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Review Article

Clinical Pharmacology of Metronidazole in Infants and Children

Running title: Metronidazole in infants and children

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Abstract

Metronidazole is active against a wide variety of anaerobic protozoal parasites and anaerobic bacteria. Metronidazole is a prodrug requires reductive activation of the nitro group, has anti-oxidant action, and inhibits DNA replication in susceptible organisms. In preterm infants, the metronidazole dosing consists of a loading dose of 15 mg/kg followed by a maintenance dose of 7.5 mg/kg once-daily. In children, the dose varies according the infection to be treated and ranges from 400 mg thrice-daily to 2 grams once-daily. The elimination half-life of metronidazole is about 20 hours in infants and about 6 hours in children. This drug is extensively metabolised in humans and the hydroxy-metronidazole is the major metabolite. Metronidazole has been found efficacy and safe but may cause encephalitis and cerebritis in infants and children. Metronidazole interacts with drugs and the interaction with busulfan has been extensively studied. The treatment and the prophylaxis with metronidazole have been reported. This antibiotic penetrates into the cerebrospinal and cured the meningitis caused by Bacteroides fragilis. Metronidazole is transferred across the human placenta and migrates into the breast-milk in significant amounts. The aim of this study is to review the metronidazole dosing, efficacy, safety, effects, pharmacokinetics, metabolism, toxicity, treatment, prophylaxis, penetration into the cerebrospinal fluid, treatment of meningitis, in infants and children, and metronidazole transfer across the human placenta and migration into the breast-milk.

Key words: metronidazole; dosing; pharmacokinetics; metabolism; treatment; prophylaxis; placental-transfer; breast-milk

Introduction

Metronidazole is active in-vitro against a wide variety of anaerobic protozoal parasites and anaerobic bacteria. Metronidazole is clinically effective in trichomoniasis amebiasis, and giardiasis (see references 8, 11-13, 58). Metronidazole manifests antibacterial activity against all anaerobic cocci; gram-negative bacilli including Bacteroides species (see references 7, 72-77); anaerobic spore-forming, gram-positive bacilli such as Clostridium (see references 7, 8, 55, 57); and microaerophilic bacteria such as Helicobacter (see references 8, 16, 30) and Campylobacter species. Nonsporulating gram-positive bacilli often are resistant, as are aerobic and facultatively anaerobic bacteria [1].

Mechanism of action of metronidazole

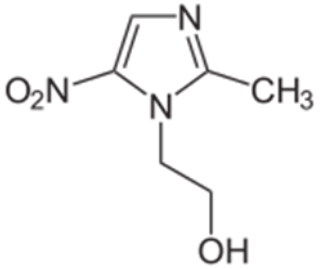
Metronidazole is a prodrug requiring reductive activation of the nitro group by susceptible organisms. Unlike their aerobic counterparts, anaerobic and microaerophilic pathogens [e.g., the amitochondriate protozoa trichomonas vaginalis (see reference 7), Entamoeba histolytica, and G. lamblia and various anaerobic bacteria (see reference 7)] contain electron transport components that have a sufficient negative redox potential to donate electrons to metronidazole. The single-electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by radical-mediated mechanisms that target DNA. Metronidazole is catalytic recycled; loss of the active metabolite's electron regenerates the parent compound. Increasing levels of O_2 inhibit metronidazole-induced cytotoxicity because O_2 competes with metronidazole for electrons. Thus O_2 can both decrease reductive activation of metronidazole and increase recycling of the activated drug. Anaerobic or microaerophilic organisms susceptible to metronidazole derive energy from the oxidative fermentation of ketoacids such as pyruvate. Pyruvate decarboxylation, catalysed by pyruvate-ferredoxin oxidoreductase, produces electrons that reduce ferredoxin, which in turn catalytically donates its electrons to biological electron acceptors or to metronidazole [2]. Metronidazole had anti-oxidant action which was not exerted by the scavenging of reactive oxygen species, but by having an effect on neutrophil cell functions. Beneficial effects of metronidazole in the treatment of Papulopustular rosacea can in part be attributable to this anti-inflammatory effect [3]. The primary action of metronidazole is a rapid inhibition of DNA replication. The DNA remains structurally intact, DNA polymerase activity is not directly affected, and cells retain metabolic activity, synthesizing RNA and protein at unaltered-rates (4). In-vitro data suggest that metronidazole has antioxidant activity; it may help subdue the oxidative tissue damage of intrinsic and extrinsic aging as well as prevent and treat rosacea symptoms [5].

Administration, distribution, metabolism, and excretion of metronidazole

Preparations of metronidazole are available for oral, intravenous, intravaginal, and topical administration (see references 7, 8). The drug usually is absorbed completely and promptly after oral intake and distributed to a volume approximating total body water (see tables 1 to 4, 6 and 7); less than 20% of the drug is bound to plasma proteins. A linear relationship between dose and plasma concentration pertains for doses of 200 to 2,000 mg and repeated doses every 6 to 8 hours result in some drug accumulation. The elimination half-life of metronidazole in plasma is about 8 hours in adults. With the exception of the placenta, metronidazole penetrates well into body tissues and fluids, including vaginal secretions (see reference 8), seminal fluid, saliva, breast-milk (see references 81-83), and cerebrospinal fluid (see references 69-72). After an oral dose, more than 75% of labelled metronidazole is eliminated in the urine (see references 22, 23), largely as metabolites formed by the liver from oxidation of the drug's side chain, a hydroxyl derivative and an acid (see references 22-26); about 10% is recovered as unchanged drug. There are two principal metabolites: the hydroxyl metabolite has a longer elimination half-life (about 12 hours) and has about 50% of the antitrichomonal activity of metronidazole and the formation of glucuronides also is observed. Small quantities of reduced metabolites are formed by the drug flora. The urine of some patients may be reddish brown owing to the presence of unidentified pigments derived from the drug; oxidative metabolism of metronidazole is induced by phenobarbital, prednisone, rifampin, and possibly ethanol and is inhibited by cimetidine [1, 2].

