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Original Research Article

Efficacy and Safety of Mebendazole in the Treatment of Intestinal Helminth Infections

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Abstract: Mebendazole was introduced in 1971 and is not soluble in water or other organic solvents, it is also not absorbed from the intestinal tract in a high-fat context. Both albendazole and mebendazole have a low rate of absorption in the human intestine. These drugs primarily target parasites in the stomach's lumen, and their metabolites are effective against parasites in the stomach's muscles and tissues. For instance, albendazole sulfoxide is the primary metabolite that possesses anthelmintic properties. Metabolites of mebendazole are expelled in the urine. Both drugs negatively affect the function of microtubules in parasites and mammalian cells, this results in the depletion of the parasites' glycogen stores. Current helminth control strategies involve periodic deworming with albendazole or mebendazole. However, concerns about drug resistance and the persistence of high prevalence rates suggest the need for additional strategies, such as improved water, sanitation, and hygiene, and optimized treatment regimens. Albendazole and mebendazole are highly effective against *Ascaris lumbricoides*, with a single dose of albendazole showing a cure rate of 96% and mebendazole showing a cure rate of 92.3%. Mebendazole's efficacy against hookworms varies, but a recommended dosing regimen improves effectiveness. Mebendazole's effectiveness against *Trichuris trichiura* depends on the dosing regimen. It is less effective against hymenolepiasis, where praziquantel is preferred. Mebendazole has also been used to treat *Giardia lamblia* infections. In summary, STH infections are a significant health issue, and albendazole and mebendazole are commonly used drugs for treatment. However, there is a need for additional strategies to address drug resistance and improve treatment efficacy. Mebendazole has potential side effects and should be used with caution, especially during pregnancy.

Keywords: Anthelmintic Properties; Albendazole; Drug Resistance; Helminth Control; Mebendazole; Treatment Regimens.

1. INTRODUCTION

Soil-transmitted helminth infections (STH) are worm infections that are transmitted through soil and affect humans by localizing in the human intestine. They are classified as neglected tropical diseases (NTDs); these include roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and hookworms (*Ancylostoma duodenale* and *Necator americanus*) (Lenk *et al*., 2016, Lundin *et al*., 2024).These infections are common in underdeveloped countries; one-third of the world's population is infected with at least one type of STH. The World Health Organization had committed itself to the fight against neglected tropical diseases (Organization, 2015).

Soil-transmitted helminth infections (STH) are worm infections of the human intestine that are transmitted through soil (Jourdan *et al*., 2018). They are classified as neglected tropical diseases (NTDs). The major species include roundworms (Ascaris lumbricoides), whipworms (*Trichuris trichiura*), and hookworms (*Ancylostoma duodenale* and *Necator americanus*) (Alexander *et al.*, 2019, Singh and Singh, 2023). These infections are very common in developing

countries, where about one-third of the population is infected with at least one type of STH (Belyhun *et al*., 2010). The World Health Organization has taken up the issue of neglected tropical diseases. Chronic STH infection can lead to malnutrition, growth retardation, intellectual developmental disabilities (IDD), and impaired cognitive function, affecting school attendance and future economic productivity (PROSPER *et al*., 2022). STH can occur as a single infection or as a combination of all three groups of infections. The World Health Organization recommends albendazole and mebendazole (both benzimidazoles) to combat STH infections (Moser *et al*., 2019). However, recent studies have reported unsatisfactory cure and egg loss rates with albendazole treatment, possibly due to drug resistance. Studies in Uganda and Kenya have shown lower cure and egg loss rates for caterpillars after treatment with albendazole (Curico *et al*., 2022). A 2007 systematic review reported higher cure rates for *Trichinella* with mebendazole compared to albendazole. The role of mebendazole has also been suggested in a study by Speich *et al*., and demonstrated higher cure rates for caterpillars in Ethiopia (NGONJO, 2020).

