risk of amiodarone toxicity consists in the prolongation of the QT interval and the simultaneous loss of atrioventricular conduction [22]. Ninety-five children who received amiodarone develop adverse-effects which occur in 27 of 95 children (28.4%). The adverse-effects caused by amiodarone are: keratopathy (11 cases), abnormal thyroid function test (6 cases), chemical hepatitis (3 cases), rash (3 cases), peripheral neuropathy (2 cases), hypertension (1 case) and vomiting (1 case). All adverse-effects disappear when amiodarone is discontinued or the dose is reduced [23]. When digoxin is combined with amiodarone, the digoxin serum concentration should be monitored carefully, with appropriate reduction of the digoxin dose [24]. Amiodarone induced pulmonary fibrosis in an infant [25] and a case of acute pulmonary toxicity is observed in an infant who received amiodarone [26].

Metabolism of amiodarone in human liver microsomes

Human CYP1A1 and CYP3A4 and rat CYP2D1 and 2C11 convert amiodarone to desethyl-amiodarone. Ketoconazole inhibits the in-vivo formation-rate of desethyl-amiodarone by inhibiting other CYP isoforms besides CYP3A in human and rat [27]. The metabolism of amiodarone into desethyl-amiodarone by CYP1A1 or CYP3A4 plays an important role in the hepatocellular toxicity of amiodarone [28]. CYP3A isozyme(s) mainly metabolize amiodarone into its N-deethylated derivative in human hepatic microsomal fractions [29].

Amiodarone inhibits cytochrome P-450 enzymes (CYPs) and P-glycoprotein

Amiodarone, and its circulating human metabolites, inhibit CYP2C9, CYP2D6, and CYP3A4 in human liver microsomes. The minor metabolite of amiodarone, N,N-didesethylamiodarone, inhibits CYP1A2, CYP2C9, or CYP3A4, while amiodarone and N-monodesethylamiodarone inhibit CYP2D6. The time-

dependent inhibition experiments show that N,N-didesethylamiodarone is a potent inactivator of both CYP2D6 and CYP3A4. For N,N-didesethylamiodarone and N-monodesethylamiodarone, the mechanism of inactivation appears to occur through a metabolic intermediate complex [30]. Amiodarone weakly inhibits CYP2C9, CYP2D5, and CYP3A4, desethyl-amiodarone competitively inhibits CYP2D6 and inhibits noncompetitively CYP2A6. The interactions between amiodarone and other drugs might occur via the inhibition of CYPs by its N-alkylated metabolite, desethyl-amiodarone, rather than by amiodarone itself. In addition, the inactivation of CYPs by desethyl-amiodarone, as well by amiodarone, contributes to the drug interactions [31]. Amiodarone is a potent inhibitor of P-glycoprotein [32]. Amiodarone inhibits CYP2C9 and P-glycoprotein [33] and inhibits CYP3A4, CYP2J2, and P-glycoprotein [34].

Pharmacokinetics of amiodarone in infants and children

Dallefeld et al. [35] studied the pharmacokinetics of amiodarone in 16 infants and 29 children aged up to 2 years. The median (interquartile range) postnatal age is 40 days (20 to 171), and the body-weight is 3.9 kg (3.1 to 6.0). Amiodarone was intravenously infused at a dose of 0.6±0.7 mg/kg and the duration of infusion was 50.8±64.9 hours.

Table 1. Pharmacokinetic parameters of amiodarone which are obtained in 45 infants and children, by Dallefeld et al. [35].

Parameter	Estimate	%RSE	2.5%	Bootstrap median	97.5%	Shrinkage fraction
Structural model[a]						
Ka (h^{-1})	0.18	25	0.04	0.17	0.28	---
TBC (L/h)	1.03	18	0.62	1.03	1.49	---
DV (L)	2.59	33	1.20	2.65	5.29	---
Q	14.7	21	7.10	13.2	21.2	---
Bioavailability	0.53	14	0.40	0.56	0.78	---
Interindividual variability, CV%						
TBC	49	12	31	44	67	0.55
DVc	121	55	96	115	165	0.63
Q	90	32	65	79	126	0.59
DVp	101	19	83	96	126	0.45
Q	125	56	104	121	266	0.34
DVd	84	40	46	76	489	0.67
%Residual error						
%Proportional error	74	10	58	73	88	0.13
Exponent of PTN on residual error	-1.26	17	-2.04	-1.28	-0.82	---

[a]Pharmacokinetic parameters normalized to median weight in kg. Ka = absorption rate constant. TBC = total body clearance. DV = distribution volume. Q = intercompartmental clearance. %RSE = %relative standard error. DVc = central distribution volume. DVp = peripheral distribution volume.

