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Review Article

Clinical Pharmacology of Anti-Helminthic Agents in Paediatric Patients

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Abstract

The anti-helminth agents used in paediatric patients are: albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel. Albendazole, ivermectin, mebendazole, and praziquantel have been extensively studied whereas little information is available for diethylcarbamazine and levamisole. The dosing of albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel has been reviewed. The efficacy and safety, and the treatment of children with albendazole have been reviewed and albendazole poorly migrates into the breast-milk. The treatment of children with diethylcarbamazine, administered alone or combined with other drugs, has been reviewed. The efficacy and safety and the treatment of infants and children with ivermectin have been reviewed and ivermectin migrates into the breast-milk in significant amounts. Levamisole treats nephrotic syndrome in children. The efficacy and safety and the treatment of infants and children with mebendazole have been reviewed and mebendazole is undetectable in the breast-milk. The efficacy and safety and the treatment of children with praziquantel have been reviewed and praziquantel poorly migrates into the breast-milk. The aim of this study is to review the dosing of albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel, the efficacy and safety of albendazole, ivermectin, mebendazole, and praziquantel, the treatment of infants and children with ivermectin and whit mebendazole, the treatment of children with albendazole, diethylcarbamazine, levamisole, and praziquantel, and the migration into the breast-milk of albendazole, ivermectin, mebendazole, and praziquantel.

Keywords: Albendazole; Breast-milk; Diethylcarbamazine; Efficacy-safety; Ivermectin; Levamisole; Mebendazole; Praziquantel; Treatment

Introduction

The anti-helminth agents used in paediatric patients are: albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole and praziquantel.

Mechanisms of action of the anti-helminth agents

Albendazole is variable and erratically absorbed after oral administration; absorption is enhanced by the presence of fatty foods and possibly by bile salts. Administration following food, especially a fatty meal, enhances absorption by up to 5-fold in humans. The activity of albendazole against tissue-dwelling helminths is attributable to its active metabolite albendazole sulfoxide. The better bioavailability of the parent compound and the activity of albendazole sulfoxide explain why albendazole is more active than mebendazole sulfoxide explain why albendazole is more active than mebendazole against tissue-dwelling helminths. The level of albendazole sulfoxide is enhanced 3.2-fold by grapefruit juice. However, grapefruit juice shortens its elimination half-life by 46%. It has been suggested that albendazole is metabolized by CYP3A4 enzymes in the intestinal mucosa, a process that can be inhibited by grapefruit juice. After a 400 mg oral dose, albendazole cannot be detected in plasma because the drug is rapidly metabolized in the liver and possibly in the intestine, to albendazole sulfoxide, which has potent anthelmintic activity. Both (+) and (-) enantiomers of albendazole sulfoxide are formed; the (+) enantiomer reaches much higher peak plasma concentrations in humans and is cleared much more slowly than the (-) form. Albendazole sulfoxide is about 70% bound to plasma proteins and has a highly variable plasma elimination half-life of 4 hours to 15 hours. It is well distributed into various tissues, including hydatid cyst, where it reaches a concentration of about 20% that in plasma. Oxidation of the sulfoxide derivatives to the nonchiral sulfone metabolite of albendazole, which is pharmacologically inactive, is probably rate limiting in determining the clearance and therefore the plasma elimination half-life of the bioactive (+) sulfoxide metabolite. The mechanisms of action of diethylcarbamazine against filarial species are unknown. Microfilarial forms of susceptible filarial species are most affected by diethylcarbamazine. These developmental forms of *Wuchereria bancrofti, Brugia malayi*, and *Loa loa* rapidly disappear from human blood after consumption of the drug. Microfilaria of *Onchocerca volvulus* rapidly disappears from the skin after diethylcarbamazine administration, but the drug does not kill microfilariae in nodules that contain the adult (female) worms. The drug has some activity against the adult life-cycle stages of *Wuchereria bancrofti*, *Brugia malayi*, and *Loa loa* but negligible activity against the adult *Onchocerca volvulus.* Ivermectin immobilizes the organisms by inducing tonic paralysis of the musculature. Avermectins induce paralysis by activating a family of ligand-gated Cl^- channels, particularly glutamate-gated Cl^- channels found only in invertebrates. Ivermectin probably binds to glutamate-activated Cl^- channels found in nematode nerve or muscle cells and causes hyper-polarization by increasing intracellular chloride concentration, resulting in paralysis. Glutamate-gated