An efficacy study of a single dose of 500 mg mebendazole in six countries reported higher egg laying rates for roundworms, hookworms, and *trichinella* (Knopp *et al*., 2012). A study in China showed higher cure rates for *Trichinella* with mebendazole compared to albendazole. Both albendazole and mebendazole are effective against roundworms, caterpillars, and hookworms by interfering with microtubule formation and inhibiting glucose uptake, resulting in worm death (Yurttaş *et al*., 2019, Al-Mekhlafi *et al*., 2013).

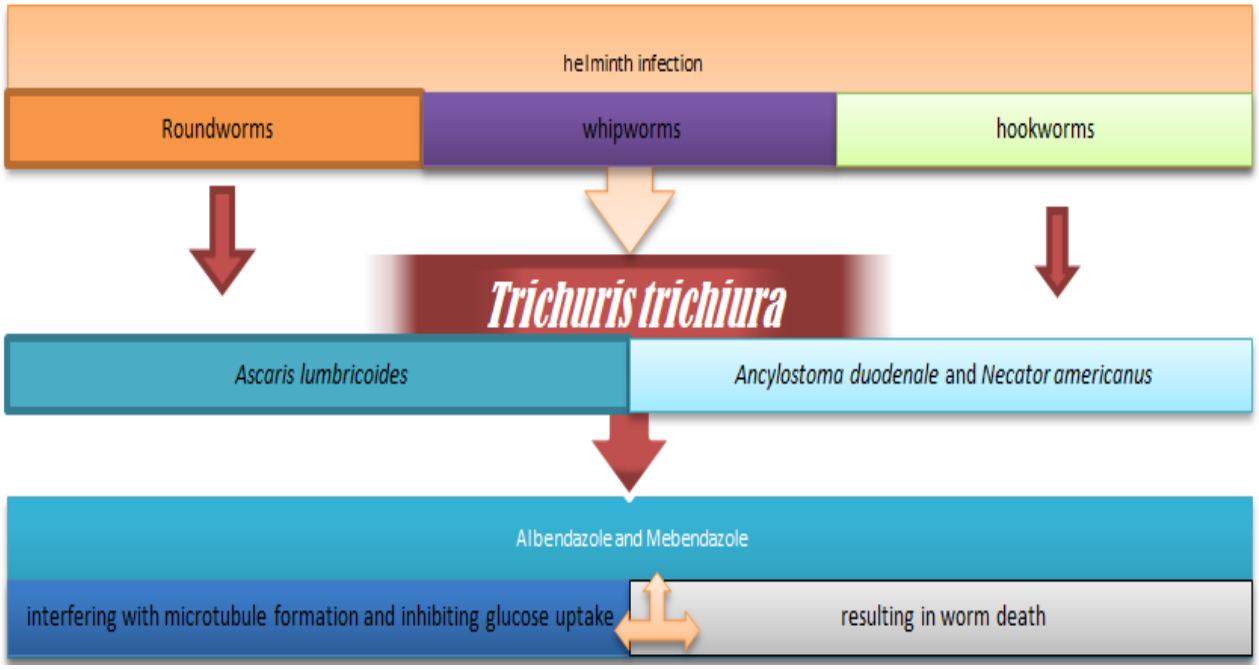

Illustration chart 1: Types of worms with the mechanism of action of mebendazole treatment

MATERIALS AND METHODS

A comprehensive literature search was conducted using PubMed, Google Scholar, and databases to identify relevant articles on the use of mebendazole in the treatment of worm infections. The data collected from the literature were analyzed qualitatively to assess the drug's mechanism of action, pharmacokinetics, efficacy, and safety. PowerPoint was used to create illustrative diagrams to visualize the action of mebendazole on these parasites. Excel was utilized to compile and analyze the data on the prevalence of worm infections and the effectiveness of mebendazole in various clinical trials.

