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Review Article

Clinical Pharmacology of Digoxin in Infants and Children

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Abstract

Digoxin is a cardiac glycoside and it is used for the treatment of supraventricular tachycardia, atrial flutter, and re-entrant arrhythmias. Digoxin may be administered orally or intravenously and the tablet oral bioavailability is 75%. The oral treatment of digoxin consists in a loading dose followed by a maintenance dose in infants and children and the loading and maintenance doses vary according to infant and child age. The pharmacokinetics of digoxin have been studied in 11 infants and children, aged 1 month to 15 years, the median elimination half-life is 42 hours and it varies from 8.3 hours to 77.0 hours being longer in infants. Digoxin diffuses in body-tissues, reaches higher concentrations in tissues than in serum, and the right atrial appendage to serum ratio of digoxin varies 10.7 ng/ml to 318 ng/ml (mean, 92.5). The interaction of digoxin with drugs has been extensively studied and digoxin co-administered with drugs may induce toxicity in infants and children. Digoxin verapamil and quinidine are substrates of P-glycoprotein and verapamil and quinidine inhibit the clearance of digoxin increasing its serum concentrations. The treatment with digoxin has been studied in infants and children. Digoxin is transferred across the human placenta, reaches similar concentrations in the maternal and newborn serum and digoxin migrates into the breast-milk in significant amounts. The aim of this study is to review the published data on digoxin dosing, efficacy, safety, pharmacokinetics, serum and tissue concentrations, drug interactions, toxicity, treatment in infants and children and digoxin placental transfer and migration into breast-milk.

Keywords: Digoxin; Dosing; Efficacy; Safety; Pharmacokinetics; Tissue concentration; Drug interaction; Toxicity; P-glycoprotein; Treatment; Placenta; Breast-milk

Introduction

Mechanisms of action of digoxin

Digitalis glycosides exert positive inotropic effects and have been used in heart failure, they are rarely prescribed. Their inotropic action result from increased intracellular Ca^{2+}, which also forms the basis for arrhythmias related to cardiac glycoside intoxication. Cardiac glycosides increase phase 4 slope (e.g., increase the rate of automaticity) especially if $[K]_o$ is low. These drugs (e.g., digoxin) also exert prominent vagotomic actions, resulting in inhibition of Ca^{2+} current in the atrioventricular node and activation of acetylcholine-mediated K^+ currents in the atrium. Thus, the major "indirect" electrophysiological effects of cardiac glycosides are hyper polarization, shortening of atrial action potential, and increased in atrioventricular nodal refractoriness. The last action accounts for the utility of digoxin in terminating re-entrant arrhythmias involving the atrioventricular node and in controlling ventricular response in patients with atrial fibrillation. Cardiac glycosides may be especially useful in the last situation because many such patients have heart failure, which can be exacerbated by other atrioventricular nodal-blocking drugs such as Ca^{2+} channel blockers or β blockers. However, sympathetic drive is increased markedly in many patients with advanced heart failure, so digitalis is not very effective in decreasing the rate; on the other hand, even a modest decrease in the rate can ameliorate heart failure. Similarly, in other conditions in which high sympathomimetic tone drives rapidly atrioventricular conduction (e.g., chronic lung disease and thyrotoxicosis), digitalis therapy may be the only marginally effective in slowing the rate. In heart transplant patients, in whom innervation has been ablated, cardiac glycosides are ineffective for rate control. Increased sympathetic activity and hypoxia can potentiate digitalis-induced changes in automaticity and delayed after depolarization, thus increasing the risk of digitalis toxicity. A further complicating feature in thyrotoxicosis is increased digoxin clearance. The major electrocardiography effects of cardiac digitalis are PR prolongation and a nonspecific alteration in ventricular repolarization (manifested by depression of the ST segment), whose underlying mechanism is not well understudied [1].

Absorption, distribution, metabolism, and elimination of digoxin

The only digitalis glycoside used in the U.S. is digoxin. Digitoxin (various generic preparations) also is used for chronic oral therapy outside the U.S. Digoxin tablets are incompletely absorbed and the bioavailability is 75%. In some patients, intestinal microflora may metabolize digoxin, markedly reducing bioavailability. In these patients, higher-than-usual doses are required for clinical efficacy; toxicity is a serious risk if antibiotics are administered that destroy intestinal microflora. Inhibition of P-glycoprotein also may play a role in cases of toxicity. Digoxin is 20% to 30% protein bound. The antiarrhythmic effect of digoxin undergoes relatively slow distribution to effector site(s); therefore, even with intravenous therapy, there is a

