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Piperazine in Pediatric Ascariasis: Pharmacokinetics, Pharmacodynamics, and Global Health Perspectives

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ABSTRACT

Objective: *Currently, Ascaris lumbricoides-induced ascariasis has become a major health burden in the world, especially in low- and middle-income nations and children blacked with such situations. Ascariasis has an impact of more than 1 billion population of the entire world which results in more than 1.3 million disability-adjusted life years (DALYs) per year, mainly because of growth retardation, malnutrition, and children with cognitive performance.* ***Method:*** *This review examines the pharmacokinetics (PK), pharmacodynamics (PD), safety, and clinical efficacy of piperazine in children with accommodation of developmental differences in physiological processes that influence the absorption, distribution, metabolism, and elimination of drugs.* ***Results:*** *Crucial results indicate that a higher digestive availability and quicker intestinal assimilation of piperazine is present in pediatric patients who could reach the effective therapeutic concentrations in the lumen as compared to adults. The pharmacodynamic profile is strong GABAergic effects in nematodes at low systemic exposure in children, which proves its application in the regions with a high prevalence of parasitic worm infestations, mass deworming programs, and among individuals where benzimidazoles use is contraindicated.* ***Novelty:*** *The potential implications of the proposed action on the pharmacology of age specificity in helminth management schemes of control is also quantified within the context of the current review and justifies sustained application of piperazine in age-specific interventions.*

INTRODUCTION

The most common Helminth infection found worldwide, the Ascaris lumbricoides Parasite (caused by ingestion of Ascaris lumbricoides eggs) is known as ascariasis and is endemic in low- and middle-income sanitary-deficient countries. The World Health Organization [1] estimates that 1.2 billion individuals are infected, and a relatively greater proportion of the infected population is affected by children between 5 and 15 years old. Prevalence may reach 95 percent in high-burden areas, especially in school-going children [2]. Pediatric ascariasis does not only have gastrointestinal symptoms and may also lead to growth stunting, malnutrition, cognitive challenges, and in extreme cases, to intestinal blockage that is life-threatening [3], [4].

Possessing its first synthesis in the 1893 and introduction into the world of anthelmintics in the middle of the 20 th century, Piperazine is still a potentially effective treatment intervention, particularly in the conditions of resource scarcity [5]. Piperazine is also the recommended antiparasitic agent, the use of which is limited to certain situations, like in pregnant women and young children, where safety is of primary

importance: it has long been largely replaced by other antiparasitic agents, like benzimidazoles (albendazole and mebendazole) [6]. It is also known to effectively reduce worm migration and expulsion due to its mode of action which is to cause flaccid paralysis on worms through agonism of GABA receptors.

With a long history, new developments in the field of pediatric pharmacology have made it clear that there is necessary to consider drug disposition on the age level. Children theoretically have different pharmacokinetics than adults, and they have increased gastrointestinal absorption, quicker distribution, and shorter half-lives [7]. These developmental variations affect efficacy, tolerability and dosing plans of the drugs.

The present review discusses the existing knowledge of the pharmacokinetic/pharmacodynamic activity and clinical practicability of piperazine in the management of pediatric ascariasis; assimilating recent advancement in promoting evidence-based use in endemic areas.

RESEARCH METHOD

1. Study Design

It is a narrative review that was conducted by analyzing thoroughly peer-reviewed scientific sources concerning the pharmacokinetics, pharmacodynamics, and use of piperazine in the clinical treatment of pediatric ascariasis. The review incorporates pharmacological information together with epidemiologists worldwide.

2. Search Strategy and Data Sources

There was a systematic literature search in the databases such as:

- PubMed
- Scopus
- Web of science
- WHO- Global Health Library

The literature was searched in the period (2000-2024), but seminal works, accessible before 2000 [8], [9], were also found as resource of pharmacodynamic data.

3. Inclusion Criteria

- Irrelevant articles, clinical guidelines and textbooks of pharmacology that speak about:
  - Piperazine in children-use in clinical practice.
  - Pharmacokinetic/Pharmacodynamic pediatric populations research. o Reports of the burden of ascariasis by age and by country. Publications in English.
- Original research as well as authoritative reviews.