Therapeutic uses of metronidazole

Metronidazole cures genital infections with Trichomonas vaginalis in more than 90% of cases. The preferred treatment is 2 grams of metronidazole as a single oral dose for both males and females (see reference 8). When repeated courses or higher doses of metronidazole are required, it is recommended that intervals of 4 to 6 weeks elapse between courses. Leukocyte counts occur before, during, and after each course. Treatment failures owing to the presence of metronidazole-resistant strains of Trichomonas vaginalis are becoming increasingly common. Most of these cases can be treated successfully by giving a second 2 grams dose to both patient and sexual partner. In addition to oral therapy, the use of a 500 to 1,000 mg vaginal suppository may be beneficial in refractory cases (see reference 8). Metronidazole is the agent of choice for the treatment of all symptomatic forms of amebiasis (see reference 8), including amoebic colitis and anaerobic liver abscesses. The recommended dose is 500 to 700 mg of metronidazole taken orally thrice-daily for 7 to 10 days in adults and in children the dose is 35 to 50 mg/kg daily given in three divided doses for 7 to 10 days (see reference 8). Amoebic liver abscesses have been treated successfully by short courses of metronidazole. Entamoeba histolytica persists in most patients who recover from acute amebiasis after metronidazole therapy, so it is recommended that all individuals also be treated with a luminal amoebicide [1].



Metronidazole molecular structure (molecular weight = 171.15)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "metronidazole dosing infants, children", metronidazole efficacy, safety infants, children", "metronidazole effects infants, children", "metronidazole pharmacokinetics infants, children", "metronidazole metabolism", "metronidazole drug interactions", "metronidazole toxicity infants, children", "metronidazole treatment infants, children", "metronidazole prophylaxis infants, children", "metronidazole penetration into the cerebrospinal fluid", "metronidazole treatment of meningitis infants, children", "metronidazole placental transfer", and "metronidazole migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [6], NEOFAX® by Young and Mangum [7], and The British National Formulary for Children [8] were consulted.

Results

Administration schedules to infants and children

Administration to infants [6]

Preterm and term infants. Give: a 15 mg/kg intravenous loading dose. Then 7.5 mg/kg, orally or intravenously once-daily in infants with a postmenstrual age of 26 to 34 weeks, thrice-daily in infants with a postmenstrual age greater than 34 weeks. Higher doses have been used in meningitis.

Metronidazole is reserved for treatment of meningitis, ventriculitis, and endocarditis caused by Bacteroides fragilis and other anaerobes resistant to penicillin; treatment of serious intra-abdominal infections; treatment of infections caused by Trichomonas vaginalis, and treatment of clostridium difficile colitis. Metronidazole is incompatible with aztreonam and meropenem [7].

Administration schedules to children [8].

Oral treatment of anaerobic infections

Children aged 2 months to 11 years. Give: 7.5 mg/kg twice-daily usually treated for 7 days (for 10 to 14 days in clostridium difficile infection).

Children aged 12 to 17 years. Give: 400 mg thrice-daily usually treated for 7 days (for 10 to 14 days in clostridium difficile infection).

Administration by rectum

Children aged 1 to 11 months. Give: 125 mg thrice-daily for 3 days, then 125 mg twice-daily, for usual total treatment of 7 days.

Children aged 1 to 4 years. Give: 250 mg thrice-daily for 3 days, then 250 mg twice-daily for usual total treatment of 7 days.

Children aged 5 to 9 years. Give: 500 mg thrice-daily for 3 days, then 500 mg twice-daily for usual total treatment of 7 days.

Children aged 10 to 17 years. Give: 1 gram thrice-daily, then 1 gram twice-daily for usual total treatment of 7 days.

Intravenous treatment of anaerobic infections

Children aged 2 months to 17 years. Give: 7.5 mg/kg thrice-daily (maximum per dose = 500 mg) usually treated for 7 days (for 14 days in Clostridium difficile infection).

Oral treatment of Helicobacter pylori in combination with clarithromycin and omeprazole

Children aged 1 to 5 years. Give: 100 mg twice-daily.

Children aged 6 to 11 years. Give: 200 mg twice-daily.

Children aged 12 to 17 years. Give: 400 mg twice-daily.

Oral treatment of Helicobacter pylori in combination with amoxicillin and omeprazole

Children aged 1 to 5 years. Give: 100 mg thrice-daily.

Children aged 6 to 11 years. Give: 200 mg thrice-daily.

Children aged 12 to 17 years. Give: 400 mg thrice-daily.

Oral treatment of Fistulating Crohn's disease

Children. Give: 7.5 mg/kg thrice-daily usually given for 1 month but should not be used longer than 3 months because of concerns about peripheral neuropathy.

Vaginal treatment of Fistulating Crohn's disease using vaginal gel

Children. Give: 1 application daily for 5 days, the dose should be administered at night.

Vaginal treatment of bacterial vaginosis

Children. Give: 1 application daily for 5 days, the dose should be administered at night.

Oral treatment of acute ulcerative gingivitis

Children aged 1 to 2 years. Give: 50 mg thrice-daily for 3 days.

Children aged 3 to 6 years. Give: 100 mg twice-daily for 3 days.

Children aged 7 to 9 years. Give: 100 mg thrice-daily for 3 days.

Children aged 10 to 17 years. Give: 200 to 250 mg thrice-daily for 3 days.

Oral treatment of acute oral infections

Children aged 1 to 2 years. Give: 50 mg thrice-daily for 3 to 7 days.

Children aged 3 to 6 years. Give: 100 mg twice-daily for 3 to 7 days.

Children aged 7 to 9 years. Give: 100 mg thrice-daily for 3 to 7 days.

Children aged 10 to 17 years. Give: 200 to 250 mg thrice-daily for 3 to 7 days.

Oral prophylaxis of surgery

Children aged 1 month to 11 years. Give: 30 mg/kg (maximum per dose = 500 mg) to be administered 2 hours before surgery.

Children aged 12 to 17 years. Give: 400 to 500 mg, to be administered 2 hours before surgery, then 400 to 500 mg thrice-daily for up to 3 doses (in high-risk procedures).

Surgical prophylaxis by rectum

Children aged 5 to 9 years. Give: 500 mg, to be administered 2 hours before surgery, then 500 mg thrice-daily if required for up to 3 days (in high risk procedures).

Children aged 10 to 17 years. Give: 1 gram to be administered 2 hours before surgery, then 1 gram thrice-daily if required for up to 3 days (in high risk procedures).

Intravenous prophylaxis of surgery

Children aged 1 month to 11 years. Give: 30 mg/kg (maximum per dose = 500 mg) to be administered up to 30 min before the procedure, then 500 mg thrice-daily is required for up to 3 further doses (in high risk procedures).

Children aged 12 to 17 years. Give: 500 mg to be administered up to 30 min before the procedure, then 500 mg thrice-daily is required for up to 3 further doses (in high risk procedures).

Oral treatment of invasive intestinal amebiasis and extra-intestinal amebiasis (including liver abscesses)

Children aged 1 to 2 years. Give: 200 mg thrice-daily for 5 days in intestinal infection (for 5 to 10 days in extra-intestinal infection).