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lag of several hours between drug administration and the development of the ventricular rate in atrial fibrillation. To avoid intoxication, a loading dose of approximately 0.6 mg to 1 mg digoxin is administered over 24 hours. Measurement of post-distribution serum digoxin concentration and adjustment of the daily dose (0.0625 mg to 0.5 mg) to maintain concentrations of 0.5 ng/ml to 2 ng/ml are useful during chronic digoxin therapy. Some patients may require and tolerate higher concentrations, but with an increased risk of adverse-effects. The elimination half-life of digoxin ordinarily is about 36 hours in adults, so maintenance doses are administered once-daily. Renal elimination of unchanged drug accounts for 80% of digoxin elimination. Digoxin doses should be reduced (or dosing interval increased) and serum concentrations monitored closely in patients with impaired excretion owing to renal failure or in patients who are hypothyroid. Digoxin undergoes primary hepatic metabolism and may be useful in patients with fluctuating or advanced renal dysfunction. Digitoxin metabolism is accelerated by drugs such as phenytoin and rifampin that induce hepatic metabolism. Digitoxin's elimination half-life is even longer than that of digoxin (about 7 days) in adults; is highly protein bound, and its therapeutic concentrations range is 10 ng/ml to 30 ng/ml. Digoxin, quinidine, verapamil, diltiazem, cyclosporine, itraconazole, propafenone, and flecainide decrease digoxin clearance, likely by inhibiting P-glycoprotein, the major route of digoxin elimination. New steady-state digoxin concentrations are approached after 4 to 5 half-lives (i.e., in about a week). Digitalis toxicity results so often with quinidine or digoxin that it is routine to decrease the dose of digoxin if these drugs are started. In all cases, digoxin concentrations should be measured regularly and the dose adjusted if necessary. Hypokalaemia, which can be caused by many drugs (e.g., diuretics, amphotericin B, and corticosteroids), potentiate digitalis-induced arrhythmias [1] (Figure 1).

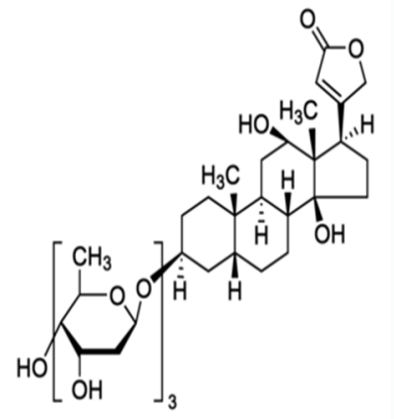

Figure 1: Digoxin molecular structure (molecular weight = 780.938 grams/mole).

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "digoxin dosing infants, children", digoxin efficacy, safety infants, children", "digoxin pharmacokinetics infants, children", "digoxin serum concentration infants, children", "digoxin tissue concentration infants, children", "digoxin drug interactions", "digoxin toxicity infants, children", "digoxin P-glycoprotein transport", "digoxin treatment infants, children", "digoxin placental transfer", and "digoxin 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 digoxin to infants and children

Intravenous and oral administration to infants [2]: Digoxin is used in the treatment of heart failure caused by diminished myocardial contractility and in the treatment of supraventricular tachycardia, atrial flutter, and atrial fibrillation. Follow heart rate and rhythm closely. Perform periodic electrocardiograms to assess both desired effects and signs of toxicity. Follow closely (especially in infants receive diuretics or amphotericin B) for decreased serum potassium and magnesium, or increased calcium and magnesium, all of which predispose digoxin toxicity. Assess renal function. Be aware of drug interactions, may follow serum drug concentrations if assay is available that excludes endogenous digoxin-like substances. Therapeutic serum concentration is 1 ng/ml to 2 ng/ml. Digoxin is incompatible with amiodarone, dobutamine, fluconazole, and propofol [3] (Table 1).

Table 1: Conventional starting doses (in µg/kg) for digoxin in infants.

Body-weight	Total slow intravenous infusion	Total oral loading dose	Daily oral maintenance dose
<1.5 kg	20	25	5
1.5 kg to 2.5 kg	30	35	7.5
>2.5 kg	35	45	10

Administration to children [4]: Oral treatment of supraventricular arrhythmia and chronic heart failure: Children aged 1 month to 1 year. Give initially 45 µg/kg in 3 divided doses for 24 hours, and then 10 µg/kg daily in 1 to 2 divided doses.

