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REVIEW ON NITAZOXANIDE: A BROAD SPECTRUM ANTIPARASITIC AGENT

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ABSTRACT
Nitazoxanide is a thiazolide antiparasitic agent that shows excellent in vitro activity against a wide variety of parasites as well as some bacteria. It has been used as a single agent to treat mixed infections with intestinal parasites i.e. protozoas and helminths. It was originally discovered in 1975 by Jean Francois Rossignol & It was initially developed as a veterinary antihelminthic with activity against intestinal nematodes, cestodes, and liver trematodes & In humans, nitazoxanide has been reported to be effective against a broad range of parasites, including *Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum, Cyclospora cayetanens,* etc. The main objective of this review is to study detailed profile of nitazoxanide like physicochemical properties, pharmacokinetics, clinical uses, and adverse effects of Nitazoxanide.

KEYWORDS: Nitazoxanide, Antiparasitic agent, protozoa, helminths, etc.

INTRODUCTION
Intestinal parasitic infections rank amongst the most important causes of morbidity and mortality worldwide there has been very little recent effort by the pharmaceutical industry to develop agents to treat human parasitic infections.[1,2]

Nitazoxanide is a thiazolide broad-spectrum antiparasitic agent. In contrast with other agents, it is being primarily developed to treat human parasitic infections as well as bacterial infections. It was first described in 1975 by Jean Francois Rossignol and was initially developed as a veterinary anthelminthic with activity against intestinal nematodes, cestodes and liver trematodes.[3] In humans, nitazoxanide has been reported to be effective against a broad range of parasites including *Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum, Cyclospora cayetanensis, Trichomonas vaginalis, Vittaforma corneae, Encephalitozoon intestinalis, Isospora belli, Blastocystis hominis, Balantidium coli, Enterocytozoon bieneusi, Ascaris lumbricoides, Trichuris trichura, Taenia saginata, Hymenolepis nana, and Fasciola hepatica* as well as some bacteria including *Clostridium difficile & Helicobacter pylori.*[4-10]

Also, It has been used as a single agent to treat mixed infections with intestinal parasites i.e. protozoas and helminths. It is the first and only US FDA-approved drug for treatment of Cryptosporidium infection and is the first new drug approved for treatment of Giardia infection.[11,12]

Drug profile of nitazoxanide
Physicochemical properties of nitazoxanide
Nitazoxanide is chemically 2-(Acetolyloxy)-N-(5-nitro-2-thiazolyl) benzamide with molecular formula $C_{12}H_9N_3O_5S$. Its molecular weight is 307.28 g/mol. Nitazoxanide is a light yellow crystalline powder. It is poorly soluble in ethanol and practically insoluble in water. It has boiling point of 394°C & Melting point of 202°C. [13, 14]

Chemical class of nitazoxanide
Nitazoxanide belongs to the class of drugs known as thiazolides. The structure of nitazoxanide is shown in Fig.1.[15]

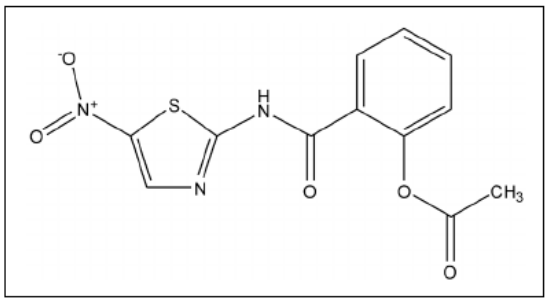

Fig. 1: Structure of Nitazoxanide.