This table shows that amiodarone is rapidly absorbed, the distribution volume is larger than the water volume, the central distribution volume is similar to the peripheral distribution volume, and there is a remarkable interindividual variability of the total body clearance and the distribution volume.

Table 2. Comparison of empirical Bayesian of pharmacokinetic parameters which are grouped according to the age. Figures are the median (90% confidence intervals), by Dallefeld et al. [35].

Age group	N	TBC (L/h/kg)	DVss (L/kg)	$^{\alpha}$Half-life (h)	$^{\beta}$Half-life (h)	$^{\gamma}$Half-life (h)
0 to 2 months	27	0.27 (0.16-0.38)	99.4(63.5-173)	0.09 (0.06-0.18)	9.29 (4.11-24.0)	420 (277-926)
2 months to 1 year	4	0.27 (0.14-0.28)	89.0 (86.0-107)	0.11 (0.06-0.28)	11.7 (6.9-47.9)	515 (349-1,180)
1 to 2 years	14	0.20 (0.14-0.24)	101 (87.0-167)	0.13 (0.08-0.16)	12.7 (60.2-20.9)	637 (522-1,099)
Combined age groups	42	0.25 (0.14-0.36)	93.0 (68.0-174)	0.09 (0.06-0.18)	10.4 (4.40-27.9)	497 (297-1,161)

TBC = total body clearance. DVss = distribution volume at the steady-state. α, β, and γ are the half-life of each phase of the tri-phasic decline of serum concentrations.
This table shows that the distribution volume is larger than the water volume; amiodarone is rapidly absorbed following intravenous infusion as $^{\alpha}$half-life is short. β and γ half-lives increase with the infant maturation and child development, and there is a remarkable interindividual variability in the pharmacokinetic parameters.

Interaction of amiodarone with drugs

Amiodarone increases edoxaban concentrations in the low-dose arm (27.3±24.5 ng/ml versus 21.9±20.8 ng/mL, P-value < 0.001) and in the high-dose arm (58.5±53.2 ng/ml versus 43.2±41.1 ng/ml), P-value < 0.001) [36]. Short-term intravenous amiodarone enhances the anticoagulant effect of warfarin [37]. The minor metabolite of amiodarone, namely N,N-didesethylamiodarone, is a major contributor to the interaction between warfarin and amiodarone [38]. The magnitude of the interaction between amiodarone and warfarin peaks at 7 weeks which results in a 44% reduction in the warfarin dose. The warfarin dose inversely correlates with the maintenance dose of amiodarone (r^2 = 0.94, P-value < 0.005). The magnitude of the amiodarone and warfarin interaction is highly dependent on the maintenance dose of amiodarone [39]. Amiodarone potentiates the warfarin effects, increases the prothrombin time by 22% to 108%, and lowers the warfarin requirement by 25% to 50% [40]. Amiodarone depress the vitamin K-dependent coagulation factors caused by warfarin and may lead to serious bleeding. The maintenance dose of warfarin should be halved when amiodarone and warfarin are prescribed together [41]. Amiodarone may interact with β-blocking agents and some of the calcium antagonists producing symptomatic sinus bradycardia and sinus arrest, especially in a latent or overt sick sinus syndrome. During surgery, amiodarone may induce hypotension and an atropine-resistant bradycardia, possibly by interacting with anaesthetic agents [42]. Amiodarone interacts with a type Ia or Ic drug or with a β-blocking drug and

can slow the rate of ventricular tachycardia to make the ventricular tachycardia hemodynamically well tolerated [43]. Amiodarone affects the phenytoin pharmacokinetics and when phenytoin is co-administered with amiodarone the dose of phenytoin should be reduced at least by 25% [44]. Amiodarone inhibits phenytoin metabolism and the dose of phenytoin doses should be reduced when phenytoin is co-administered with amiodarone [45]. The serum concentrations of amiodarone during weeks 5 and 6 of therapy are 0.25±0.09 and 0.19±0.07 µg/ml, respectively. Following co-administration of phenytoin the serum concentrations of amiodarone increase up to 0.36±0.12 µg/ml (P-value = 0.011) and 0.38±0.13 µg/ml (P-value = 0.004) on the 5th and 6th weeks of combined therapy, respectively, indicating that phenytoin inhibits the metabolism of amiodarone [46].