Children aged 2 to 4 years. Give initially 35 µg/kg in 3 divided doses for 24 hours, and then give 10 µg/kg in 1 to 2 divided doses.

Children aged 5 to 9 years. Give initially 25 µg/kg in 3 divided doses (maximum per dose=750 µg) for 24 hours, and then 6 µg/kg daily in 1 to 2 divided doses (maximum dose=250 µg per day).

Children aged 10 to 17 years. Give initially 0.75 to 1.5 mg in 3 divided doses for 24 hours, and then 62.5 to 250 µg daily in 1 to 2 divided doses, higher doses may be necessary.

Intravenous administration of supraventricular arrhythmia and chronic heart failure: Children aged 1 month to 1 year. Give initially 35 µg/kg in 3 with divided doses, and then 10 µg/kg daily in 1 to 2 divided doses. Children aged 2 to 4 years. Give initially 35 µg/kg in 3 divided doses for 24 hours, and then 10 µg/kg in 1 to 2 divided doses. Children aged 5 to 9 years. Give initially 25 µg/kg in 3 divided doses (maximum per dose=500 µg) for 24 hours, and then 6 µg/kg daily divided in 1 to 2 divided doses (maximum dose=250 µg daily). Children aged 10 to 17 years. Give initially 0.5 to 1 mg in 3 divided doses for 24 hours, and then 62.5 to 250 µg daily in 1 to 2 divided doses, higher doses may be necessary.

Dose adjustment due to interactions: The manufacturer advises reduce the dose by half if digoxin has been given with concurrent use of amiodarone, dronedarone, and quinine [4].

Dose equivalence and conversion: The dose may need to be reduced if digoxin (or another cardiac glycoside) has been given in the

preceding 2 weeks. When switching from intravenous to oral route may need to increase the dose by 20% to 33% to maintain the same plasma-digoxin concentration [4].

Efficacy and safety of digoxin in infants and children

Digoxin use in infants with single ventricle congenital heart disease is associated with significantly reduction of inter stage mortality [5]. There is no difference in supraventricular tachycardia recurrence in infants treated with digoxin or propranolol [6]. Digoxin is associated with fewer episodes of supraventricular tachycardia recurrence but more frequent hypotension in hospitalized infants compared to propranolol [7]. Digoxin is effective and safe in treating supraventricular tachycardia recurrence in children [8].

Pharmacokinetics of digoxin in infants

Gong et al. [9] studied the pharmacokinetics of digoxin in 107 infants with a postnatal age and body-weight of 126 ± 99 days and 5.5 kg ± 1.9 kg, respectively. Infants were given digoxin in the form of an elixir (0.005%, 30 ml/bottle) and the doses were calculated on a 1.2 ml/kg to 1.6 ml/kg. Digoxin was administered orally for more than 6 days and infants with serious hepatic or renal dysfunction were excluded from the study.

Table 2 shows that the distribution volume is similar to the water volume, digoxin is rapidly absorbed, and there is a remarkable interindividual variability in the total body clearance and in the distribution volume.

Pharmacokinetics of digoxin in children

Lares-Asseff et al. [10] investigated the pharmacokinetics of digoxin in 11 children with congestive heart failure aggravated by other diseases. Digoxin was administered orally and the dosing consisted in a loading dose of 7.40 μg/kg ± 1.45 μg/kg followed by a maintenance dose of 2.55 μg/kg ± 0.73 μg/kg once-daily.

This table shows that digoxin is rapidly absorbed following oral dosing, is slowly eliminated, the median distribution volume is similar to the water volume, and the pharmacokinetic parameter markedly vary among subjects. This variability may be accounted by the wide range of subject age (Table 3).

Subjects of group A comprised children aged 1 month to 3 years and subjects of group B included children aged 8 to 15 years. The analysis of the effect of age on drug distribution is significantly different (P-value<0.05). Significant statistical differences (P-value<0.01) are found for the pharmacokinetic parameters in subjects of groups A and B.

Table 2: Pharmacokinetic parameters of digoxin which are obtained in 107 infants, by Gong et al. [9].

	Final model		Bootstrap (N = 1,000)	
Parameter	Estimate	%RSE	Median	95% CI
TBC/F (L/h/70 kg)	10.4	6	10.3	8.8 - 11.6
DV (L/70 kg)	1,100	18.7	1,100	663 - 1,537
%Interindividual variability				
TBC/F	35.1	29.4	34.6	31.1 - 38.1
DV/F	58	88.7	53.1	38.7 - 67.5
Residual error model (%) proportional				
---	10.1	69.8	9.9	7.5 - 12.2

TBC: Total Body Clearance; DV: Distribution Volume; % RSE: %Relative Standard Error; CI: Confidence Interval; F: Oral Bioavailability

The absorption rate constant (Ka) is 0.718 h^{-1}.