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Cl^- channels probably are one of several sites of ivermectin action amongst invertebrates. Avermectins also bind with high affinity to GABA-gated and other ligand-gated Cl^- channels in nematodes such as Ascaris and in insect, but the physiological consequences are less defined. Lack of high-affinity avermectin receptors in cestodes and trematodes may explain why these helminths are not sensitive to ivermectin. Avermectins also interact with GABA receptors in mammalian brain, but their affinity for invertebrate's receptors in about 100-fold higher. Levamisole is a cholinergic anthelminthic. The drug is a potent muscle and nerve L-subtype selective nicotinic acetylcholine receptor channel agonist. Opening of these channels produces depolarization, calcium entry, and increase in sarcoplasmic calcium, producing spastic muscle contraction, resulting in passive elimination of the worms. Levamisole was also shown to inhibit fumarate reductase and hence succinate production, the main source of ATP, which is key for the survival of worms. With regard to mammalian cells, levamisole inhibits alkaline phosphatases in most tissues. The immunomodulatory activity of levamisole has been explained as a stimulation of antibody formation and enhancement of T cell activation and proliferation. Mebendazole is an effective drug for treatment of some gastrointestinal nematode infections. It is only administered orally, with the same dose schedule applying to adults and two children aged more than 2 years old. For treatment of enterobiasis, a single 100 mg tablet is taken and if the patient is not cured, a second dose should be given after 3 weeks. For control of ascariasis, trichuriasis, or hookworm infections, the recommended regimen is 100 mg of mebendazole taken in the morning and evening for 3 consecutive days (or a single 500 mg tablet administered once). If the patient is not cured 3 weeks after treatment a second course should be given. A 3-day mebendazole regimen is more effective than single doses of either mebendazole (500 mg) or albendazole (100 mg). Praziquantel has two major effects on adult schistosomes. At the lowest effective concentrations, it causes increased muscular activity, followed by contraction and spastic paralysis. Affected worms detach from blood vessel walls migrate from the mesenteric veins to the liver. At slightly higher concentrations, praziquantel causes tegumental damage and exposes a number of tegumental antigens. The clinical efficacy of this drug correlates better with tegumental action. The drug is ineffective against juvenile schistosomes and therefore is relatively ineffective in early infection. An intact immune response is believed to be required for the clinical efficacy of the drug. The primary site of action of praziquantel is uncertain. The drug may act through generation of reactive oxygen species. It also promotes an influx of Ca^{2+} and possibly interacts with the variant Ca^{2+} channel Ca-varβ, which is found in schistosomes and other praziquantel-sensitive parasites. However, Ca^{2+}

Influx does not correlate with sensitivity to the drug. Praziquantel inhibits adenosine flux, but definitive evidence that this action contributes to the anthelmintic effect is lacking [1].

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "albendazole children", "diethylcarbamazine children", ivermectin children", "levamisole children", "mebendazole children" and "praziquantel children". In addition, the book "The Pharmacological Basis of the Therapeutics" has been consulted [1].

Results

Albendazole

Chemical structure of albendazole (molecular weight=265.33 g/mol) (Figure 1).

Administration of albendazole to children [2]: Oral administration of albendazole to treat chronic strongyloides infection.

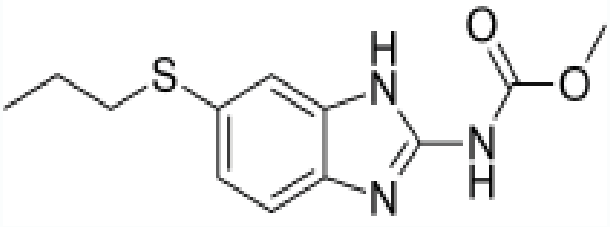

Figure 1: Chemical structure of albendazole (molecular weight=265.33 g/mol).

Administration to children

Children aged 2 to 17 years: Give: 400 mg twice-daily for 3 days, the dose may be repeated after 3 weeks if necessary.