Treatment with amiodarone in infants and children

Intravenous amiodarone can be used to treat neonatal flutter being an effective therapy in infants with haemodynamic stability [47]. Amiodarone is a first-line treatment in paediatric patients with postoperative junctional ectopic tachycardia [48]. Early treatment of postoperative tachyarrhythmia with amiodarone is safe and has beneficial effects on arrhythmia control in paediatric patients with cardiac disease [49]. The overall efficacy of intravenous amiodarone is dose-dependent in children with arrhythmia, but the adverse-effects are common and are dose-related [50]. Amiodarone should be used with close follow-up in paediatric patients who have atrial fibrillation, left ventricular dysfunction, and ventricular arrhythmias [51]. Amiodarone can be used safely and effectively to control junctional ectopic tachycardia in most children [52]. Amiodarone is an extremely effective treatment for infants and children with tachyarrhythmias resistant to conventional treatment [53].

Transfer of amiodarone across the human placenta

Amiodarone therapy during pregnancy may cause foetal and neonatal hypothyroidism and less frequently goiter. Thus, the use of amiodarone in pregnancy should be limited to maternal and foetal tachyarrhythmias which are resistant to other drugs [54]. Amiodarone was detectable in only 50% of foetal plasma suggesting that amiodarone is poorly transferred from the mother to the foetus [55]. The transfer of amiodarone across the human placenta was investigated in two cases and amiodarone is poorly transferred from the maternal to foetal blood [56].

Migration of amiodarone into the breast-milk

A very limited exposition of amiodarone in breastfed newborns is expected after a single administration of amiodarone to their mothers [57]. The concentrations of amiodarone in the breast-milk are very low in mothers treated with amiodarone [58]. Amiodarone can be given during pregnancy but it is advisable to administer amiodarone at the low doses as possible in order to have as low as possible amiodarone concentration in the breast-milk [59].

Discussion

Amiodarone is a class III antiarrhythmic drug and it is used in the treatment of life-threatening or drug-resistant refractory supraventricular, ventricular tachyarrhythmias, and junctional ectopic tachycardia. Prolongation of the PR, QRS, and QT intervals and sinus bradycardia are frequent during chronic therapy. Amiodarone is a structural analogue to thyroid hormone and some of its antiarrhythmic actions may be attributable to interaction with nuclear thyroid hormone receptors. Amiodarone is highly lipophilic, concentrates in many body-tissues, the oral bioavailability is about 30%, and is eliminated slowly. The efficacy of amiodarone depends on the duration of therapy and on plasma concentration and elevated plasma concentrations do not predict toxicity [1]. Amiodarone may be administered intravenously or orally. In infants, the dosing of amiodarone consists in a loading dose of 5 mg/kg given by intravenous infusion followed by a maintenance dose of 10 mg/kg once-daily and the oral dosing consists in a loading dose of 15 mg/kg followed by a maintenance dose of 5 to 10 mg/kg [2]. In children, the treatment of supraventricular and ventricular arrhythmias require an initial oral dose of 5 to 19 mg/kg twice-daily, followed by a maintenance dose of 5 to 10 mg/kg once-daily. An alternative dose, to treat these diseases, consists in 5 to 10 mg/kg given by intravenous infusion followed by 300 µg/kg/hour [4]. Amiodarone has been found efficacy and safe in infants and children [5-14]. Intravenous amiodarone alone, or in combination with digoxin, is efficacy and safe in controlling refractory and life-threating supraventricular tachyarrhythmia in infants [5]. Oral amiodarone is an effective treatment for drug-refractory foetal tachycardia, re-entrant supraventricular tachycardia, and junctional ectopic, or ventricular tachycardia [6]. Intravenous amiodarone successfully treats tachycardia in infants [7, 8]. Prophylactic amiodarone prevents early junctional ectopic tachycardia in children after heart surgery [9], intravenous amiodarone is efficacy and safe in controlling tachyarrhythmias [10] and arrhythmia [11] in paediatric patients. Intravenous amiodarone is an effective and safe antiarrhythmic agent in children with life-threatening and chronic tachyarrhythmias and depressed left ventricular systolic functions [12], and intravenous amiodarone is an effective and safe antiarrhythmic agent to treat supraventricular tachycardia in children [13, 14]. The adverse-effects caused by amiodarone in infants and children have been reported in several occasions [15-26]. Amiodarone causes thyroid dysfunctions in infants and children and the thyroid function tests should be monitored when paediatric patients are treated with amiodarone [15-19]. Amiodarone causes cardiovascular collapse in children [20], causes toxicity in a child with supraventricular tachycardia [21]. Amiodarone prolongs QT interval and the simultaneous loss of atrioventricular conduction [22], and causes various adverse-effects in about 30% of children [23]. The serum concentration of digoxin should be carefully monitored when the digoxin is combined with amiodarone with appropriate reduction of digoxin dose [24]. Amiodarone induces pulmonary fibrosis [25] and lung toxicity [26] in infants. Amiodarone is converted into desethyl-amiodarone by human CYP1A1 and CYP3A4 [27, 28] and plays an important role in liver toxicity. Amiodarone is metabolized into N-deethylated derivative by CYP3A enzymes in human liver microsomes [29]. Amiodarone, and its circulating metabolites, inhibit CYP2C9, CYP2D6, and CYP3A4 in human liver microsomes. The minor metabolite of amiodarone, N,N-didesethylamiodarone, inhibits CYP1A2, CYP2D6 and CYP3A4 while amiodarone and N-monodesethylamiodarone inhibits CYP2D6 and N,N-didesethylamiodarone inhibits CYP2D6 and CYP3A4. Amiodarone is a weakly inhibitor of CYP2C9,