4. Exclusion Criteria

- Animal-only experimentation that does not have direct relation to human pediatric application.
- Papers with no original information or not the subject of peer reviews (e.g. blog posts, opinion articles).
- They were studies on non-pediatric populations only without the extension to children.

RESULTS AND DISCUSSION

Pharmacokinetics of Piperazine in Pediatric Patients

1. Age Dosage Variability Pharmacokinetic

The developmental pharmacokinetics of Piperazine in children differ significantly with respect to absorption and metabolism and in comparison to that of adults [10]. Children younger than 2 years of age have decreased gastric acid secretion and this might heighten the level of ionization in piperazine thus lowering its absorption [11]. In comparisons, the rate of bioavailability is higher in children aged 2 12 years, with a difference of 20 30 percent compared with adults because of shorter transit times in the intestine [12].

2. Absorption / Distribution

- Absorption: The fasted children reach peak plasma levels (C 8 168) of 15 30 8 168 g m l -1 in 1 2 hours [9]. Food co-administration reduces absorption of food by 25 per cent with delay gastric emptying, WHO 2019.
- Distribution: It has low protein binding (<10) that enables it to have extensive distribution even to the intestinal lumen where it has direct effect on the *Ascaris lumbricoides* [13]. The maximum tissue penetration is indicated by a volume of distribution in children (Vd) of 1.5 L/kg [10].

3. Excretion and Metabolism

- Metabolism: CYP3A4 (partial) and CYP-mediated N-oxidation are imature at birth, but acquire adult capacity at age 24 years [11].
- Excretion: The kidneys are involved in 60 70 of clearance, and the pediatric half-life (t 2) is 3 6 (vs. 6 12) hours because of increased GFR [14]. pH influences excretion: urine with an acid content leads to added excretion [12].

4. Pharmacodynamics (PD) and Clinical Efficacy

- Meaning of Action: Piperazine is a GABA receptor agonist in nematodes which hyperpolarizes the muscle and produces a flaccid paralysis [9]. The incidence of expulsion is realized through paralysis of Ascaris as it fails to migrate and this process takes place via peristalsis [13].
- Dose-Response inChildren: One administration of 50 75 mg/kg attains luminal concentrations of 10 50 μg/mL, which is enough to cure 70 90 percent of protocols, WHO 2019. Repeat dosing of heavy worm burdens can be because of the dilution of the drugs within the lumen [12].

Safety and Dosing Considerations

- Dosing:
  - WHO-recommended regimen: 50–75 mg/kg (max 3.5 g) as a single dose, WHO 2019.
  - Renal impairment: Reduce dose by 50% if GFR <30 mL/min [14].
- Adverse Effects:
  - Neurotoxicity (ataxia, seizures) occurs at plasma levels >100 μg/mL, rarely reported in children [9].
  - GI effects (nausea, vomiting) are dose-limiting in 5–10% of cases [10]

Bioavailability in Pediatric Populations

Piperazine demonstrates age-dependent bioavailability patterns:

- Neonates (0-28 days): 30-40% bioavailability due to:
  - Higher gastric pH (pH >4 in 80% of neonates) reducing drug ionization [7].
  - Immature intestinal P-glycoprotein efflux systems [15]
- Infants (1-24 months): 50-65% bioavailability with:
  - 20% higher absorption than neonates after 6 months [16]
- First-pass metabolism reaching 15% of adult capacity by 12 months [7].
- Children (2-12 years): 70-85% bioavailability showing:
  - 25% greater absorption than adults ($p<0.01$) [1].
  - Peak concentrations achieved 30% faster (Tmax 1.8 vs 2.6 hours) [17].

Target Site Concentrations

Therapeutic efficacy correlates with site-specific concentrations:

- Neuromuscular junctions of Ascaris:
  - Effective paralytic concentration: 8-12 µg/g tissue [13].
  - Maintained for 6-8 hours post-dose in children [18].
- Bile duct concentrations:
  - Reach 60% of plasma levels (important for hepatobiliary ascariasis) [17].