Oral administration of albendazole to treat hydatid disease, in conjunction with surgery, to reduce the risk of recurrence or as primary treatment in inoperable cases

Children aged 2 to 17 years: Give: 7.5 mg/kg twice-daily (maximum per dose=400 mg twice-daily) for 28 days followed by 14 days break and repeat the treatment for up 2 to 3 cycles. Oral administration of albendazole to treat hookworm infection

Children aged 2 to 17 years: Give: 400 mg for 1 dose.

Efficacy and safety of albendazole in children

Albendazole, co-administered with praziquantel, is efficacy and well-tolerated in children [3]. A single oral dose of 800 mg of albendazole provides high efficacy against hookworm, is well-tolerated, and should be considered for community-based strategies targeting in children [4]. Albendazole is found efficacy and safe in children with helminth infection [5]. Albendazole suspension is effective as metronidazole in the treatment of giardia infection in children and albendazole is safe and has fewer side-effects compared to metronidazole [6].

Treatment of children with albendazole

Albendazole, administered orally at a dose of 400 mg daily for 7 consecutive days, effectively treats *Trichuris trichiura* infection in the 1st and 2nd weeks of treatment [7]. A single oral dose of 400 mg of albendazole is effective for the treatment of mild, moderate, and severe ascariasis in children [8]. Albendazole, administered orally at a daily dose of 400 mg effectively treats children infected by ascariasis and trichuriasis [9]. Two consecutive oral doses of 400 mg of albendazole effectively treat children infected by *Ascaris lumbricoides* [10].

Migration of albendazole into the breast-milk

After a single oral dose of 400 mg of albendazole, albendazole and albendazole sulfoxide poorly migrate into the breast-milk [11].

Diethylcarbamazine

Diethylcarbamazine chemical structure (molecular weight=199.298 g/mol) (Figure 2).

Administration of diethylcarbamazine to children [12]: Oral administration of diethylcarbamazine to treat *Wuchereria bancrofti*

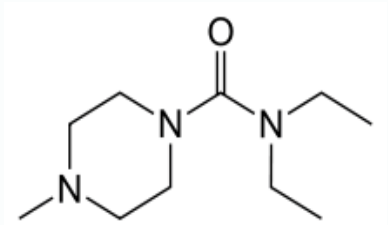

Figure 2: Diethylcarbamazine chemical structure (molecular weight=199.298 g/mol).

and *Brugia malayl* infections.

Administration to children

Children aged 1 month to 9 years: Give: 1 mg/kg daily in divided doses on the first day, and then increase the dose to 3 mg/kg daily in divided doses, the dose should be increased gradually over 3 days.

Children aged 10 to 17 years: Give: 1 mg/kg daily in divided doses on the first day, and then increase the dose to 6 mg/kg daily in divided doses, the dose should be increased gradually over 3 days.

Oral administration of diethylcarbamazine to treat *Loa loa* infection

Children aged 1 month to 9 years: Give: 1 mg/kg daily in divided doses on the first day, and then increase the dose to 3 mg/kg daily in divided doses, the dose should be increased gradually over 3 days.

Children aged 10 to 17 years: Give: 1 mg/kg daily in divided doses on the first day, and then increase the dose to 6 mg/kg daily in divided doses, the dose should be increased gradually over 3 days.

Treatment of children with diethylcarbamazine administered alone or combined with other drugs

A single oral dose of diethylcarbamazine controls the infection caused by *Wuchereria bancrofti* in children [13]. The administration of diethylcarbamazine produces a great diminution of worm in children [14]. Albendazole, administered alone and albendazole combined with diethylcarbamazine, has similar efficacies in the treatment of trichuriasis in terms of cure rate and egg reduction rate in children [15]. In children, the triple-drug regimen (ivermectin, diethylcarbamazine, and albendazole) has been shown to be safe and more efficacious for clearing *Wuchereria bancrofti* microfilariae than the standard two-drug regimen of diethylcarbamazine plus albendazole [16]. Diethylcarbamazine, co-administered with iodine, is a concurrent intervention for lymphatic filariasis in children [17].

Ivermectin

Ivermectin molecular structure (molecular weight=875.106 g/mol) (Figure 3).

Administration of ivermectin to children [18]: Oral administration of ivermectin to treat Strongyioides infection.