Digoxin serum concentrations in infants and young children

Huang et al. [11] measured the serum concertation of digoxin in 291 infants and children with a median age of 1.1 years and 64.3% were male. Digoxin was administered orally as a solution and serum samples were obtained 6 hours after the last dose. The mean serum concentration of digoxin in infants aged <1 month was higher than that in older children. There is a statistically significant difference (P-level<0.01) in mean serum digoxin infants aged <1-month, older infants, and children.

The therapeutic serum concentration of digoxin ranges from 0.8 ng/ml to 2 ng/ml. This table shows that the serum concentration of digoxin falls within the therapeutic interval (Table 4).

Plasma concentrations of digoxin in adult patients and infants

O'Malley et al. [12] measured the plasma concentration of digoxin in 16 adult patients and in 13 infants. This table shows that the digoxin dose is 5 times higher in infants than in adults, consequently the plasma concentration of digoxin is higher in infants, and the digoxin plasma concentration is higher in older than younger infants (Table 5).

Tissue concentration of digoxin in infants and children

Kim et al. [13] measured the concentration of digoxin in post-mortem infants and children. Digoxin was administered orally or intravenously or intramuscularly and the daily dose ranged from 2.6 μg/kg to 33.3 μg/kg.

This table shows that the concentration of digoxin widely varies in tissues and the highest concentration has been found in myocardium, kidney and liver (Table 6). Table 7 shows that digoxin diffuses in all body-tissues and the highest concentration appears in the small intestine, large intestine, and gall bladder.

Wagner et al. [14] measured the concentration of digoxin in the serum and right atrial appendage in 25 children aged 9 months to 18 years (mean ± SD = 4.5 ± 0.9 years) and weighing 3.7 kg to 88.0 kg (mean ± SD = 18.2 ± 5.2). Each child had been taken digoxin over a long term of 21 months for up to 24 hours before open heart surgery.

Table 8 shows that the concentration of digoxin is higher in the right atrial appendage that in serum and there is a remarkable interindividual variability in the concentration of digoxin in serum and in the right atrial appendage.

Interaction of digoxin with drugs

Digoxin co-administered with clarithromycin reduces the digoxin clearance by 56% to 60% and the elimination half-life becomes 82% longer [15]. Renal dysfunction occurs with the use of clarithromycin and digoxin. Renal failure is due to the inhibition of digoxin clearance caused by drugs which inhibit P-glycoprotein thus reducing the renal efflux of digoxin increasing the digoxin serum concentrations [16]. The combination of quinidine and digoxin causes new ventricular tachycardia, ventricular fibrillation, extra systole, or sudden death [17]. The serum digoxin concentration increases from 1.4 ng/ml to 3.2 ng/ml during quinidine therapy in 25 of 27 patients (92.6%) [18]. An increase in serum digoxin concentration occurs in 90.0% of patients given quinidine [19]. The decrease of biliary excretion of digoxin by quinidine is accompanied by a linear increase in sinusoidal efflux of digoxin's primary metabolite, digoxigenin bisdigitoxoside

Table 3: Pharmacokinetic parameters of digoxin which are obtained in 11 children with congestive heart failure aggravated by other diseases aged between 1 month to 15 years. Figures are the minimum, maximum, and median values, by Lares-Asseff et al. [10].

Values	Distribution rate constant (h^{-1})	Distribution half-life (h)	Elimination half-life (h)	Distribution volume (L/kg)	Total body clearance ml/kg/h	K_{21}	$AUC_{0-\infty}$
Minimum	0.0928	0.3472	8.3	0.654	6	0.047	120.2
Maximum	0.734	1.1254	77	6.25	331	0.2504	873.2
Median	0.2419	0.862	42	1.01	15	0.1451	213.6

K_{21}: Transference Rate-Constant; $AUC_{0-\infty}$: Area Under the plasma Concentration from 0 hour to infinite

Table 4: Digoxin serum concentration which is measured in 291 infants and children 6 hours after the last digoxin administration, by Huang et al. [11].

