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REVIEW ARTICLE **OPEN ACCESS**

A Prospective Update on Nitazoxanide

V. M. Thorat[1], Abhijit Patil[2] and Abhijeet Nashte[3]
[1] Department of Pharmacology, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth "Deemed To Be University", Karad.
[2 , 3] Department of Medicine, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth "Deemed To Be University", Karad.

ABSTRACT
According to many studies, not only does NTZ kill protozoa and helminthes, but it is also used to treat and prevent a wide range of gram-negative organisms, protozoa, and helminthes. This is because NTZ is an antiprotozoal agent. Studies have provided conclusive evidence in support of this assertion. In addition, various studies were conducted to investigate the safety of ingesting NTZ and found that it is both safe and bioavailable for use in children and adults when taken orally. For both age groups, this was shown to be true.Thus, in our review, we have discussed the history, mechanism, adverse effects, and action of SARS-CoV-2.
Key words: *Mechanism, Adverse Effects, SARS-Cov-2, NTZ, Protozoa and Helminthes*

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INTRODUCTION

Studies have also concluded that nitazoxanide (NTZ) is an innovative drug that effectively combats parasites and protozoa, offering a broad range of effectiveness. It has been studied and found to be a nitrothiazole derivative.[1] Studies have shown that it works well against nematodes, cestodes, and trematodes that live in the intestines.[1] This is why it was first used to treat worms in animals. Furthermore, studies have concluded that, in 2002, "NTZ received approval from the US Food and Drug Administration (FDA) for human use".[2] Additionally, studies have shown that, "aside from its effectiveness in treating helminthiasis, it is also utilized for the treatment of intestinal protozoal infections".[3] In addition to this, studies have shown that, for individuals with weakened immune systems, like those with AIDS or HIV infection, this treatment is beneficial for addressing cryptosporidiosis and diarrhea caused by Giardia lamblia, as well as managing both conditions.[4,5,6,7,8] Researchers have found that NTZ can effectively treat flu, as well as Giardia intestinalis and Cryptosporidium parvum.[9] In addition, research has indicated that NTZ has demonstrated efficacy against the hepatitis C virus (HCV) and has proven to be effective in treating the hepatitis B virus (HBV).[10]

HISTORY

Studies have concluded that NTZ is a chemical molecule with the molecular formula 2-acetyloxy-N-5-nitro-2-thiazolyl.[11] Furthermore,according to studies, it has been classified as a member of the benzamide derivative of the nitrothiazole family. In 1975, after a study by Jean Francois Rossignol,[12] it was first used as a "pharmaceutical for the treatment of hepatic trematodes and intestinal cestodes".[12] Since 1996, this drug has been extensively used as an anthelminth in Latin America. In 2002, the FDA authorized the use of "NTZ for treating diarrhea caused by Cryptosporidium species and G. intestinalis in children". In 2004, "permission was expanded to include adults with G. Intestinalis".[12] Research has shown that "NTZ is useful in combating anaerobic bacteria, including Helicobacter pylori, bacteria, and Clostridium species".[13] The precise method by which NTZ works is still unclear; however, it operates by inhibiting the activity of the pyruvateferredoxin oxidoreductase (PFOR) enzyme, which is essential for anaerobic energy metabolism.[13]

MECHANISM

Studies have concluded that "NTZ interferes with the pyruvate ferredoxin oxidoreductase (PFOR) enzyme cycle, which is essential for the energy metabolism of anaerobic bacteria."[14] It messes with the

mitochondrial membrane and damages cell membranes.[14] Furthermore, studies have shown that ,the PFOR protein's DNA sequence seems to be the same in Giardia lamblia and Cryptosporidium parvum.[15] As a result, according to researches, its effects was on drug detoxification, unfolded protein response, anti-cytokine activity, and c-Myc suppression, this chemical may also impede the growth of cancer cells. Hence, studies also concluded that after being given, it is broken down into its active metabolites, tizoxanide and tizoxanideglucur.[15]