2. Treatment Using Mebendazole against Pathogenic Helminthes

2.1. Infectious Pathogenic Helminths and Treatment:

In contrast, mebendazole has variable efficacy against hookworm infections. A 500 mg single dose of mebendazole was reported to have low cure rates at 15.0% and 17.6% with ERR 98.0% and 76.3%, respectively (Chai *et al*., 2021) while 600 mg total (100 mg twice daily) for three days had CR as high as 80.0% with ERRs ranging from 41.0-100% based on twenty-seven studies considered WHO recommended dose depending also likely significantly type a as well (Organization, 1995): for example duodenale had where 71.4%, and can be active highly effective poorly moderate depending variable variable significantly types on against while dose recommended duodenale activity highly effective poorly moderate variable different another one former latter As mentioned formerly (Reckhow, 2014, Arendse, 2000). In contrast, the efficacy of mebendazole against hookworms is a little lower (Soukhathammavong *et al*., 2012). A single dose of 500 mg of mebendazole was reported to have cure rates of 15.0% and 17.6% with ERRs of 0-98.0% and 76.3%,

respectively (Silber *et al*., 2017); however, when given at double this amount (100 mg twice daily) for three days as in the WHO recommendation (total 600 mg), it had CRs of 80.0% and ERRs of 41.0-100%, according to 27 studies (Organization, 1995). The activity spectrum may also be different for mebendazole depending on the species: e.g., at recommended doses, it has a CR of 71.4% and an ERR of 97.3% against *Ancylostoma duodenale* but only a CR:52.0%, ERR:91.2% versus Nematode (Keiser and Utzinger, 2010, Seo *et al*., 1977, Yokogawa, 1980).

H. nana has relatively low response rates to standard 3-day mebendazole therapy (18-40% CR). For H. nana (KEYSTONE and MURDOCH, 1979), the drug of choice is praziquantel: a single dose of 15-25 mg/kg. A second treatment after 14 days is recommended concurrently with prophylaxis of relapses (Chai and chemotherapy, 2013). H. nana has a rather good resistance to standard three days of mebendazole treatment; CR varies from 18% to 40%. The drug of choice for H. nana is praziquantel: one dose of 15-25 mg/kg. A repeat dose after two weeks is indicated to prevent relapses (Rim *et al*., 1984).

Mebendazole has been used to treat infections with *Giardia lamblia* In 1975 (Escobedo *et al*., 2018), Hutchison et al. achieved a 40% CR with 200 mg daily for 3 days later; a higher dose of 600 mg daily for either 3 or 5 days cured 95% of patients, including children. However, more recent research has proved that mebendazole at a dose of 600 mg daily for five days is not effective among adults with giardiasis (Hutchison *et al*., 1975, Al-Waili *et al*., 1988).

Mebendazole has been shown to be effective against Taenia spp. infections when administered in multiple doses, such as 100 mg twice daily for 3 days, 300 mg twice daily for 3 days, or 500 mg once daily for 3 days. The cure rate (CR) for the 500 mg once-daily regimen for 3 days was 100%, compared to only 50% for a single 500 mg dose (Soh *et al*., 1974, Chavarria *et al*., 1977, Steinmann *et al*., 2011). However, reports and research have indicated the use of mebendazole against enterobiasis, where the standard dose of 100 mg as a single dose has been shown to be satisfactory for the treatment of enterobiasis in both adults (88% complete response) and children (91%). Higher doses, such as 100 mg twice daily for 3 days (total of 600 mg) or single doses of 200 mg or 400 mg, have shown similar therapeutic effects (Brugmans *et al*., 1971, Georgiev, 2001).