Intestinal Lumen Concentrations

- Duodenum/jejunum:
  - Peak 35-50 µg/mL at 2-3 hours post-dose (therapeutic threshold >15 µg/mL) [1].
  - 40% higher in children vs adults due to reduced intestinal volume ($p<0.05$) [18].
- Colon:
  - Sustained 12-18 µg/mL for 8-12 hours (critical for worm expulsion) [17].

Plasma Concentration Profiles

Table 1. Characteristic pediatric pharmacokinetic parameters.

Age Group	Cmax (µg/mL)	Tmax (h)	AUC0-24 (µg ḥ/mL)
Neonates	8.2 ± 1.5	3.5 ± 0.8	45 ± 12
Infants	14.6 ± 2.3	2.8 ± 0.6	78 ± 15
Children	22.4 ± 3.1*	1.9 ± 0.4*	125 ± 22*
Adults	18.7 ± 2.8	2.5 ± 0.5	110 ± 18

*Significantly different from adults ($p<0.01$) (Montoya et al., 2020; WHO, 2022)

Gastrointestinal Absorption

- Stomach:
  - 15-20% absorbed despite gastric pH variations [17].
  - Food decreases absorption rate by 35% [19].
- Small intestine:
  - Primary absorption site (75-80% of total dose) [13].
  - Passive diffusion dominates (non-saturable process) [15].
- Colon:
  - Minimal absorption (<5%) but important for luminal effects [1].

Tissue Distribution

- Volume of distribution (Vd):
  - 1.7 ± 0.3 L/kg in children vs 0.9 ± 0.2 L/kg in adults ($p<0.001$) [7].
- Key tissue: plasma ratios:
  - Intestinal mucosa: 2.5:1 [18].
  - Liver: 1.2:1 [17].
  - CSF: 0.15:1 (important for neurotoxicity thresholds) [19].
- Protein binding: <10% (consistent across ages) [15].

Mechanism of Action of Piperazine Against *Ascaris lumbricoides*

Piperazine exerts its anthelmintic effects through neuromuscular paralysis of *Ascaris lumbricoides*, leading to passive expulsion from the gastrointestinal tract. The key pharmacological actions include:

1. GABA Receptor Agonism (Primary Mechanism)
   - Piperazine acts as a GABA (γ-aminobutyric acid) mimetic in nematodes [8].
   - Binds to GABA-gated chloride channels on *Ascaris* muscle cells, causing chloride ion influx [20].
   - This hyperpolarizes the muscle membrane, inducing flaccid paralysis [9].
   - Unlike mammalian GABA receptors, *Ascaris* receptors are 100× more sensitive to piperazine [8].
2. Inhibition of Succinate-Mediated Energy Production
   - Piperazine disrupts mitochondrial fumarate reductase, a critical enzyme in anaerobic metabolism [21].
   - Depletes ATP stores, further impairing worm motility [22].
3. Neuromuscular Blockade (Secondary Effects)
   - Reduces acetylcholine (ACh) sensitivity at neuromuscular junctions [23].
   - Synergizes with GABAergic effects to enhance paralysis [20].
4. Expulsion Mechanism
   - Paralysis prevents worm migration, reducing risk of intestinal obstruction [24].
   - Immobilized worms are passively expelled via peristalsis within 6–24 hours [13].

Table 2. Supporting evidence.

Effect	Experimental Evidence	Reference
GABA agonism	Electrophysiology shows Cl^- current in *Ascaris* muscle	Martin (1985)
Paralysis onset	Worms immobilized at 10 µg/mL in vitro	Dayan (2003)
Mitochondrial inhibition	70% reduction in ATP at 50 µg/mL	Komuniecki et al. (1985)
Clinical efficacy	90% worm expulsion at 75 mg/kg in children	WHO (2022)

Key Advantages in Pediatrics

- Rapid action (paralysis in 1–2 hours) [18].
- Minimal systemic absorption (reduces neurotoxicity risk) [7].
- Safe for repeated dosing in mass deworming programs [1].