Children aged 3 to 6 years. Give: 200 mg 4 times-daily for 5 days in intestinal infection (for 5 to 10 days in extra-intestinal infection).

Children aged 7 to 9 years. Give: 400 mg thrice-daily for 5 days in intestinal infection (for 5 to 10 days in extra-intestinal infection).

Children aged 10 to 17 years. Give: 800 mg thrice-daily for 5 days in intestinal infection (for 5 to 10 days in extra-intestinal infection).

Oral treatment of urogenital trichomoniasis

Children aged 1 to 2 years. Give: 50 mg thrice-daily for 7.

Children aged 3 to 6 years. Give: 100 mg twice-daily for 7.

Children aged 7 to 9 years. Give: 100 mg thrice-daily for 7 days.

Children aged 10 to 17 years. Give: 200 mg thrice-daily for 7 days, alternatively 400 to 500 mg twice-daily for 5 to 7 days, alternatively 2 grams for 1 dose.

Oral treatment of giardiasis

Children aged 1 to 2 years. Give: 500 mg once-daily for 3 days.

Children aged 3 to 6 years. Give: 600 to 800 mg once-daily for 3.

Children aged 7 to 9 years. Give: 1 gram once-daily for 3 days.

Children aged 10 to 17 years. Give: 2 grams once-daily for 3 days, alternatively 500 mg twice-daily for 5 to 7 days.

Efficacy and safety of metronidazole in children

Ceftazidime-avibactam plus metronidazole is well tolerated, with a safety profile similar to ceftazidime alone, and appeared effective in paediatric patients with complicated intraabdominal infection due to gram-negative pathogens, including ceftazidime-non-susceptible strains [9]. Compared to clindamycin and tobramycin, meropenem is associated with a reduced length of hospital stay and a shorter duration of therapy among paediatric patients with complicated intraabdominal infections. Meropenem is well tolerated by children and has a safety profile [10]. A 3-day course of nitazoxanide suspension is as efficacious as a standard 5-day course of metronidazole suspension in treating giardiasis in children [11]. One hundred and fifty children of either sex, aged 2 to 10 years, were randomised to receive either a single dose of 400 mg of albendazole suspension or 22.5 mg/kg daily metronidazole in 3 divided doses for 5 consecutive days. At the end of therapy, majority of children in both treatment groups were giardia symptom free. Adverse-effects were noted in 3 children in the albendazole group, and in 20 children in the metronidazole group thus albendazole suspension is as effective as metronidazole in the treatment of giardia infection in children [12] of 82 children, 37 children (45.1%) received furazolidone and 45 children (54.9%) received metronidazole for treating giardia infections. No statistically significant differences in efficacy between treatments were found. With the exception of one case of urticaria, which occurred in a child who received metronidazole, both drugs were well tolerated. Furazolidone and metronidazole are equally safe and effective in treating children with giardiasis [13].

Effects of metronidazole in infants and children

Infants receiving total parenteral nutrition for more than 2 weeks were divided into three groups. In infants of group A the total parenteral nutrition was given alone, infants of group B received metronidazole at a dose 25 mg/kg daily for the first 2 weeks of total parenteral nutrition, and

infants of group C received metronidazole at a dose of 50 mg/kg daily for the first 3 weeks of total parenteral nutrition. Several parameters of liver function tests during the first 4 weeks were compared among these three groups of infants. There was no significant difference of these parameters between group A and group B. Although there was no significant difference of alkaline phosphatase, gamma-glutamyl transpeptidase, direct bilirubin, and total bile acid between infants of groups A and C, glutamic oxaloacetic and glutamic pyruvic transaminases of infants of group C remained significantly lower than those of group A. The administration of metronidazole at a dose of 50 mg/kg daily for 3 weeks prevented the elevation of transaminases during total parenteral nutrition in infants suggesting the possible involvement of intestinal anaerobic flora in the pathogenesis of total parenteral nutrition-associated liver dysfunction [14]. Of 96 children, 48 children (50.0%) were treated with metronidazole and 48 children (50.0%) received placebo. Eradication of Dientamoeba fragilis was significantly greater in the metronidazole group [15]. Sixty-two children, aged <18 years, were infected with Helicobacter pylori and were treated with amoxicillin at a dose of 75 mg/kg daily, metronidazole at a dose of 25 mg/kg daily and esomeprazole at a dose of 1.5 mg/kg daily for 2 weeks. The treatment with amoxicillin, metronidazole, and esomeprazole for 2 weeks is a good option in children infected with a double resistant Helicobacter pylori strain [16].

Radioisotope experiments with [^{14}C] metronidazole revealed that the compound was taken up by both resistant and susceptible bacteria although there was a difference in the rate and extent of accumulation. Metronidazole's antimicrobial activity against anaerobic bacteria is bactericidal and independent of growth-rate [17]. The antimicrobial activity of metronidazole was investigated in anaerobic bacteria by use of time-viability studies. This antimicrobial agent has a rapid onset of bactericidal activity under proper reducing conditions [18].

Pharmacokinetics of metronidazole in infants

Cohen-Wolkowiez et al. [19] studied the pharmacokinetics of metronidazole in 13 infants with gestational, postnatal ages and body-weight of 24 weeks (range, 22 to 25), 53 days (range, 7 to 97), and 1,410 grams (range, 678 to 2,537) respectively (group A), in 14 infants with gestational, postnatal ages and body-weight of 28 weeks (range, 26 to 29), 32 days (range, 0 to 97), and 1,510 grams (range, 850 to 3,611), respectively, (group B) and in 5 infants with gestational, postnatal ages and body-weight of 31 weeks (range, 30 to 32), 33 days (range, 8 to 71), and 1,658 grams (range, 1,230 to 3,850), respectively (group C). Metronidazole dose was 7.6 mg/kg (range 4.2 to 14.2) infants of group A, 7.8 mg/kg (range, 6.2 to 15.1) infants of group B, and 9.0 mg/kg (range, 6.5 to 15.4) infants of group C.

			Bootstrap confidence interval		
Parameter	Point estimate	%RSE	25.%	Median	97.5%
TBC (L/h)	0.0397	10.9	0.0307	0.0398	0.0483
DV (L)	1.07	15.0	0.85	1.12	1.37
TBC, PMA	2.49	29.8	1.01	2.57	4.20
Scavenged samples	0.713	12.3	0.581	0.721	0.899
Interindividual variance of total body clearance (%coefficient of variance)					
---	42.5	28.5	24.2	40.4	52.8
Blood draws	13.5	24.5	0.30	13.3	15.7
Scavenged	29.0	17.9	23.7	27.8	34.9

TBC = total body clearance. DV = distribution volume. PMA = postmenstrual age. %RSE = %relative standard error.