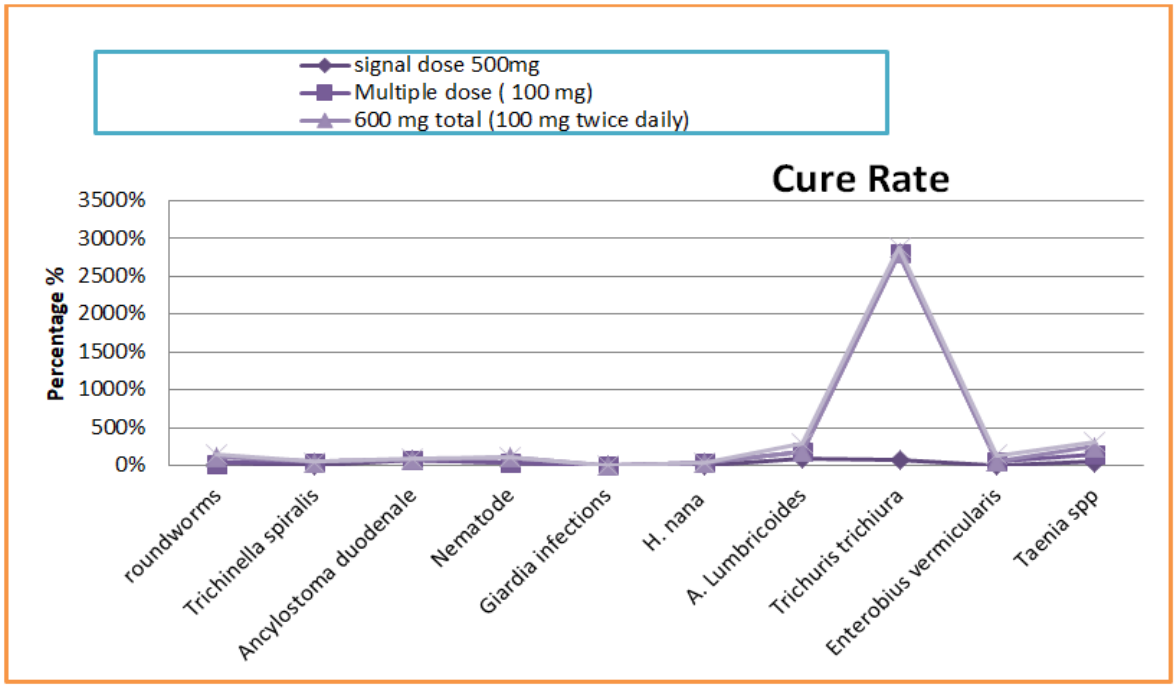

Illustration chart 2: Types of doses of mebendazole treatment with the cure rate against types of intestinal worms (Prepared by the author and publisher)

2.2 Current Approach to Helminth Control Periodic Deworming

Currently, control of hookworms and other soil-transmitted helminths is achieved through regular deworming (also known as preventive chemotherapy). Schoolchildren and other high-risk groups are given a single dose of albendazole (400 mg) or mebendazole (500 mg) regularly (Tchuem Tchuenté, 2011, Palmeirim *et al*., 2018a, Taylor-Robinson *et al*., 2019). While these drugs are effective against roundworms, they have limited effectiveness against whipworms when given as a single dose. In addition, a recent systematic review and network meta-analysis found that a single dose of albendazole had acceptable efficacy against hookworms, with a cure rate (CR) of 80%, while a single dose of mebendazole had a much lower CR of 33% for hookworm infections (Palmeirim *et al*., 2018a, Kabatende *et al*., 2023).

Globally and in Tanzania, individualized treatment with multiple doses of mebendazole, 100 mg twice daily for three days, is recommended (Palmeirim *et al*., 2018b). However, little research has been done on the effectiveness of this multiple dose regimen. Existing studies show mixed results, with cure rates ranging from 31% to 100%. Preventive chemotherapy is the cornerstone of helminth control and is recognized for its cost-effectiveness in global public health (Gabrielli *et al.*, 2011). The drugs albendazole and mebendazole are widely used with varying efficacy against various soil-transmitted helminthes (Moser *et al*., 2017). Studies on Pemba Island found that hookworm prevalence was as high as 36% to 97% even when schoolchildren were regularly treated (Albonico *et al*., 1997). This suggests that other strategies are needed to effectively control and eradicate these infections, including improved water supply, sanitation and hygiene, and optimized treatment options (e.g., combination chemotherapy) (Bockarie *et al*., 2013).

