Nitazoxanide

Nitazoxanide (NTZ) is a novel broad-spectrum antiparasitic agent originally discovered in 1980s by J.F. Rossignol. Nitazoxanide is effective in broad range of parasitic and protozoal infections including Giardia lamblia, Entamoeba histolytica, Cryptosporidium spp., Ascaris lumbricoides, Hymenolepis nana and Taenia solium/saginata. In combination, these are responsible for 44% of diarrhea and wide variety of symptomatology among children(1). This drug has been approved by US FDA (in Nov 2002) as well as by Drug controller general of India (DCGI) (in June 2004), for treatment of diarrhea caused by Cryptosporidium parvum and Giardia lamblia, in children 1-11 years of age(2,3).

Structure and mechanism of action

Nitazoxanide is a nitrothiazole derivative. Chemically it is 2-Acetyloxyl-N-(5-nitro-2 thiazolyl) benzamide. The chemical structure of nitazoxanide is related to metronidazole. Both compounds have a nitro group in the 5-position of the heterocyclic ring. The antiparasitic activity of nitazoxanide is believed to be due to interference with the Pyruvate-Ferredoxin Oxidoreductase (PFOR) enzyme dependent electron transfer reaction, which is essential for anaerobic energy metabolism of the parasites. However, interference with PFOR enzyme-dependent electron reaction may not be the only pathway by which nitazoxanide exhibits its antiprotozoal activity.

Pharmacodynamics

Following oral administration in humans, nitazoxanide is rapidly hydrolysed to an active metabolite, tizoxanide (diacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. Nitazoxanide and its metabolite, tizoxanide, are readily reduced by PFOR enzymes from the parasites by transfer of electrons. This reduced form of nitazoxanide deprives parasite of their energy and eradicate them.

Pharmacokinetics

Following oral administration of nitazoxanide, maximum plasma concentration of active metabolites is observed within 1-4 hrs. The parent nitazoxanide is not detected in plasma. In plasma, more than 99% of tizoxanide is bound to proteins. Tizoxanide is excreted in urine, bile and feces. Pharmacokinetics of nitazoxanide has not been studied in pediatric patients less than one year of age as well in patients with impaired hepatic and or renal function.

Spectrum of activity

In preclinical studies, nitazoxanide and its metabolites have demonstrated activity against protozoa, helminth and bacteria.

In vitro efficacy has been demonstrated against Cryptosporidium parvum, Giardia lamblia, Trichomonas vaginalis, Entamoeba histolytica(4), Echinococcus granulosus(5) and H. pylori(6). Nitazoxanide has been shown to be clinically efficacious against various protozoa (Cryptosporidium parvum, Giardia lamblia) and
helminth (*Trichuris trichura*, *Ascaris lumbricoides*, *Hymenolepis nana*, *Fasciola hepaticum*) (1,7-11).

**Therapeutic usage**

FDA approved indications: Nitazoxanide has been approved by US FDA as well as DCGI for treatment of diarrhoea caused by *Cryptosporidium parvum* and *Giardia lamblia*, in children aged 1-11 years of age (2,3).

(A) *Cryptosporidium parvum*

(i) *In-vitro and animal studies:* In cell culture NTZ consistently reduced parasite growth by more than 90% with little evidence of drug-associated cytotoxicity, in contrast to 80% reduction produced by paromomycin (PRM). However, in contrast to its efficacy in vitro, NTZ was ineffective at reducing the parasite burden in *C. parvum*-infected, anti-gamma-interferone-conditioned SCID mice. Combined treatment with NTZ and PRM was no more effective than treatment with PRM alone. Finally, NTZ was partially effective at reducing the parasite burden in a genobiotic piglet diarrhea model when given orally for 11 days at 250 mg/Kg/day but not at 125 mg/Kg/day. However, the higher dose of NTZ induced a drug-related diarrhea in piglets that might have influenced its therapeutic efficacy (12).

(ii) *Non-AIDS patients:* Various studies (Table I) have shown that use of nitazoxanide has been associated with significant clinical and parasitological improvement in children and adults with *Cryptosporidiosis* (8,10). In a well-designed randomised placebo controlled trial by Amadi, *et al.*, *Cryptosporidium parvum* stool eradication rate was 52% with clinical response rate of 56% in children treated with nitazoxanide compared to 23% in placebo group (8). In another series of trials by Rossignol, *et al.*, clinical efficacy of nitazoxanide was around 81% in treating diarrhea caused by *Cryptosporidium parvum* both in adults and children (10). Moreover, efficacy of nitazoxanide is comparable to albendazole, mebendazole, metronidazole and quinfinamide, for treating these infections (13-16).

(iii) *HIV associated infections:* The efficacy of nitazoxanide in treatment of *C. parvum* infection in HIV positive patients remains arguable. A study by Doumbo, *et al.*, from Africa demonstrated 95% efficacy in reducing *C. parvum* oocysts in stools (17). Similar results were documented by Rossignol, *et al.*, with lower parasitological cure rates (63% with 1 g/day and 67% with 2 g/day) (18). However, in a study on Zambian children in 2002, no benefit from nitazoxanide was documented in HIV seropositive patients as compared to diarrhoea resolution rates of 56% in treated vs 23% in HIV seronegative patients (8).