CYP2D5, and CYP34A, and desethyl-amiodarone inhibits competitively CYP2D6 and noncompetitively CYP2A6 [30]. The N-alkylated metabolite and desethyl-amiodarone interact with several drugs [31] and amiodarone inhibits P-glycoprotein [32-34]. The pharmacokinetics of amiodarone have been studied in infants and young children [35]. Following intravenous dosing, amiodarone is rapidly absorbed, mean absorption half-life is 0.09 hours, and the mean elimination half-life is 10.4 hours. The mean distribution volume is 93.0 L/kg thus it is larger than the water volume suggesting that amiodarone diffuses in body-tissues. The interaction of amiodarone with drugs has been extensively studied [36-46]. Amiodarone increases the serum concentration of edoxaban [36], interacts with warfarin [37-41], and the metabolite of amiodarone, namely N,N-didesethylamiodarone, is a major contributor to the interaction between amiodarone and warfarin interaction [38]. Amiodarone potentiates the anticoagulant effect of warfarin, this effect is depending on amiodarone dose, and the dose of warfarin should be reduced when warfarin is co-administered with amiodarone [37, 39]. Amiodarone increases the prothrombin time caused by the potentiation of warfarin effects and the dose of warfarin should by reduced when it is combined with amiodarone [40]. Amiodarone depresses the vitamin K-dependent coagulation factors caused by warfarin leading to serious blending [41]. Amiodarone interacts with β-blocking agents and some calcium antagonists producing bradycardia and sinus arrest, and amiodarone may induce hypotension and bradycardia when it is co-administered with anaesthetic agents [42]. Amiodarone interacts with type 1a or 1c drug or with a β-blocking drug and can slow the rate of ventricular tachycardia [43]. Amiodarone affects phenytoin pharmacokinetics [44] and phenytoin metabolism [44] and the dose of phenytoin should be reduced when phenytoin is co-administered with amiodarone [44, 45]. Phenytoin increases the serum concentration of amiodarone due to the inhibition of amiodarone metabolism [46]. The treatment with amiodarone has been studied in infants and children [47-53]. Intravenous amiodarone treats neonatal flutter in infants with haemodynamic stability [47], amiodarone is a first-line treatment in paediatric patients with postoperative junctional ectopic tachycardia [48], and amiodarone controls arrhythmia in paediatric patients [49, 50]. Amiodarone treats atrial fibrillation, left ventricular dysfunction, and ventricular arrhythmias in paediatric patients but amiodarone should be used with close follow-up [51]. Amiodarone effectively controls junctional ectopic tachycardia in children [52], and amiodarone treats children with tachyarrhythmias resistant to conventional treatment [53]. Amiodarone should not to be used in pregnant women because amiodarone may cause neonatal hypothyroidism [54] however amiodarone is poorly transferred across the human placenta [55, 56], and poorly migrates into the breast-milk [57-59].

In conclusion, amiodarone is a class III antiarrhythmic drug and it is used in the treatment of life-threatening or drug-resistant refractory supraventricular, ventricular tachyarrhythmias, and junctional ectopic tachycardia. The efficacy of amiodarone depends on the duration of therapy and on the plasma concentration. The oral bioavailability of amiodarone is about 30%, amiodarone is highly lipophilic, diffuses in body-tissues, is slowly eliminated, and amiodarone mean elimination half-life is 10.4 hours in infants and young children. Amiodarone may be administered intravenously or orally in infants and children. Amiodarone has been found efficacy and safe in infants and children but amiodarone may induce adverse-effects. Amiodarone is metabolized by different CYPs, the major metabolite is desethyl-amiodarone, and amiodarone inhibits various CYPs and P-glycoprotein. Amiodarone interacts with different drugs and when it is co-administered with warfarin enhances the warfarin effect causing risk of bending. The treatment with amiodarone has been extensively studied in infants and children, and amiodarone is poorly transferred across the human placenta and poorly migrates into the beast-milk. The aim of this study is to review the clinical pharmacology of amiodarone in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.
This article is a review and drugs have not been administered to men or animals.

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