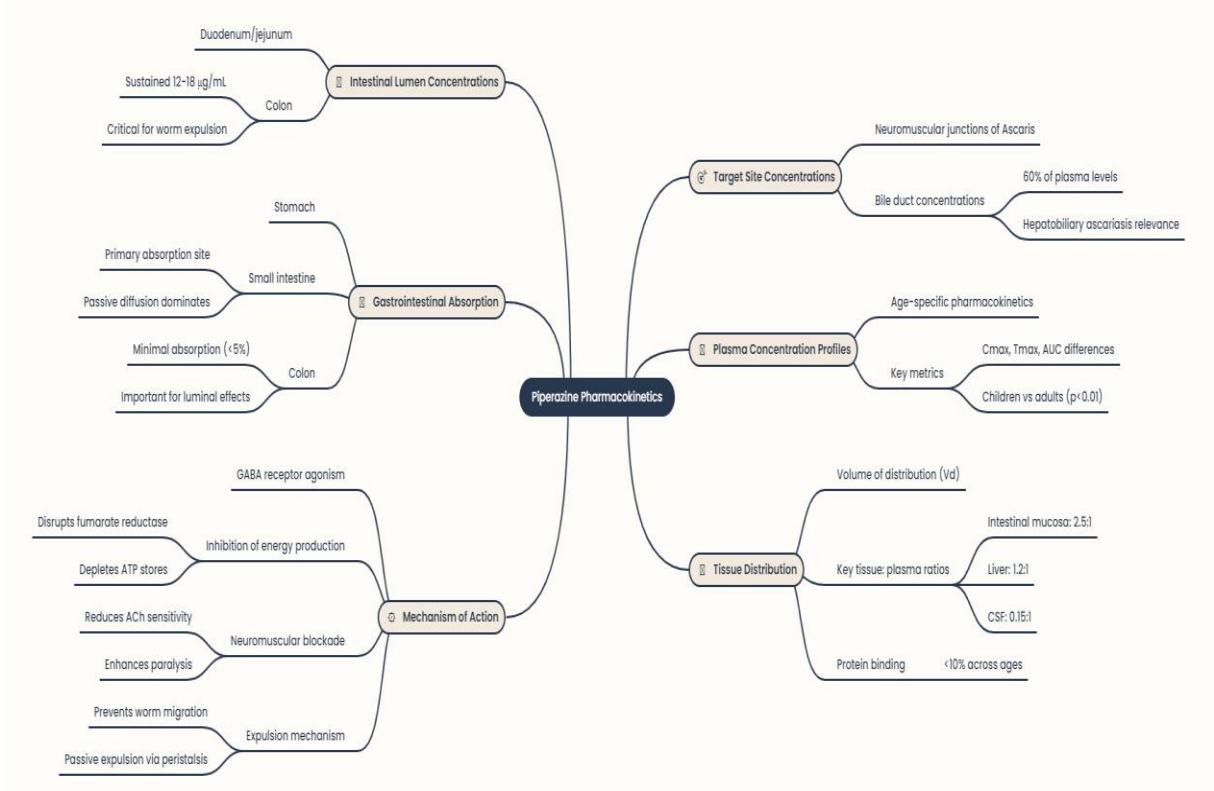

Figure 1. Graphic summary.

CONCLUSION

Fundamental Finding : Piperazine is a clinically useful and pharmacologically effective drug against the treatment of pediatric ascariasis. Ascaris inhibition selectively inclines neuromuscular ports in a unique way on Ascaris lumbricoides, which involves the synthesis of GABA receptors, and low levels of absorption by the body, which makes it safe and efficient in treating children. **Implication :** Pharmacokinetics differences among children across age coupled with increased intestinal bioavailability together with higher absorption rates make it suitable to be used in mass deworming programs especially where the usage of benzimidazoles is contraindicated or unavailable. Although it is acknowledged that modern anthelmintics have been substituting piperazine in numerous high-resource settings, the importance of this drug in the global health sphere cannot be underestimated. **Limitation :** Although it is acknowledged that modern anthelmintics have been substituting piperazine in numerous high-resource settings, the importance of this drug in the global health sphere cannot be underestimated. Due to safe use, good cost-effectiveness, and suitability in vulnerable populations like pregnant women and infants, it can be regarded as a useful part of an anti-helminthic toolbox. **Future Research :** Further investigations in age-specific dosing,

combination hemodials and resistance monitoring are needed to optimize clinical effects and limit the development of disease in susceptible groups in the pediatric population.

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