		Serum digoxin concentration (% Subjects)			Serum concentration (ng/ml) mean ± SD	Daily digoxin dose (ng/ml) mean ± SD
Age range	N	<0.8 ng/ml	0.8 ng/ml - 2.0 ng/ml	>2.0 ng/ml		
<1 month	45	9 (20.0)	28 (62.2)	8 (17.7)	1.29 ± 0.58	6.35 ± 1.98
1 month - 1 year	184	65 (35.3)	112 (60.3)	7 (3.8)	0.98 ± 0.46	7.34 ± 1.58
1 - 2 years	36	24 (66.7)	10 (27.8)	2 (5.6)	0.81 ± 0.69	7.72 ± 1.43
>2 years	26	13 (50.0)	13 (50.0)	0 (0.0)	0.88 ± 0.34	5.87 ± 1.07

Table 5: Clinical data, dose of digoxin, and plasma digoxin concentrations. Figures are the mean ± SD, by O'Malley et al. [12].

Subjects	N	Age		Blood urea mg/100 ml	Dose (µg/kg)	Dose (µg/m²)	Plasma concentration of digoxin (ng/ml)
		Mean ± SD	Range				
Adults	16	66.7 ± 12.0 years	46-85 years	48.6 ± 17.3	5 ± 2	180 ± 90	1.4 ± 1.1
Infants	13	65.0 ± 68.0 days	12-225 days	45.8 ± 14.1	24 ± 3	390 ± 0.05	2.8 ± 1.5
>1 month	5	135 ± 65.4 days	63-225 days	44.6 ± 10.4	24 ± 5	410 ± 80	14 ± 0.5
<1 month	8	23.4 ± 6.3 days	12-30 days	46.5 ± 16.0	23 ± 2	380 ± 40	3.8 ± 1.2

Table 6: Tissue concentrations of digoxin which are measured in preterm, term, and children. Figures are ng/gram wet tissue, by Kim et al. [13].

		Myocardium					
	Number of subjects	Right ventricle	Left ventricle	Skeletal muscle	Kidney	Liver	Fat
Premature infants							
Mean	7	187	191	37	73	56	8
± SD		67	71	33	43	34	5
Term infants							
Mean	4	180	196	32	198	50	6
± SD		84	36	17	69	34	2
Children							
Mean	4	60	74	8	232	41	4
± SD		14	37	6	27	25	4

Table 7: Concentrations of digoxin which are measured in different organs obtained from post-mortem preterm, and term infants, and children. Figures are ng/gram wet tissue, by Kim et al. [13].

Value	Sp	Skin	Lung	Brain	Adr	Thy	Thym	Test	Ov	Panc	Sto	Sm int	La int	Gall Bl	Uri Bl
Premature infants															
X	12	13	27	7	16	30	18	6	14	27	23	53	54	35	14
SD	2	7	7	8	14	9	6	3	---	10	14	31	40	36	6
N	5	7	4	4	6	5	4	2	1	5	7	7	7	6	3
Term infants															
X	16	22	26	14	25	32	15	15	---	61	31	93	70	71	18
SD	6	13	14	15	7	18	5	13	---	22	21	62	51	9	15
N	4	4	3	4	3	4	4	3	---	2	4	4	4	4	2
Children															
X	8	38	17	21	14	21	6	---	4	21	71	75	52	70	11
SD	5	30	5	12	7	18	---	---	---	4	67	69	22	107	---
N	3	4	2	3	3	2	1	---	1	2	3	3	4	3	1

X: Mean; SD: Standard Deviation; Sp: Spleen; Adr: Adrenals; Thy: Thyroid; Thym: Thymus; Test: Testicle; Ov: Ovary; Panc: Pancreas; Sto: Stomach; Sm int: Small Intestine; La Int: Large Intestine; Gall Bl: Gall Bladder; Uri Bl: Urinary Bladder

Table 8: Concentrations of digoxin which are measured in 25 children undergoing open heart surgery. Figures are the minimum, maximum, mean, and standard deviation (SD), by Wagner et al. [14].

Values	Serum digoxin concentration (ng/ml)	Right atrial appendage digoxin concentration (ng/gram)	Right atrial appendage to serum concentration ratio
Minimum	<0.11	2.61	10.7
Maximum	1.14	159	318
Mean	0.54	46.8	92.5
± SD	0.07	8.4	16.3

[20]. Antiarrhythmic drugs, such as quinidine and amiodarone, can markedly increase the steady-state serum digoxin levels [21]. In children, the clearance of digoxin decreases by a half following carvedilol treatment, the serum digoxin concentration increases, and two children developed toxicity [22]. The co-administration of digoxin and itraconazole leads to digoxin toxicity due to enhancement of digoxin serum concentration [23], and patients receiving itraconazole and digoxin concomitantly developed elevated serum concentration of digoxin [24]. In patients with atrial fibrillation, digoxin-amiodarone combination therapy is associated with high mortality-rate [25].