Administered to children

Children aged 5 to 17 years: Give: 200 µg/kg for 2 days. Oral administration of ivermectin to treat onchocerciasis

Children aged 5 to 17 years: Give: 150 µg/kg for 1 dose, retreatment at intervals of 6 to 12 months, depending on symptoms, must be given until adult worms die out.

Efficacy and safety of ivermectin in infants and children

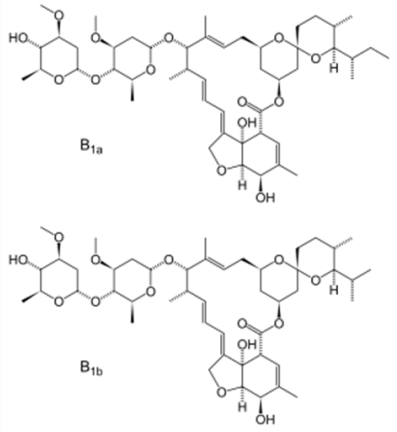

Figure 3: Ivermectin molecular structure (molecular weight=875.106 g/mol).

Ivermectin has been found efficacy and safe for the treatment of scabies in infants and young children [19]. Ivermectin has been found efficacy and safe and reduces helminth rate in infants and children [20]. Ivermectin has been found efficacy and safe and reduces helminth rate in children [21]. Ivermectin is safe, well-accepted, and effectively reduces the microfilarial loads and ivermectin is the first drug to control human onchocerciasis in children [22]. Administration of ivermectin during the malaria transmission season reduces malaria episodes among children without significantly increasing harms [23].

Treatment of infants and children with ivermectin

Ivermectin is generally well-tolerated in infants and topical treatment with ivermectin effectively treats scabies in infants [24]. Ivermectin is a promising effective and safe chemoprophylactic drug in management of COVID-19 in children [25]. Annual and twice-annual treatments with ivermectin over a period of up to 17 years have a significant impact on helminth infection in children [26].

Migration of ivermectin into the breast-milk

Ivermectin was administrated orally at a dose of 150 mg/kg to 4 lactating mothers. The average peak concentration of ivermectin in the milk is 15 µg/ml (range, 11 to 21) which occurred 4 hours after dosing [27]. A lactating woman received a single oral dose of 200 mg of ivermectin and the peak concentration of ivermectin in the milk is 20.8 µg/ml which occurred 6 hours after the dose [28]. These results indicate that ivermectin migrates into the breast-milk in significant amounts.

Levamisole

Levamisole molecular structure (molecular weight=204.29 g/mol) (Figure 4).

Administration of levamisole to children [29]: Oral administration of levamisole to treat Roundworm infection

Administration to children

Children: Give: 2.5 to 3 mg/kg (maximum per dose=150 mg) for 1 dose.

Oral administration of levamisole to treat Hookworm infection

Children: Give: 2.5 mg/kg (maximum per dose=150 mg) for 1 dose, the dose should be repeated after 7 days in severe infections.

Oral administration of levamisole to treat nephrotic syndrome

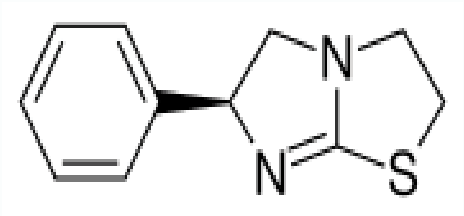

Figure 4: Levamisole molecular structure (molecular weight=204.29 g/mol).

(initiated under specialist supervision)

Children: Give: 2.5 mg/kg once-daily on alternative days (maximum per dose=150 mg).

Treatment with levamisole in children suffering from nephrotic syndrome

Clinical outcome is superior in mycophenolate mofetil group than in the levamisole group in children with nephrotic syndrome [30]. Levamisole reduces the episodes of nephrotic syndrome in children [31]. Levamisole prevents the recurrence of nephrotic syndrome in children [32]. Levamisole administered for 6 months is a safe and effective therapy in children with steroid dependent nephrotic syndrome [33]. Levamisole is of benefit in children with steroid-sensitive nephrotic syndrome but not in steroid-resistant nephrotic syndrome [34]. Levamisole does not cure nephrosis but reduces the incidence of nephrosis relapses in children [35].

Mebendazole

Mebendazole molecular structure (molecular weight=295.298 g/mol) (Figure 5).