(B) *Giardia:* Several trials have documented the equivalent efficacy of 3 days of nitazoxanide as compared to 5 days of metronidazole for the treatment of giardiasis.

**Other indications**

(i) *Protozoan infections:* Clinical efficacy of nitazoxanide has been shown in intestinal amoebiasis and *Trichomoniasis* (1,8,10). In a study by Diaz, *et al.*, stool elimination rate of various protozoa was 84% with nitazoxanide in children between 2-12 yrs of age (1).

(ii) *Helminth infections:* Nitazoxanide has been shown to be clinically effective against a wide range of nematodes (*Enterobius vermicularis*, *Ascaris lumbricoides*, *Trichuris trichura*), cestodes (*T. saginata / solium*, *Hymenolepis nana*) and trematodes (*Fasciola hepaticum*) (1,7,11). Efficacy equivalent to mebendazole and quinfinamide was documented against various helminths by Davilla, *et al.*, in Mexico (14). Similar effectiveness was documented by
Diaz, et al., from the same country by with 95% parasite elimination rates(1). Similar rates were specifically documented against *T. saginata* (95%) and *H. nana* (90%) infections by Rossingnol, et al.(11). The efficacy of the drug against *Fasciola hepatica* was only upto 60% in adults and 40% in children between 2-12 years of age(7).

**Dose and method of administration**

(a) For pediatric patients aged 12-47 months - 100 mg every 12 hr for 3 consecutive days for Amebiasis, Giardiasis, Cryptosporidiosis and helminth infections.

(b) For paediatric patients aged 4-11 years-200 mg every 12 hrly for 3 consecutive days for Amebiasis, Giardiasis, Cryptosporidiosis and helminth infections.

(c) For adults - 500 mg every 12 h for 3 consecutive days for Amebiasis, Giardiasis, Cryptosporidiosis and helminth infections.

Nitazoxanide tablets can be taken with or without food, however oral suspension should be taken with food. For dispersible tablets, disperse the tablets in two tablespoonful of drinking water before administration. Diabetic patients should be aware that oral suspension contains 1.48 g of sucrose / 5 mL.

**Safety profile**

(a) *Side effects and tolerability*: Nitazoxanide is very well tolerated and minimal side effects such as headache, nausea and abdominal discomfort have been recorded, with no significant changes in hematological and clinical chemistry values. In clinical studies of 613 HIV-negative pediatric patients who received NTZ in oral suspension, the most frequent adverse events reported regardless of causality assessment were: abdominal pain (7.8%), diarrhea (2.1%), vomiting (1.1%) and headache (1.1%). These were typically mild and transient in nature. In placebo controlled clinical trials, the rates of occurrence of these events did not differ significantly from those of the placebo. None of the 613 pediatric patients discontinued therapy because of adverse events(19). Adverse events occurring in <1% of the patients are: (i) Digestive system–nausea, anorexia, flatulence, appetite increase; (ii) Skin–pruritus, sweat; (iii) Special senses–eye discoloration (pale yellow); (iv) Respiratory system–rhinitis; (v) Nervous system–dizziness; (vi) Urogenital system–discolored urine.

(b) *Contraindications*: Nitazoxanide is contraindicated in patients with a prior hypersensitivity to nitazoxanide. The drug must be administered with caution to patients with hepatic, biliary and renal disease.

(c) Use during pregnancy and lactation: no adequate and well-controlled studies in pregnancy and lactation.

**Drug interaction**

Nitazoxanide inhibits the cytochrome P4502C9 enzyme and that administration of nitazoxanide could, therefore, affect the metabolism of drugs that are metabolised by this enzyme such as warfarin, phenytoin etc. Tizoxanide is highly bound to plasma proteins (>99%). Therefore, caution should be used when administering nitazoxanide with other highly plasma protein bound drugs with narrow therapeutic index.

In summation nitazoxanide is an important antiparasitic and antiprotozoal drug with proven efficacy for treatment of Cryptosporidium infection and Giardiasis. It has the added advantages of a shorter duration of treatment (3 days) and lack of alteration of taste (seen with metronidazole) when used for treatment of Giardiasis. The role of the drug in treatment of *C. parvum* infection in AIDS patients also warrants further clarification. For the treatment of parasitic infestations it offers a wider spectrum
of activity in comparison with albendazole which includes _T. saginata_ and _T. solium_ against which the latter is ineffective although the duration of treatment required is longer (3 days). Its role in treatment of _H. pylori_ infection requires further exploration given the paucity of data comparing regimens incorporating the drug to the accepted standard regimens, although the drug carries the theoretical advantage of being effective against metronidazole resistant strains of _H. pylori_ in vitro. It may also be informative to explore its role in empirical treatment of children with chronic diarrhea and recurrent abdominal pain considering its wide coverage of the predominant infective etiological agents in such cases (particularly important in Indian setting). Thus, the drug offers a newer equally efficacious alternative for the treatment of Giardiasis, _C. parvum_ and helminthic infestations particularly in children with poor tolerance to metronidazole and albendazole although its role in these and other parasitosis deserve further clarification particularly in Indian setting.

REFERENCES


14. Davilla-Gutierrez CE, Vasquez C, Trujillo-Hernandez B, Hverta M. Nitazoxanide compared with quinbamide and mebendazole in...