Digoxin-amiodarone interaction is multifactorial and the serum digoxin level must be monitored when digoxin is combined with amiodarone [26]. Amiodarone increases the plasma concentration of digoxin [27]. The amiodarone combined with digoxin increases the digoxin serum levels and the serum digoxin levels should be monitored during concurrent digoxin-amiodarone therapy [26]. When propafenone is given with digoxin, the serum concentrations of digoxin increase because propafenone inhibits the renal clearance of digoxin mediated by P-glycoprotein [28]. Antacids and kaolin-pectin reduce the oral bioavailability of digoxin [29]. A significant interaction between cyclosporine and digoxin has been observed; the distribution volume of digoxin decreased by 71% and the digoxin plasma clearance decreased by 53% [30]. Neomycin clearly depresses the digoxin absorption-rate [31].

Toxicity induced by digoxin in infants and children

Toxic serum digoxin concentrations (mean, 2.6 ng/ml) are present in 6.9% of infants treated with digoxin. Nausea and vomiting occur in 36.4% infants followed by tachycardia which occurs in 29.5% infants [32]. Toxicity of digoxin is observed in newborn infants with plasma digoxin concentration >5 ng/ml [33]. Serum digoxin concentration of 14.2 ng/ml induces toxicity in an infant [34]. Signs and symptoms of digoxin toxicity occur in pediatric patients with a digoxin concentration >2 ng/mL (2.6 nmol/L) [35]. Digoxin specific Fab fragments should be promptly administered to any infant or child with significant life-threatening symptoms following acute digoxin intoxication [36]. Digoxin serum concentration >2 ng/ml is associated with toxic effects especially in infants and children receiving concomitant diuretic therapy [37]. Digoxin serum concentration of 3.6 ng/ml is associated with toxicity in infants and children [38]. Toxic effects of digoxin are caused by a digoxin serum concentration of 4.4 ng/ml in infants and children [39].

Effects of P-glycoprotein digoxin transport

Verapamil inhibits the digoxin active secretory transport from the renal apical membranes supporting the theory that verapamil inhibits digoxin secretion in the renal tubular cells due to P-glycoprotein inhibition [40]. Concomitant rifampin-digoxin therapy may affect digoxin disposition in humans by induction the P-glycoprotein [41]. Quinidine and digoxin are substrates of P-glycoprotein; quinidine is a potent inhibitor of digoxin transport by inhibition of P-glycoprotein with consequent increase of plasma digoxin concentration [42]. Digoxin is actively secreted by the renal tubular cell via the P-glycoprotein drug efflux pump and commonly interacting drugs inhibit the renal tubular secretion of digoxin increasing digoxin serum concentration [43]. Verapamil decreases *in-vivo* and *in-vitro* digoxin renal tubular secretion, which is suggested to be mediated by P-glycoprotein, an ATP-dependent multidrug efflux pump [44]. The absorption of digoxin from the human jejunum is increased by drugs that inhibit P-glycoprotein [45]. The digoxin levels increase in a stepwise fashion in patients with an increasing number of co-administered P-glycoprotein inhibitors [46].

Treatment with digoxin in infants and children

A digoxin loading oral dose of 25 μg/kg in term infants (aged <1 month) and 35 μg/kg in children (aged 1 month to 2 years) should be followed by a maintenance dose of 10 μg/kg once-daily in infants and a maintenance dose of 15 to 25 μg/kg daily in children [47]. Digoxin remains an effective treatment option in infants with supraventricular tachycardia [48]. Digoxin cardioversion may be an effective initial therapy of infants with atrial flutter [49]. In children with dilated cardiomyopathy with ataxia syndrome, digoxin has beneficial properties when combined with angiotensin-converting enzyme inhibitors and with β-receptor antagonist [50]. Flecainide and digoxin combination treatment offers a safe and effective treatment for fetal supraventricular tachycardia with fast restoration of sinus rhythm [51].