Table 1. *Population pharmacokinetics of metronidazole and model estimates in preterm infants, by Cohen-Wolkowiez et al. [19].*

This table shows that the distribution volume of metronidazole is similar to the water volume and there is a limited interindividual variability in the total body clearance and in the distribution volume.

	TBC (L/h)		TBC (L/h/kg)		DV (L)		DV (L/kg)		*Half-life (h)	
GA (wk)	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
< 26	0.033	0.010, 0.187	0.024	0.010, 0.086	1.00	0.48, 1.81	0.71	NA	20.5	5.7, 49.9
26-29	0.040	0.012, 0.274	0.026	0.012, 0.076	1.08	0.60, 2.58	0.71	NA	18.6	6.5, 38.7
30-32	0.071	0.019, 0.285	0.029	0.015, 0.074	1.18	0.88, 2.75	0.71	NA	16.7	6.7, 31.1
Overall	0.041	0.012, 0.274	0.025	0.012, 0.076	1.06	0.54, 2.58	0.71	NA	19.1	6.5, 38.7

GA = gestational age, wk = week. TBC = total body clearance. DV = distribution volume. *Elimination half-life. NA = not applicable.

Table 2. *Individual empirical Bayesian pharmacokinetic parameter estimates by gestational age group, by Cohen-Wolkowiez et al. [19].*

This table shows that the total body clearance, expressed as L/h, increases with the gestational age, the distribution volume is independent by the gestational age, and the elimination half-life increases with the gestational age but this variation is limited.

Suyagh et al. [20] investigated the pharmacokinetics of metronidazole in 32 preterm infants with a median postmenstrual, postnatal ages, and body-weight of 30.0 weeks (range, 25.0 to 37.79) 12 days (range, 1 to 55), and 1,000 grams (range, 510 to 3,710), respectively. Metronidazole was administered intravenously at a loading dose of 15 mg/kg followed by a maintenance dose of 7.5 mg/kg. The maintenance dose was administered thrice-daily to 19 infants or twice-daily to 13 infants.

	Base model		Final model		*Bootstrap		
Parameter	Estimate	%CV	Estimate	%CV	Mean	%CV	-0.53
TBC (L/h)	0.0250	9.16	0.0247	4.53	0.0247	4.77	1.32
DV (L/kg)	0.7130	7.91	0.7260	7.78	0.7356	8.46	1.83
PMA, TBC	---	---	0.107	10.19	0.109	13.11	-3.61
%CV	50.70	23.27	23.37	34.62	22.52	19.60	-3.61
%CV	33.17	42.00	31.94	47.06	31.46	31.01	-1.65
RV (µg/ml)	4.01	17.14	4.00	18.56	3.98	9.19	-0.49

Table 3. *Metronidazole population-parameter estimates from the base and final models developed from the original data set of 32 preterm infants and mean parameter estimates from the final model fitted to the 1,000 bootstrap samples, by Suyagh et al. [20].*

Total body clearance at 30 weeks of postmenstrual age per 1.0 kg of body-weight. DV = distribution volume. PMA = postmenstrual age. %CV = %coefficient of variation. RV = residual variability. *%difference = ([Bootstrap mean estimate – final model estimate]/final model estimate]/final model estimate)*100.

This table shows that the distribution volume is lower than the water volume and there is a remarkable interindividual variability in the total body clearance and in the distribution volume. This variability may be explained by the wide difference in the postmenstrual, postnatal ages and body-weight among these preterm infants.

Parameter	Median	5th Percentage	95th Percentage
Total body clearance (L/h)	0.0244	0.0078	0.0867
Distribution volume (L)	0.702	0.374	1.814
Elimination half-life (h)	19.694	13.038	40.678
Total body clearance (L/h/kg)	0.0237	0.0128	0.0423
Distribution volume (L/kg)	0.756	0.497	0.9901

Table 4. *Individual Bayesian estimates obtained from the final model, by Suyagh et al. [20].*

This table shows that the distribution volume is lower than the water volume and there is a remarkable interindividual variability in the pharmacokinetic parameters.

Dosage regimen	PMA (week)	$BC_{max,ss}$ (µg/ml)[a]	BC_{ss} (µg/ml)[b]	$BC_{min,ss}$ (µg/ml)[c]	BC median (µg/ml)
LD 15 mg/kg	24 to 37	---	---	---	20.6 (10.8 - 38.5)
7.5 mg daily	24	37.0 (21.3 – 58.1)	31.2 (19.5 – 48.0)	26.7 (12.8 – 44.5)	
	25	31.0 (17.2 – 48.8)	25.1 (15.7 – 41.0)	20.5 (9.3 – 35.8)	
10 mg daily	26	35.5 (21.0 – 57.7)	28.0 (17.3 – 43.8)	21.4 (9.0 – 37.1)	
	27	32.1 (17.9 – 51.7)	24.1 (15.2 – 38.3)	18.1 (7.3 – 32.5)	
7.5 mg twice-daily	28	37.3 (22.0 – 57.2)	31.8 (20.9 – 49.9)	27.2 (14.6 – 44.9)	
	33	28.2 (16.0 – 46.5)	22.6 (14.7 – 36.8)	17. 9 (6.6 – 31.4)	
10 mg twice-daily	34	36.0 (21.7 – 56.5)	28.9 (18.2 – 45.9)	22.1 (9.9 – 39.5)	
	37	33.1 (18.3 – 51.0)	25.8 (16.0 – 39.5)	19.8 (7.5 – 34.2)	

Table 5. *Blood concentrations of metronidazole simulated by using the developed pharmacokinetic model with suggested dosing regimens. Figures are the median and (2.5th and 97.5th percentile), by Suyagh et al. [20].*

LD = loading dose. PMA = postmenstrual age. BC = blood concentration of metronidazole. [a]Blood concentration of metronidazole obtained at steady-state immediately after drug administration. [b]Mean blood concentration obtained at steady-state. [c]Blood concentration of metronidazole obtained immediately after administration of the loading-dose.

This table shows that the blood concentration of metronidazole decrease with increasing postmenstrual age and there is a remarkable interindividual variability of metronidazole blood concentration.

Pharmacokinetics of metronidazole in children

Lares-Asseff et al. [21] studied the pharmacokinetics of metronidazole in 10 severely malnourished children, aged 4 to 43 months, and in 10 children, aged 3 to 25 months, who were studied after nutritional rehabilitation. A single oral dose of 30 mg/kg metronidazole was administered to all children.