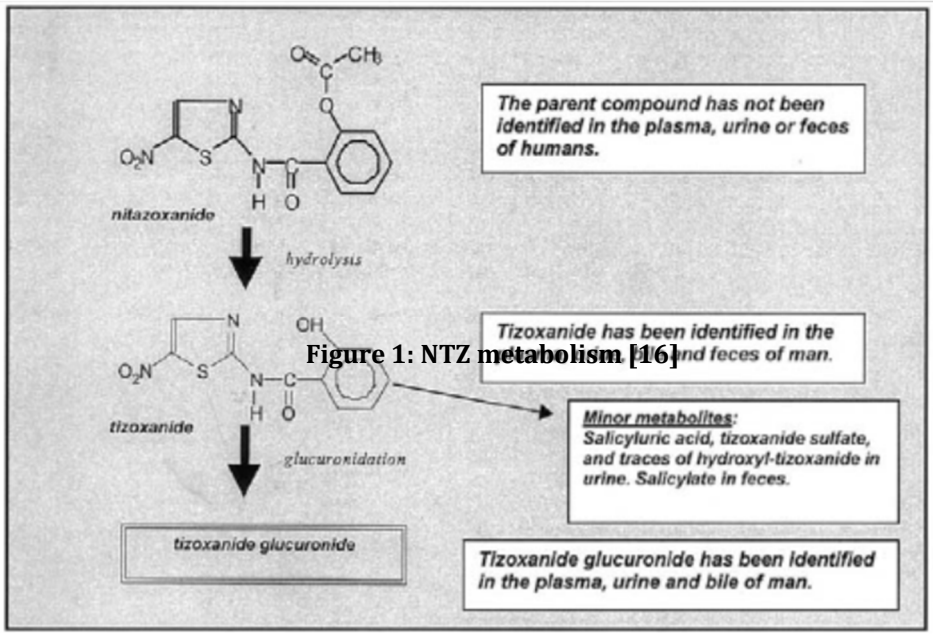

Figure 1: NTZ metabolism [16]

ADVERSE EFFECTS

Studies have been proved that, there have been no major negative incidents reported during human trials.[16] Studies have also shown that, "the most common and least severe adverse events include mild and temporary gastrointestinal symptoms like nausea, vomiting, and diarrhea whereas, adverse events such as anorexia, flatulence, increased appetite, enlarged salivary glands, fever, infection, malaise, elevated creatinine levels, elevated levels of alanine aminotransferase in serum, pruritus, sweat, pale yellow sclerae, rhinitis, dizziness, and discolored urine were reported in more than 1% of the over 2000 HIV-uninfected patients who took part in clinical trials".[7] In a study where, "patients were treated with NTZ did not show significant changes in their electrocardiography, vital signs, hematologic, clinical chemistry, or urinalysis parameters".[17] Studies have concluded that, when NTZ is taken within the recommended dosage of 4 g, it has been found to be well tolerated regardless of whether it is taken with or without meals.[18]

DOSE & PHARMACOKINETIC PROPERTY

According to the findings of research, NTZ may be administered orally as an oral solution (100 mg/5 mL) or as a tablet (500 mg), and it is required to be taken twice a day for a total of three consecutive days. Studies have also concluded that eating increases the rate at which NTZ is absorbed into the body. However, whereas studies have also concluded that urine is responsible for excreting 25% of the absorbed oral dosage, bile is responsible for excreting 75% of it.[19] Furthermore, research has shown that after being taken by mouth, NTZ reaches a plasma concentration of 2 mg/L within 2–4 hours, and it is completely eliminated from the body through the urine after 7.3 hours. According to studies, plasma esterase's action destroys it in the plasma and causes the production of similarly active des-acetyl derivatives (des-acetyl-nitazoxanide) like tizoxanide (TTZ).[20] Additionally, studies have also concluded that NTZ is distinguishable from other similar drugs by its very high level of plasma protein binding, which is more than 99%. Researchers have found that TTZ then goes through conjugation, mostly by glucuronidation, to make tizoxanide glucuronide, which is the main NTZ metabolite in humans. TTZ is known to retain some action in its own right.[21] Different in vitro studies have shown that NTZ and TTZ do not have an inhibitory effect on cytochrome P450. Because of this, it is expected that taking NTZ with other drugs will not have any major effects.[20]

ANTIVIRAL EFFECTS OF NTZ

As shown by several research and laboratory studies, NTZ has antiviral activity that is effective across a wide range of applications. As a result of this, significant attempts were made to implement this effect in clinical practice. In addition, studies have shown that new pharmaceutical forms of NTZ with controlled release are being made to meet the growing need for this treatment. In addition to one strain of influenza B, NTZ and its active metabolite, TTZ, have been shown to suppress the replication of 16 other influenza H1N1 strains.[22] NTZ synergized the effects of oseltamivir against influenza A HINI and avian influenza A H5N9. This was shown in a previous study.[23] NTZ is effective against influenza because it inhibits the maturation of viral hemagglutinin at the post-translational stage. This is the mechanism by which NTZ works. NTZ, on the other hand, had no effect on viral neuraminidase, M2 protein, viral entrance, viral adsorption, or viral infectiousness.[24] Furthermore, NTZ increases the synthesis of interferon-alpha (IFN-) and beta by fibroblasts, both of which have inhibitory effects on the maturation of the influenza H1N1 virus[25] Studies have concluded that certainly, both in vitro and clinical trials have shown that nitazoxanide and oseltamivir work very well together. Since they don't directly affect viral RNA or protein, resistance should be less likely to form. Researchers looked at hepatitis C and the influenza A virus (PR8 strain) and found that the gene ratio of resistant strains did not change after being exposed to nitazoxanide. The viruses were still susceptible to other directly acting antivirals. To support this claim, we point out that these studies showed that the gene ratio of resistant strains was not observed. These findings provide credence to the theory that the effect of NTZ is more cell-mediated than virus-mediated, as the term suggests.[26]