Transfer of digoxin across the human placenta

The transfer of digoxin across the human placenta was studied in 20 pregnant women and digoxin reached significant concentration in the newborn infants [52]. The ^{3}H-digoxin activity was demonstrated in the umbilical cord blood five minutes after injection of the drug into the maternal blood and the foetal plasma concentrations of ^{3}H-digoxin approximated to the maternal value 30 minutes after drug administration [53]. Digoxin rapidly crosses the human placenta and reaches similar concentrations in the newborn and maternal sera [54]. The transfer of digoxin was studied using the perfused human placenta. The time to achieve equal concentrations on bottom sites of the placenta is estimated to be 268 min ± 34 min and these data are consistent with *in-vivo* data obtained in humans suggesting that digoxin is rapidly transferred across the human placenta [55]. The transfer of digoxin was investigated in the human placenta perfusion using three concentrations of serum albumin in the maternal and foetal circuits. Maternal and foetal serum albumin concentrations may influence the transplacental digoxin transfer, and this should be considered when treating foetuses with transplacental glycosides [56].

Migration of digoxin into the breast-milk

The concentration of digoxin is 0.41 ng/ml and 0.78 ng/ml in the breast-milk of two lactating women taking digoxin orally at a dose of 0.25 mg daily [57]. The concentration of digoxin in the breast-milk is 1.9 ng/ml in a lactating woman taking 0.75 mg digoxin daily during pregnancy and postpartum [58]. Digoxin concentration of 0.825 ± 0.015 nmol/L is found in milk samples obtained daily between the third and seventh days postpartum [59]. The kinetics of digoxin transfer from the plasma to breast-milk was investigated in 11 lactating women. After intravenous or oral administration of a single digoxin dose of 0.5 mg or 0.75 mg, the maternal and breast-milk were sampled. A rapid equilibrium occurred between the maternal serum and the breast-milk compartments and the breast-milk to serum ratio ranges from 0.6 to 0.7 [60].

Discussion

Digoxin is a ardiac glycoside and exerts positive inotropic effects resulting from increased intracellular Ca^{2+}, increase phase 4 slope especially if $[K^{+}]_{o}$ is low, exerts prominent vagotomic actions resulting in inhibition of Ca^{2+} current in the atrioventricular node, activation of acetylcholine-mediated K^{+} current in the atrium, and increases the atrioventricular nodal refectories. The last action accounts for the utility of digoxin in terminating re-entrant arrhythmias involving the atrioventricular node and in controlling ventricular response in patients with atrial fibrillation. Digoxin may be administered orally or intravenously and the bioavailability of digoxin tablets is 75%. Intestinal microflora may metabolize digoxin reducing its bioavailability, and antibiotics which destroy the intestinal microflora increase the bioavailability of digoxin [1]. Digoxin oral treatment consists in a loading dose followed by a maintenance dose in infants and children and the loading dose and the maintenance dose vary according to the infant and child ageing [2,4]. Digoxin has been found