	Ka (h^{-1})	Absorption half-life (h)	Ke (h^{-1})	Elimination half-life (h)	DV (L/kg)	TBC (L/kg/h)	AUC (µg/ml*h)	Peak (µ/ml)	T_{max} (h)	T_{lag} (h)
Mean	0.9876	1.28	0.0730	11.73	1.500	0.094	191.65	10.48	3.44	0.33
+SD	0.7253	1.35	0.0350	6.10	0.879	0.054	110.70	5.27	1.96	0.30

Ka = Absorption-rate constant. Ke = elimination-rate constant. DV = distribution volume. Peak = peak concentration. T_{max} = time to reach the peak concentration. T_{lag} = time to appear metronidazole in the blood.

Table 6. *Pharmacokinetic parameters of metronidazole which were obtained in 10 severely malnourished children. Figures are the mean+SD, by Lares-Asseff et al. [21].*

	Ka (h^{-1})	Absorption half-life (h)	Ke (h^{-1})	Elimination half-life (h)	DV (L/kg)	TBC (L/kg/h)	AUC (µg/ml*h)	Peak (µg/ml)	T_{max} (h)	T_{lag} (h)
Mean	0.630	1.87	0.1370	5.68	1.598	0.187	140.04	10.49	4.48	0.41
+SD	0.4700	1.34	0.0540	1.97	0.975	0.066	46.95	3.44	1.70	0.29
P-value	0.0939	0.1903	0.0524	0.0039	0.5288	0.0052	0.1655	0.6305	0.1655	0.4616

Ka = Absorption-rate constant. Ke = elimination-rate constant. DV = distribution volume. Peak = peak concentration. T_{max} = time to reach the peak concentration. T_{lag} = time to appear metronidazole in the blood.

Table 7. *Pharmacokinetic parameters of metronidazole which were obtained in 10 nutritionally rehabilitated children. Figures are the mean+SD, by Lares-Asseff et al. [21].*

The P-value was calculated between the values reported in table 6 and those reported in table 7 using the Mann Whitney test. Lares-Asseff et al. [21] showed the data for each of 10 children in both studies and the statistical analysis was computed on the values reported for each child.

The data reported in tables 6 and 7 show that the elimination half-life is longer in malnourished children than in nutritionally rehabilitated children and the total body clearance is smaller in malnourished children. In both groups of children, the elimination half-life is shorter than that in infants, the total body clearance and the distribution volume are greater in children than that of infants. For comparison with infants see the tables the tables 1, 2, 3 and 4. The shorter elimination half-life and the greater total body clearance observed in children may be due to a faster elimination of metronidazole in children. Metronidazole is eliminated by renal rout and by metabolism and both elimination pathways are greater in children. The lower distribution volume of metronidazole observed in infants may be explained by a reduce diffusion of metronidazole in solid tissues.

Metabolism of metronidazole in humans

Following metronidazole administration, the urine contains unchanged metronidazole, the corresponding acid, 2-methyl-5-nitroimidazole-1-ylacetic acid, and a second metabolite which is metronidazole-glucuronide [22]. Metronidazole is extensively metabolised by the liver into 5 metabolites. The hydroxy-metabolite has biological activity of 30 to 65% and a longer elimination half-life than the parent compound. The majority of metronidazole and its metabolites are excreted in urine and faeces and < 12% is excreted as unchanged drug in the urine [23]. The hepatic production of hydroxy-metronidazole [1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole], the major oxidative metabolite of metronidazole, is significantly lowered in patients with liver failure. Peak plasma concentration of this metabolite is lower, the time taken to achieve peak concentration is longer and the AUC is reduced in liver-diseased patients than in healthy subjects (P-value < 0.05 for all these parameters). Similarly, the urinary recovery of hydroxy-metronidazole is lower in patients with liver disease. The excretion of the other major oxy-metabolite, 1-acetic acid-2-methyl-5-nitroimidazole, appears reduced to great extent in patients with liver disease. In a patient with renal function impairment and with cirrhosis had reduced elimination of metronidazole and its metabolites. In this patient, the principal mechanism for delayed elimination of metronidazole metabolites is the impaired hepatic rather than the reduced renal function [24]. Individuals with chronic hepatitis demonstrated a significantly reduced capacity to metabolize metronidazole compared to healthy individuals and the hydroxy-metabolite to metronidazole ratio is 0.0478+0.0044 and 0.0742+0.0232 in diseased patients than in heathy subjects. Patients with moderate to severe liver cirrhosis have a reduced plasma hydroxy-metronidazole to metronidazole ratio (0.0300+0.0032) than healthy subjects (0.0438+0.0027). This ratio is 0.0455+0.0026 in patients with mild chronic hepatitis and 0.0478+0.0044 and in patients with viral hepatitis. These results suggest an impairment of metronidazole metabolism occurs in liver-diseased patients [25]. Metronidazole metabolism is reduced in patients with hepatic disease as illustrated by a lower hydroxy-metronidazole to metronidazole ratio 10 min after the end of metronidazole infusion, thus the metabolism of metronidazole is impaired in patients with liver disease [26].

Interaction of metronidazole with drugs

Metronidazole administered to a dose of 250 mg thrice-daily combined with warfarin given at a dose of 7 mg daily induces intracerebral haemorrhage [27]. Metronidazole increases the risk of warfarin blending at international normalized ratio > 4.5-fold [28]. Metronidazole was administered at a dose of 400 mg thrice-daily and silymarin was co-administered at a dose of 140 mg daily. Co-administration of silymarin increases the total body clearance of metronidazole and hydroxy-metronidazole by 29.5% and 31.9%, respectively and there is a significant decrease in the elimination half-life, peak concentration and AUC of metronidazole and its metabolites (P-value < 0.05 for all parameters). The urinary excretions of the acid-metronidazole metabolite, hydroxy-metronidazole as well as metronidazole are decreased. These results indicate that silymarin may induce both intestinal P-glycoprotein and CYP3A4 [29]. Amoxicillin and metronidazole combination results in 48.0% inhibition of omeprazole metabolism. This drug combination not only increases the antibacterial effects but also enhances the effect of omeprazole by inhibiting its metabolism by CYP2C19. These results indicate that this drug interaction causes complex effects and the dose of omeprazole must be adjusted when is co-administered with amoxicillin and metronidazole for the eradication of Helicobacter pylori [30]. Busulfan is metabolized by hepatic oxidation via the cytochrome CYP3A4 system as well as through conjugation with glutathione and metronidazole inhibits the metabolism of busulfan [31]. The metabolism of busulfan occurs by hepatic conjugation to glutathione catalysed by GSTA1 and also by CYP3A4. Concomitant use of metronidazole results in higher busulfan trough concentrations and higher risk of veno-occlusive disease caused by inhibiting these metabolic pathways [32]. The co-administration of metronidazole with busulfan results in a significant increase (P-value < 0.001) in busulfan levels (807+90 ng/ml) during the last 2 days of combined therapy compared to 452+68 ng/ml during the first 2 days without metronidazole administration [33]. Metronidazole interacts with antiretroviral medications such as zidovudine, nevirapine and ritonavir [34]. Metronidazole co-administered with amiodarone prolongs the QT interval [35].