Mechanism of action of nitazoxanide
There are many mechanisms of nitazoxanide. The most widely accepted mechanism of nitazoxanide is believed to be the disruption of the energy metabolism in

anaerobic microbes by inhibition of the pyruvate ferredoxin/flavodoxin oxidoreductase (PFOR) cycle.[16]

Pharmacokinetics of nitazoxanide

Nitazoxanide is moderately absorbed from the GIT with 67% of the drug eliminated in the feces & 33% in the urine. After absorption nitazoxanide is rapidly hydrolyzed to its desacetyl derivative, tizoxanide, which is the active metabolite. Following oral administration the peak plasma concentration is achieved within 1-4 hour. Tizoxanide is heavily protein bound in circulation over 99% and its urinary elimination half-life is 7.3 hour. On administration with food the bioavailability of nitazoxanide is almost doubled.[17]

Clinical uses of nitazoxanide

1] Antiprotozoal

A] Cryptosporidiosis

Nitazoxanide is the only US FDA approved drug for treatment of Cryptosporidium infection caused by *Cryptosporidium parvum.* It was approved for use in treating Cryptosporidium infection in children aged 1–11 years on the basis of 2 double-blind, randomized, placebo-controlled clinical trials in Egypt and Zambia with 50 children in each trial. A higher dose and/or extended duration of treatment may be required to achieve a sustained clinical and parasitological response in the irnmunecompromised population, especially those with CD4 count < 50 cells/ mm^3.[18,19]

B] Giardiasis

Nitazoxanide is approved for the treatment of infections due to *Giardia intestinalis* in patient's ≥ 1 year of age. Nitazoxanide may have a role in treating metronidazole resistant giardiasis. Open-label clinical studies in Mexico and Egypt evaluating nitazoxanide for treatment of mixed parasitic infections with protozoa and helminths have demonstrated eradication rates for *Giardia intestinalis* of 71%–94% with nitazoxanide treatment.[20,21]

C] Other protozoaI infections

Nitazoxanide has shown activity in clinical trials against numerous protozoan infections in addition to cryptosporidiosis and giardiasis. Five clinical studies from Egypt and Mexico have evaluated nitazoxanide's efficacy in treatment of *Entamoeba histolytica* and *Entamoeba* dispar and have found parasite eradication rates of 69% – 96%. Parasite eradication rates for *Blastocystis hominis* in clinical studies have ranged from 97% to 100%. One clinical study demonstrated a 100% eradication rate for *Isospora belli*.[22,23]

2] Anthelminthic

In various studies Nitazoxanide has been found to be effective against *Ascarias lumbricoides*, *Hymenolepis nana*, *Trichuris trichura*, *Enterobius*, *Ankylostomata*, *Stongyloides*, *Taenia saginata* and *Fasciola hepatica*. Clinical studies in Mexico have shown parasite elimination rates ranging from 48% for heavy infection to 100% for light infections with Ascarias. A three day course of nitazoxanide was demonstrated to have a higher cure rate and statistically significant egg reduction rate 21-30 days after treatment for trichuriasis in children aged 2-11 years, compared with a single 400mg dose of albendazole. Nitazoxanide has shown good activity against enterobiasis eradication (80-100%), ankylostomiasis (96%) and strongyloidiasis (94%). Nitazoxanide has been used as a single agent to treat mixed infections with intestinal parasites i.e. protozoas and helminths.[24,25]

3] Bacterial Infection

In vitro studies have demonstrated significant antibacterial activity of nitazoxanide against some bacteria, including *Clostridium difficile & Helicobacter pylori.*[26]

Side effects of nitazoxanide

Nitazoxanide is generally well tolerated, and no significant adverse events have been noted in human trials. Adverse events have been mild and transient and principally related to the gastrointestinal tract, such as abdominal pain, diarrhoea, and nausea. Nitazoxanide has been well tolerated up to the maximum dose of 4 g when taken with or without food, but the frequency of gastrointestinal side effects increases significantly with the dose level. [27, 28]

CONCLUSION

Nitazoxanide is a light yellow crystalline powder. It is poorly soluble in ethanol and practically insoluble in water. It has boiling point of 394°C & Melting point of 202°C. On administration with food the bioavailability of nitazoxanide is almost doubled. Nitazoxanide is a thiazolide compound with a broad spectrum activity against numerous intestinal protozoa, helminths, and anaerobic bacteria. It has been used as a single agent to treat mixed infections with intestinal parasites i.e. protozoas and helminths. This offers the convenience of single drug therapy of both type of infections. Considering the cost of repeated physician visits involved in the management of intestinal parasitic infections, the use of nitazoxanide is more cost effective than current treatment practices.

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