2.3. Challenges in Mebendazole Therapy: Resistance and Monitoring:

Considering the global burden of parasitic diseases and the specific large population in poor regions (Bhutta *et al*., 2014), it is very important for healthcare providers to have a complete knowledge of the profile of mebendazole—comprising its action, uses, possible side effects, and monitoring This paper is a review aiming to explain in detail the clinical applications of mebendazole, safety considerations that should be observed, and how an interprofessional approach will bring about optimal patient outcomes and deal with challenges that are still ongoing in the treatment of parasitic infections.

Although mebendazole is very safe when widely used and has a generally favorable safety profile, it is not entirely free of problems. Its adverse effects, though mild in most cases, can be rarely severe, especially with prolonged or high-dose therapy. Besides, the possibility of the parasite population developing resistance to the drug is an emerging concern that should make the use of this remedy be subject to close scrutiny and very moderate (Alonso and Tanner, 2013, Karunarathna *et al*.,).

2.4. Mechanism of Action

Mebendazole inhibits the formation of microtubules in parasitic worms. It achieves this by binding to the β-tubulin protein within the colchicine site in intestinal cells of the parasites (Ashraf, 2014). The result is that dimer units of tubulin cannot polymerize into microtubules. This action disrupts essential cellular functions, notably uptake, digestion and reproduction of glucose leading to immobilization and eventual death of parasite (Ashraf, 2014). Owing to its limited absorption through the gastrointestinal mucosa, systemic concentrations of mebendazole achieved are insufficient to cause serious side effects in extra-intestinal helminthic infections (Wong *et al*., 2020). However, resistance can develop against mebendazole because mutations occur on the β-tubulin protein whereby its affinity for the drug reduces consequently production against this specie becomes unmanageable (McIntyre, 2020).

2.5. Pharmacokinetics

Following oral administration, over 90% of the dose is found in the feces. Because most of the drug remains in the gut (the site of anthelmintic action), only a small fraction is absorbed into the bloodstream (Vercruysse and Claerebout, 2016, Lanusse *et al*., 2016). What little is absorbed is rapidly metabolized in the liver. Inducers of CYP450 (such as carbamazepine or phenytoin) are likely to reduce plasma levels of mebendazole since metabolism is primary via this route in the liver (Edwards, 2011, Patil *et al*., 2017). Mebendazole is excreted mainly in bile or urine; its half-life is 3 to 6 hours. Patients with hepatic impairment or biliary obstruction could have higher plasma levels of mebendazole (Karunarathna *et al*.,).

2.6. Toxicity of Drugs

Mebendazole is generally safe when used at recommended doses, but hepatotoxicity can occur, particularly with long-term use for conditions like echinococcosis (Mihmanli *et al*., 2016). A case of liver damage was noted in a patient with Gilbert's syndrome, where impaired glucuronidation led to toxic metabolite accumulation (Wagner *et al*., 2018). Long-term treatment (50 mg/kg daily for 9-18 months) has been found to be safe and without significant side effects in children with echinococcosis (Brahim *et al*., 2008). Other side effects at high doses include granulocytopenia, hair loss, and skin problems (Brahim *et al*., 2008). Combining mebendazole with metronidazole (both >500 mg) is risky, as it may lead to severe reactions like Stevens-Johnson syndrome (Pakala, 2021). Mebendazole is contraindicated during pregnancy due to teratogenic effects observed in high doses in experimental studies (Dayan, 2003).

CONCLUSIONS

Mebendazole has variable efficacy against hookworm infections. A single dose of mebendazole 500 mg has been reported to have low cure rates of 15.0% and 17.6% with predicted response rates of 98.0% and 76.3%, respectively; however, we conclude that when given at twice this amount (100 mg twice daily) for three days as recommended by the WHO (600 mg in total), the response rate was 80.0% and the predicted response rate was 41.0–100%. However, this study draws a firm scientific conclusion. The spectrum of activity for mebendazole may also vary depending on the species: for

example, at the recommended doses, the response rate was 71.4% and the predicted response rate was 97.3% against *Ancylostoma duodenalis* but only 52.0% and 91.2% against *Trichinella spp*.

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