Administration of mebendazole to children [36]**:** Oral

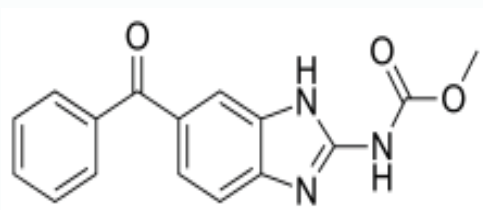

Figure 5: Mebendazole molecular structure (molecular weight=295.298 g/mol).

administration of mebendazole to treat worm infection in children.

Administration to children

Children aged 6 months to 17 years: Give: 100 mg for 1 dose if reinfection occurs a second dose may be needed after 2 weeks. Oral administration of mebendazole to treat whipworm and hookworm infections in children

Children aged 1 to 17 years: Give: 100 mg for 3 doses.

Oral administration of mebendazole to treat roundworm infections in children

Children aged 1 year: Give: 100 mg twice-daily for 3 doses.

Children aged 2 to 17 years: Give: 100 mg twice-daily for 3 doses, alternatively give 500 mg for 1 dose.

Efficacy and safety of mebendazole in children

A single dose of mebendazole is effective against hookworm infection, but the multiple dose treatment regimen of mebendazole shows higher efficacy in children. Hence, multiple doses of mebendazole better control the elimination of soil-transmitted helminth infections than a single dose [37]. A single oral dose of 500 mg of mebendazole chewable tablet is effective, safe and well-tolerated in children aged 2 years to 10 years [38]. Many adverse-symptoms were reported before treatment while very few adverse-effects are reported after treatment with mebendazole and mebendazole is well-tolerated in children [39]. Single oral dose of mebendazole shows high cure rates against lumbricoides in children [40].

Treatment of infants and children with mebendazole

Mebendazole is well-tolerated, effectively treats worm infections, and is not associated with any adverse-effects in infants [41]. The chewable formulation of mebendazole appears to be an appropriate alternative to the hard tablet of mebendazole for treatment of solid-transmitted helminthiasis and prevents infection in children aged 2 years to 4 years [42]. Parasitosis should be considered as a possible cause of halitosis in the paediatric population. Mebendazole therapy offers benefits to children with parasites as a potential cause of their halitosis [43].

Migration of mebendazole into the breast-milk

One lactating woman received a single oral dose of 100 mg of mebendazole. Mebendazole was undetectable (<1 µg/ml) in milk [44]. One lactating woman received mebendazole orally at a dose of 100 mg for 3 days. Mebendazole was undetectable in milk (<20 µg/ml) 14 hours after dosing [45]. These results indicate that mebendazole is undetectable in beast-milk.

Praziquantel

Molecular structure of praziquantel (molecular weight=312.413) (Figure 6).

Administration of praziquantel to children [46]: Oral

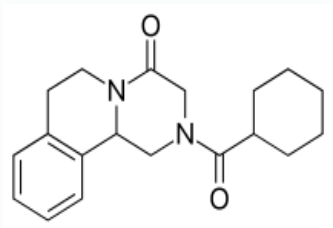

Figure 6: Molecular structure of praziquantel (molecular weight=312.413).

administration of praziquantel to treat tapeworm selenium infection.

Administration to children

Children aged 4 to 17 years: Give: 5 to 10 mg/kg for 1 dose. The dose should be taken after a high breastfeed. Oral administration of praziquantel to treat tapeworm infection (*Hymenolepis nana*)

Children aged 4 to 17 years: Give: 25 mg/kg for 1 dose. The dose should be taken after a high breastfeed. Oral administration of praziquantel to treat *Schistosoma haematobium* worn and *Schistosoma mansoni* worn infections

Children aged 4 to 17 years: Give: 20 mg/kg followed by 20 mg/kg after 4 hours to 6 hours.

Oral administration of praziquantel to treat *Schistosoma japonicum* worn infection

Children aged 4 to 17 years: Give: 20 mg/kg thrice-daily for 1

day.