Metronidazole induces toxicity in infants and children

Metronidazole induces encephalopathy in an infant, aged 5 months, thus encephalopathy is caused by metronidazole [36]. Metronidazole-induced encephalopathy is a rare and often under-recognized iatrogenic condition. Metronidazole causes acute encephalopathy, seizures, and cerebellar signs in children [37]. Brain lesions are typically located at the cerebellar dentate nucleus, midbrain, dorsal pons, medulla, and splenium of the corpus callosum following metronidazole treatment. According to diffusion-weighted imaging, most of the lesions in metronidazole-induced encephalopathy probably correspond to areas of vasogenic oedema, whereas only some of them, located in the corpus callosum, correspond to cytotoxic oedema [38]. A child, aged 12 years, was treated with metronidazole and the treatment induced encephalopathy [39]. Two children had cerebellar dysfunction after metronidazole administration. Signal changes in the dentate and red nucleus are seen by magnetic resonance imaging in these children [40]. Metronidazole-induced encephalopathy is an uncommon adverse-effect caused by treatment with metronidazole. Diagnosis is made by identifying specific radiological findings and toxic affects which occur in the cerebellum and subcortical structures. While the clinical and neuroimaging changes are usually reversible, persistent encephalopathy with poor outcomes may occur [41]. Metronidazole-induced encephalopathy is rare central nervous system toxicity, which may be completely reversible with prompt cessation of metronidazole usage [42]. Metronidazole-induced encephalopathy is a condition which is to a general lack of diagnosis awareness. This condition should be considered in metronidazole-treated patients presenting seizures, myoclonus, cerebellar signs, and encephalopathy [43]. Metronidazole can cause symptoms of central nervous system dysfunction like ataxic gait, dysarthria, seizures, and encephalopathy which may result from both short term and chronic use of metronidazole [44]. Metronidazole-induced encephalopathies is an adverse-effect caused by of metronidazole treatment which affects the dentate nuclei but may also involve the brainstem, corpus callosum, subcortical white matter, and basal ganglia [45]. Magnetic Resonance imaging findings

showed abnormal signal intensity involving dentate nuclei of cerebellum bilaterally symmetrical following metronidazole administration [46]. Metronidazole is associated with an increased risk of adverse peripheral and central nervous system events [47]. Metronidazole-induced neuro-toxicity characterized by spatial distribution of lesions in cerebellar dentate nuclei and dorsal pons [48]. Neurological toxicity caused by metronidazole is fairly common however majority of these are peripheral neuropathy with very few cases of central nervous toxicity [49]. Metronidazole can cause central nervous system toxicity; it does not seem to be a dose- or duration-related dependent. Most patients will have magnetic resonance imaging abnormalities but prognosis is excellent after metronidazole cessation [50]. Metronidazole-induced central nervous system toxicity causes a spectrum of neurological symptoms including ataxia, encephalopathy and peripheral neuropathy [51]. Neurological examination showed cerebellar dysarthria, bilateral dysmetria and an ataxic wide-based gait following metronidazole administration and the patient's symptoms and signs improved over the next 4 days after metronidazole discontinuation [52]. Patients received 400 mg twice-daily of oral metronidazole in a total dose of 16.8 to 39.6 grams for 2 to 4 weeks. It was found that patients usually suffered from the following toxic symptoms: metallic taste, headache, dry mouth and to a lesser extent nausea, glossitis, urticaria, pruritus, urethral burning and dark coloured urine. Symptoms were directly proportional to duration of therapy. Distal latency and velocity of the sural and posterior tibial nerves were distal latency and velocity of the sural and posterior tibial nerves were significantly affected (P-value < 0.01) compared to control values. These results indicate the possible motor-sensory neurotoxicity involving the lower limbs due to long-term metronidazole therapy [53]. A 5-year-old boy with Cockayne syndrome was treated with amoxicillin and metronidazole for a dental infection. He developed jaundice, drowsiness, lethargy, and anorexia after treatment but liver enzyme levels decreased following treatment cessation [54].

Treatment with metronidazole in infants and children

There is no significant correlation between bowel habit change and Clostridium difficile colonization during infancy. However, metronidazole can be used as an optional method to manage functional gastrointestinal disorders [55]. Twenty-four newborn infants, at high risk of anaerobic sepsis, were treated with intravenous metronidazole at a dose of 7.5 mg/kg thrice-daily for a mean period of 5 days and the half-life is 21.6+12.4 hours. The infection is cured and no adverse-effects are noted. The long half-life of metronidazole suggests that less frequent dosage would be appropriate [56]. Empiric metronidazole treatment cures anaerobic bacteraemia caused by Clostridium difficile in children [57]. A 3-day course of nitazoxanide suspension is as efficacious as a standard 5-day course of metronidazole suspension in treating giardiasis in children [58]. Ciprofloxacin in combination with metronidazole is well tolerated and appears to play a beneficial role in achieving clinical remission for children with active Crohn's disease particularly when there is involvement of the colon [58]. A good response to therapy with a complete cure occurs in 14 of the 15 children (93.3%) with anaerobic infection. A fair response is achieved in only one patient (6.7%). Metronidazole appears to be effective and safe in the treatment of serious anaerobic infection in children [59].

Prophylaxis with metronidazole in children

Enteral metronidazole appears effective in the prevention of acute graft versus host disease. A randomized trial is justifiable in children, especially recipients of alternative donor bone marrow transplant [60]. Metronidazole has minimal adverse-effects, is well tolerated, and seems to be a superb drug for prophylaxis in children with phlegmonous appendicitis [61]. In children with an unperforated appendix no infections occurs after single-dose metronidazole prophylaxis as opposed to 8.2% infections in untreated controls (P-value < 0.025) [62]. A single dose of one gram of metronidazole was given intra-rectally one hour before appendectomy. Single dose of metronidazole is adequate for prophylaxis in children undergoing appendectomy [63]. Prospective investigation of consecutive children suffering from non-perforating appendicitis indicates that metronidazole prophylaxis significantly reduces the risk of postoperative wound sepsis regardless the method of surgical closure [64]. The effect of a preoperative single intravenous dose of metronidazole was studied in a prospective trial of 203 children. Seventeen percent children in the control group develop a wound infection compared to 3.4% of those receiving metronidazole (P-value < 0.001). The average length of hospitalization and convalescence is significantly reduced in the metronidazole group and the use of metronidazole in prevention of wound infection is recommended [65]. Single intravenous administration of metronidazole is an effective prophylaxis in children undergoing appendectomy [66]. Prophylaxis with metronidazole is efficacy in preventing infections in children undergoing elective large bowel surgery [67]. Prophylaxis with metronidazole has beneficial effect in children undergoing gastrointestinal and gynaecological surgery [68].