efficacy and safe in infants and children [4-8]. Digoxin reduces the interstage mortality in infants with single ventricle congenital heart disease [5]. Digoxin is efficacy in treating supraventricular tachycardia recurrence in infants and digoxin has similar efficacy of propranolol [6], digoxin is associated with fewer episodes of supraventricular tachycardia recurrence but more frequent hypotension in infants [7] and digoxin is effective and safe in treating supraventricular tachycardia recurrence in children [8]. The pharmacokinetics of digoxin has been studied in 11 infants and children aged 1 month to 15 years. Following oral administration, digoxin is rapidly absorbed and the median distribution half-life is 0.862 hours and the median elimination half-life is 42 hours. When the subjects are clustered into 2 groups according to the age: 1 month to 3 years (group A) and 8 to 15 years (group B) the elimination half-life is longer in subjects of group A. The digoxin elimination half-life ranges from 8.3 to 77.0 hours in infants and children and decrease with infant maturation and child development as digoxin is mainly eliminated by renal route and the renal function increases with infant and child ageing [10]. The serum digoxin concentration was measured in 291 infants and children, aged from <1 month to >2 years, the mean serum concentration ranges from 1.29 to 0.88 and decreases with the subject ageing [11]. The tissue concentration of digoxin has been determined in different organs and the highest concentration is observed in the myocardium, kidney, and liver [13]. Digoxin accumulates in the right atrial appendage and the mean right atrial appendage to serum ratio of digoxin is 92.5 ng/ml (range, 10.7 to 318) [14]. Digoxin interacts with drugs [15-32]. Clarithromycin prolongs the elimination half-life of digoxin by reducing its clearance [15], and the combination of clarithromycin with digoxin causes renal failure due to inhibition digoxin elimination mediated by P-glycoprotein with consequent enhancement of digoxin blood concentration [16]. Quinidine increases the digoxin serum concentration causing various cardiac diseases including ventricular tachycardia, ventricular fibrillation, extra systole, or sudden death [17-21]. Carvedilol increases the serum concentration of digoxin by decreasing digoxin clearance [22]. Itraconazole leads digoxin toxicity by increasing digoxin serum concentration [23,24]. Amiodarone increases digoxin serum concentration and enhances the mortality-rate [25-27], and propafenone increases digoxin serum concentration by inhibiting the digoxin clearance mediated by P-glycoprotein [28]. Antacids and kaolin-pectin reduce the bioavailability of digoxin [29], cyclosporine decreases the distribution volume and the plasma clearance of digoxin [30], and neomycin depresses the digoxin absorption-rate [31]. Digoxin induces toxicity in infants and children [32-39]. Digoxin induces nausea, vomiting and tachycardia in infants [32]. Digoxin serum concentrations >2 ng/ml induces toxicity in infants and children [33-35,38,39]. Specific Fab fragments should be administered to infants who have high digoxin serum concentrations [36]. Concomitant administration of diuretics with digoxin produces digoxin serum concentrations >2 ng/ml thus inducing toxicity [37]. The effects of P-glycoprotein on the transport of digoxin have been reported in several occasions [40-46]. Verapamil inhibits the digoxin active secretory transport supporting the theory that the inhibition of P-glycoprotein causes reduced elimination of digoxin secretion in the renal tubular cells increasing digoxin serum concentration [40]. Greiner et al. [41] and Fromm et al. [42] observed that the disposition of digoxin is affected by the drugs that inhibit P-glycoprotein. Drugs that inhibit P-glycoprotein impair the renal secretion of digoxin [43]. Verapamil decreases the renal excretion of digoxin mediated by P-glycoprotein [44]. The absorption of digoxin from the human jejunum is increased by drugs which inhibit P-glycoprotein [45], and the serum digoxin concentration is increased when inhibitors of P-glycoprotein are co-administered with digoxin [46]. The treatment with digoxin has been reported in infant and children [47-51]. A digoxin loading oral dose of 25 μg/kg in term infants and 35 μg/kg in young children should be followed by a maintenance dose of 10 μg/kg once-daily in infants and by 15 μg/kg to 25 μg/kg in these children [47]. Digoxin effectively treats supraventricular tachycardia in infants [48] and digoxin is efficacy in the treatment of atrial flutter in infants [49]. Digoxin, combined with angiotensin-converting enzyme inhibitors and β-receptor antagonist, successfully treats children with cardiomyopathy and ataxia [50]. Digoxin and flecainide are an effective and safe treatment of foetal tachycardia with fast restoration of sinus rhythm [51]. The transfer of digoxin across the human placenta has been described *in-vivo* [52-54] and *in-vitro* using the perfused placenta [54-56]. Digoxin freely crosses the human placenta and the equilibration of digoxin concentration between the maternal and foetal compartments occurs in 268 min [55]. Digoxin migrates into the beast-milk in significant amounts [57-59] and the digoxin concentration in the breast-milk ranges from 0.41 ng/ml to 1.9 ng/ml. The ratio of the maternal serum to breast-milk ranges from 0.6 to 0.7 [60].

In conclusion, digoxin is a cardiac glycoside and it has been used to treat supraventricular tachycardia, atrial flutter, and re-entrant supraventricular tachycardia. Digoxin may be administered orally or intravenously and the bioavailability of digoxin tablets is 75%. The oral dosing of digoxin consists in a loading dose followed by a maintenance dose in infants and children and the loading dose and the maintenance dose vary according to the infant and child ageing. Digoxin has been found efficacy and safe in treating congenital heart disease and supraventricular tachycardia in infants and children. The digoxin half-life ranges from 8.3 to 77 hours and it is longer in infants and young children than in older children. The mean serum concentration of digoxin ranges from 1.29 ng/ml and 0.88 ng/ml and decreases with infant maturation and child development, and digoxin diffuses in all body-tissues and the highest concentrations appear in the heart, kidney, and liver. The interaction of digoxin with drugs has been extensively studied and several drugs increase the digoxin serum concentration by inhibiting the clearance of digoxin from the body. Of particular interest is the inhibition of P-glycoprotein by drugs which results in decreased excretion of digoxin from the body followed by an increase of serum digoxin which causes toxicity. Digoxin is freely transferred across the human placenta and migrates into the breast-milk in significant amounts. The aim of this study is to review the clinical pharmacology of digoxin 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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