Efficacy and safety of praziquantel in children

A single oral dose of 40 mg/kg of praziquantel would be less efficacious and less safe in preschool-age children than in school-age children [47]. Praziquantel, administered orally at a dose of 40 mg/kg daily, effectively reduces the infection intensity in all Schistosoma species without differences between preschool and school-aged children [48]. Praziquantel shows a flat dose-response and overall lower efficacy in preschool-aged children than in school-aged children. In the absence of treatment alternatives, a single oral dose of praziquantel of 40 mg/kg is recommended by the WHO for the treatment of *Schistosoma mansoni* infection in school-aged children [49]. Crushed praziquantel administered to preschool-aged children at an oral dose of 40 mg/kg is efficacious against *Schistosoma mansoni* and *Schistosoma haematobium* infections in a co-endemic setting of Côte d'Ivoir [50]. Praziquantel syrup and crushed praziquantel tablets have very similar efficacies in treatment of intestinal schistosomiasis infection in preschool children [51]. Praziquantel syrup is well-tolerated in preschool-aged children with moderate-to-high efficacy against *Schistosoma haematobium* infection, but considerably lower efficacy against *Schistosoma mansoni* infection in Niger [52].

Treatment of children with praziquantel

The incidence of schistosome's infection in preschool children resolves with praziquantel treatment given at an oral dose of 40 mg/kg daily [53]. A repeated oral dose of 40 mg/kg of praziquantel achieves satisfactory efficacy compared to a single dose against both *Schistosoma mansoni* and *Schistosoma haematobium* infections [54]. Praziquantel treatment enhanced, quantitatively and qualitatively, the anti-worm responses associated with protective immunity but did not alter Plasmodium-specific responses [55]. Praziquantel treatment of young children results in satisfactory cure rates and marked reduction in egg-output of *Schistosoma mansoni* with only mild and transient side-effects [56]. Praziquantel (40 mg/kg), in either crushed tablet or liquid suspension, is both safe and effective in young children infected by *Schistosoma haematobium* and by *Schistosoma mansoni* [57].

Migration of praziquantel into the breast-milk

Five lactating women received praziquantel orally at a dose of 50 mg/kg once-daily and the average concentration of praziquantel is 440 ng/ml which occurs 2 hours after the dose. By 24 hours after the dose, praziquantel is undetectable in milk [58]. Fifteen lactating women, infected by *Schistosoma japonicum*, received praziquantel orally at a dose of 30 mg/kg twice-daily. The average praziquantel concentration in the milk is 185 ng/ml. Praziquantel elimination half-life in milk is 1.9 hours and parallels plasma elimination half-life. By 24 hours after the dose, the milk concentration of praziquantel is 4 ng/ml [59]. These results indicate that praziquantel poorly migrates into the breast-milk.

Discussion

The anti-helminth agents used in paediatric patients are: albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel. Albendazole, ivermectin, mebendazole, and praziquantel have been extensively studied whereas little information is available for diethylcarbamazine and levamisole. The dosing of albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel has been reviewed in children. The efficacy and safety of albendazole [3-6] and the treatment of children with albendazole [7-10] have been reviewed and albendazole poorly migrates into the breast-milk [11]. The treatment of children with diethylcarbamazine, administered alone or combined with other drugs, has been reviewed [13-17]. The efficacy and safety [19-23] and the treatment of infants and children with ivermectin [24-26] have been reviewed and ivermectin migrates into the breast-milk in significant amounts [27,28]. The treatment of nephrotic syndrome with levamisole has been reviewed in children [30-35]. The efficacy and safety [37-40] and the treatment of infants and children with mebendazole [41-43] have been reviewed and mebendazole is undetectable in the breast-milk [44,45]. The efficacy and safety [47-52], the treatment of children with praziquantel [53-57] have been reviewed and praziquantel poorly migrates into the breast-milk [58,59].

Conclusion

The anti-helminth agents used in paediatric patients are: albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel. Albendazole, ivermectin, mebendazole, and praziquantel have been extensively studied whereas little information is available for diethylcarbamazine and levamisole. The dosing of albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel has been reviewed in children. The efficacy and safety of albendazole, ivermectin, mebendazole, and praziquantel have been reviewed. The treatment of infants and children with ivermectin and with mebendazole has been reviewed and the treatment of children with albendazole, diethylcarbamazine, levamisole, and praziquantel has been reviewed. Albendazole, mebendazole, and praziquantel poorly migrate into the breast-milk whereas ivermectin migrates into the breast-milk in significant amounts. The aim of this study is to review the clinical pharmacology of albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, and praziquantel in paediatric patients.

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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