Penetration of metronidazole into the cerebrospinal fluid (CSF)

Metronidazole was intravenously administered at a dose of 500 mg thrice-daily to 4 patients. The unbound brain metronidazole concentration-time curves were delayed compared to unbound plasma concentration-time curves but with a mean metronidazole unbound brain to plasma $AUC_{0-\infty}$ ratio equal to 102%+19% (ranging from 87 to 124%). The unbound plasma concentration-time profiles for hydroxy-metronidazole are flat, with mean average steady-state concentrations equal to 4.0+0.7 μg/ml. This micro-dialysis study confirms the extensive distribution of metronidazole in human brain [69]. Metronidazole reaches a CSF to serum ratio of AUC close to 1.0 thus metronidazole penetrates into the CSF extensively [70]. After 90 min of metronidazole oral administration the average of CSF to serum ratio was 0.43 thus metronidazole may be used in the treatment of bacterial meningitis [71]. Metronidazole was administered to 7 patients with Bacteroides fragilis infections. Serum concentration of metronidazole is several times in excess the MIC for this organism and the CSF metronidazole level is equal to that of the serum. Response to therapy with metronidazole is excellent and metronidazole appears to be effective and safe in the treatment of Bacteroides fragilis infections [72].

Treatment of bacterial meningitis with metronidazole in infants and children

An infant boy, aged 35 days, with meningitis caused by Bacteroides fragilis was treated with metronidazole combined to adjuvant surgical drainage and the infection is cured [73]. Of nine infants with Bacteroides fragilis meningitis, two (22.2%) died, four (44.4%) survived with neurologic sequelae, and three (33.3%) survived without sequelae. Predisposing conditions included abdominal sepsis, chronic otitis media, and ventricular-atrial shunt infection. Metronidazole has been the most effective therapy for Bacteroides fragilis meningitis [74]. Two infants had meningitis caused by Bacteroides fragilis. Metronidazole is the drug of choice for treating Bacteroides fragilis ventriculitis or meningitis in infants when the infective organism does not respond to chloramphenicol [75]. Paediatric focal intracranial suppurative infection has a higher regional incidence that predicted from national estimates and still causes significant mortality and morbidity. A third-generation cephalosporin plus metronidazole is the first-choice empirical treatment for suppurative meningitis in infants [76]. Four children had Bacteroides fragilis bacteraemia, one child had a brain abscess due to Bacteroides species, Fusobacterium naviforme, and Peptostreptococcus species, and one infant had Bacteroides species ventriculitis and meningitis which were treated

with metronidazole. In all cases the anaerobic pathogens are eradicated [77]. The management of multiple-organisms meningitis requires antimicrobials effective against anaerobes that penetrate the blood-brain barrier. These include metronidazole, chloramphenicol, the combination of a penicillin and a beta-lactamase inhibitor, and carbapenems [78].

Transfer of metronidazole across the human placenta

One pregnant woman received 2 grams of metronidazole 9 hours before abortion and the placenta and plasma metronidazole concentrations were 6.6 µg/gram and 13.4 µg/ml, respectively. The corresponding values of the hydroxy-metabolite were 1.8 µg/gram and 5.6 µg/ml, respectively. Nine pregnant women received 400 mg of metronidazole one hour before abortion and the plasma concentration of metronidazole ranged from < 0.1 to 9.4 µg/ml. In the placenta, the metronidazole concentration ranged from < 0.1 to 6.3 µg/gram, and in a fetal tissue the concentration ranged from 1.9 to 3.0 µg/gram. The hydroxy-metabolite concentrations in plasma, placenta, and fetal tissue are below those of metronidazole. These results are consistent with the view that metronidazole crosses the placenta in significant amounts [79]. A single intravenous infusion of 500 mg of metronidazole was given to 21 pregnant women who underwent the abortion during the first trimester of pregnancy. At the time of the evacuation (one hour after the start of the infusion) the concentration of metronidazole in serum was 13.6+0.6 µg/ml and those in the foetal tissue and in the placenta were 66% and 26%, respectively, of that in serum. Thus metronidazole penetrates in foetal tissues in significant amounts [80].

Migration of metronidazole into the human breast-milk

Breast-milk and plasma concentrations of metronidazole and hydroxy-metronidazole were measured in 12 breast-feeding mothers following multiple doses of 400 mg of metronidazole thrice-daily. Plasma concentrations of both metronidazole and its metabolite were measured in seven suckling infants. The mean breast-milk to plasma ratio was 0.9 for metronidazole and 0.76 for hydroxy-metronidazole and the mean breast-milk concentration of metronidazole (around the peak concentration) was 15.5 µg/ml. The mean breast-milk concentration of hydroxy-metronidazole was 5.7 µg/ml. In infant plasma, the metronidazole concentrations ranged from 1.27 to 2.41 µg/ml, and the corresponding concentration of hydroxy-metronidazole ranged from 1.1 to 2.4 µg/ml. Metronidazole migrates in the breast-milk at concentrations which caused no serious reactions in the infants [81]. Breast-milk concentrations of metronidazole were measured in 3 women who received a single dose of 2 grams of metronidazole for treating trichomoniasis. Highest concentrations of the drug in the beast-milk were found 2 and 4 hours after administration and they declined over the next 12 to 24 hours. It appears that if breast-feeding infant is withheld for 12 to 24 hours after the dose, infants will be exposed to a greatly reduced amount of metronidazole [82]. Eleven breast-feeding mothers received 600 mg metronidazole daily and 4 mothers received 1.2 grams daily of metronidazole. Maternal plasma concentrations were 5.0 µg/ml (range, 1.0 to 11.6 following the dose of 600 mg daily) and 12.5 µg/ml (range, 3.7 to 17.9 following the daily dose of 1.2 grams) and the corresponding infant plasma levels were 0.8 µg/ml (range, 0.3 to 1.4) and 2.4 µg/ml (range, 0.6 to 4.9) according to the two dosages. Breast-milk to plasma ratio was one and infant to mother plasma ratio was 0.15 independent of dosages. Plasma and breast-milk concentrations of the hydroxy-metabolite were below those of metronidazole. Breast-milk and maternal plasma sampled simultaneously showed almost identical concentration thus metronidazole migrates into the breast-milk in significant amounts [83].

Discussion

Metronidazole is active in-vitro against a wide variety of anaerobic protozoal parasites and anaerobic bacteria; it is clinically effective in the treatment of trichomoniasis amebiasis and giardiasis. Metronidazole is efficacy against all anaerobic cocci, gram-negative bacilli including Bacteroides species, anaerobic spore-forming, gram-positive bacilli such as Clostridium and microaerophilic bacteria such as Helicobacter, and Campylobacter species. Metronidazole is a prodrug requiring reductive activation of the nitro group by susceptible organisms [1]. The single-electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by radical-mediated mechanism that targets DNA [2]. Metronidazole has anti-inflammatory effect [3], inhibits DNA replication [4], and has antioxidant activity [5]. This antibiotic may be administered intravenously, orally, vaginally and by rectum [7, 8]. In preterm infants, the intravenous treatment consists in a loading dose of 15 mg/kg followed by a maintenance dose of 7.5 mg/kg once-daily and in term infants the maintenance dose is 7.5 mg/kg thrice-daily [7]. In children, the oral dose varies according to the infection to be treated and ranges from 400 mg thrice-daily to 2 grams once-daily [8]. Metronidazole is efficacy and safe in children [9-13]. Ceftazidime-avibactam combined with metronidazole is effective in paediatric patients with complicated intraabdominal infection due to gram-negative pathogens [9], meropenem shortens the duration of therapy in paediatric patients with intraabdominal infections [10] is efficacy in the treatment of giardiasis in children [11-13]. Metronidazole produces effects in infants and children [14-18]. Metronidazole administered at a dose of 50 mg/kg daily for 3 weeks prevents the elevation of transaminases during total parenteral nutrition in infants [14]. Metronidazole eradicates Dientamoeba fragilis [15], Helicobacter pylori [16], and anaerobic bacteria in children [17, 18]. The pharmacokinetics of metronidazole has been studied in infants and children [19-21]. In preterm infants, the elimination half-life of metronidazole ranges from 16.7 to 20.5 hours and decreases with infant maturation [19] and it is about 6 hours in children who underwent nutritional rehabilitation. In severely malnourished children, the half-life of metronidazole is significantly longer and it is about 12 hours [21]. Metronidazole total body clearance is greater in children than in infants. The longer elimination half-life and the smaller total body clearance of metronidazole observed in infants may be explained by reduced drug elimination in infants as metronidazole is cleared by both metabolism and the renal route and the metabolic-rate and the renal function increase with infant maturation and child development. The distribution volume of metronidazole approaches the water volume in children and a lower distribution volume has been observed in infants. Likely, the diffusion of metronidazole into the solid tissues is reduced in infants. Metronidazole is metabolized into 5 metabolites by cytochromes P-450 and by conjugation with glucuronic acid. The major metabolite of metronidazole is the hydroxy-metronidazole which has about half antibacterial activity of the parent compound and has a longer elimination half-life and the liver disease significantly reduces the formation of metronidazole metabolites [22-26]. Metronidazole and its metabolites are mainly eliminated with the faeces and a little percentage of metronidazole appears in the urine. Metronidazole interacts with drugs [27-35], when it is combined with warfarin increases the risk of blending [27, 28], silymarin hinders the pharmacokinetics and metabolism of metronidazole [29], amoxicillin and metronidazole inhibits the metabolism of omeprazole [30], and metronidazole inhibits the metabolism of busulfan [31-33]. Metronidazole interacts with zidovudine, nevirapine and ritonavir [34] and the co-administration of metronidazole with amiodarone prolongs the QT interval [35]. Metronidazole induces toxicity in infants and children [36-54]. In particular, metronidazole causes encephalopathy [36-45], alteration of the central nervous system functions [46-53], and develops jaundice, drowsiness, lethargy and anorexia in a child [54]. The treatment with metronidazole has been assessed in infants and children [55-59]. This drug cures gastrointestinal disorders caused by Clostridium difficile in infants [55], the anaerobic sepsis in infants [56] and bacteraemia cause

by Clostridium difficile in children [57]. Ciprofloxacin combined with metronidazole cures the Crohn's disease in children [58] and metronidazole cures serious anaerobic infections in children [59]. Metronidazole prevents the infections in children [60-67]. Prophylaxis with metronidazole has been found efficacy in preventing infections in children undergoing appendectomy [60-64], wound infection in children undergoing surgery [65] and infections in children admitted to bowel surgery [67], gastrointestinal and gynaecological surgery [68]. Metronidazole penetrates into the cerebrospinal fluid in significant amounts [69-72] and cured meningitis caused by Bacteroides fragilis in infants and children [73-77]. Metronidazole is transferred across the human placenta and achieves significant concentrations into the body tissues of foetuses aborted on the first trimester of pregnancy [79, 80]. Metronidazole migrates into the breast-milk where reaches concentrations similar to the maternal blood [81-83].

In conclusion, metronidazole is active in-vitro against a wide variety of anaerobic protozoal parasites and anaerobic bacteria. Metronidazole has anti-inflammatory effect, inhibits DNA replication, and has antioxidant activity. This antibiotic may be administered intravenously, orally, vaginally and by rectum. In preterm infants, the metronidazole intravenous dose consists in a loading of 15 mg/kg followed by a maintenance dose of 7.5 mg/kg once-daily and the maintenance dose is 7.5 mg/kg thrice-daily in term infants. In children the dose varies according to the infection to be treated and the oral dose ranges from 400 mg thrice-daily to 2 grams once-daily. Metronidazole elimination half-life is longer in infants than in children and the total body clearance is smaller in infants than in children. Metronidazole is cleared by both metabolism and by renal route and the metronidazole metabolic-rate and the renal function increase with infant maturation and child development. Metronidazole is metabolized into 5 metabolites, the main metabolite is the hydroxy metronidazole, and the overall metabolic-rate of metronidazole is reduced in patients with liver disease. Metronidazole induces encephalopathy and alteration of the central nervous system functions in infants and children, penetrates in significant extent into the cerebrospinal fluid and cured the meningitis caused by Bacteroides fragilis in infants and children. Metronidazole is transferred across the human placenta and migrates into the breast-milk where reaches concentrations similar to the maternal blood. The aim of this study is to review the clinical pharmacology of metronidazole 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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