NTZ & SARS-Cov-2

Studies have shown that ,"the presence of the angiotensin-converting enzyme 2 (ACE2) receptor is observed at significant levels in various cells, such as pulmonary alveolar type II pneumocytes, endothelial cells, and lung macrophages in COVID-19".[11]Furthermore, according to studies ,"the host cellular trans-membrane protein serine 2 (TMPRSS2) enhances the virus's attachment to ACE2 receptors by trimming the SARS-CoV-2 spike protein (SP)".[27] Furthermore, studies have also concluded that, the cytopathogenic consequences and immunological responses triggered by SARSCoV-2 infection include cell death (pyroptosis) and the generation of damage-associated molecular patterns (DAMPs).[28] Studies also concluded that, TLRs 7 and 8 play a crucial role in detecting the process, functioning as an RNA sensor to identify the NLRP3 inflammasomes.[28] Additionally, studies concluded that "pro-inflammatory cytokines such as interleukins (IL-6 and IL-8), macrophage inflammatory protein-1 alpha (MIP-1), and tumor necrosis factor-alpha (TNF-alpha) are released by alveolar macrophages when the cellular NLRP3 inflammasome is activated".[29] In addition to above, studies concluded that ,these "pro-inflammatory cytokines cause the immune cells monocytes, macrophages, and activated T cells to eliminate SARS-CoV-2".[30] Furthermore, studies told that "a type I interferon (IFN) response controls the early stage of COVID-19 by reducing viral multiplication and the cytopathic effect".[29] Additionally, studies concluded that , immunological escape happens when SARSCoV-2 lowers the level of type I IFN, which causes an abnormal immune response with too many pro-inflammatory cytokines.[31] Furthermore, studies concluded that ,cytokine storms cause acute lung injury, acute respiratory distress syndrome, and chronic obstructive pulmonary disease.[32]

Immunological effects of NTZ in COVID-19

Studies have concluded that NTZ is regarded as a potent autophagy activator in addition to its modulatory effect on the IFN pathway. Studies have concluded that , it has been reported that autophagy activators like ivermectin play a significant role in the process that results in the cytoplasmic breakdown of SARS-CoV-2 infected cells. [33] This is reinforced by the fact that autophagy activators may cause the breakdown of cytoplasm in the cells they are introduced to. The induction of autophagic cell death is beneficial for managing and reducing the quantity of inflammation that is present, as well as the length of time that inflammation is present. This is accomplished by reducing the amount of time that inflammation is present. This is due to the fact that the level of inflammation that is present may be reduced if autophagic cell death occurs. This is because the death of autophagic cells is beneficial for controlling and reducing the level of inflammation that is present. The reason for this is due to the fact that the death of autophagic cells is beneficial. In the immune cells that are present in the surrounding region, necrotic cells are regarded as potent stimulators of the inflammatory response. [34] If necrotic cells are eliminated as part of the autophagic function, this may result in a reduced inflammatory response as well as a reduction in the production of cytokines that promote inflammation. This may be the case if the autophagic function is carried out. If the autophagic function is carried out, then this may be the case. Because of this, the induction of autophagic death by NTZ may very well be the driving mechanism that lies behind its beneficial effect on COVID-19.[35] Studies have also shown that the SARS-CoV-2 infection

turns on the mammalian target of rapamycin (mTOR), which makes it easier for the virus to bind to ACE2 and cause lung lymph angioleiomyomatosis. This leads to severe inflammation in the lungs. Furthermore, research has shown that the mTOR pathway is thought to be a negative regulator of cell autophagy, which can make inflammatory responses caused by viruses stronger.[36] In their study, Lam et al. [37] demonstrated that NTZ suppresses autophagy via suppressing mTOR. As a result, NTZ may have the ability to have an effect on mitigating the pathogenesis of SARS-CoV-2 and the inflammatory disorders that are linked with it. In addition to this, studies have also concluded that NTZ has also been shown to have important effects on the immune system, such as stopping macrophages from working and stopping the release of cytokines that cause inflammation.[38] Recent studies have shown that SARS-CoV-2 infection, which is causing the progression of acute respiratory distress syndrome and acute lung injury, may be the cause of macrophage activation syndrome and high levels of pro-inflammatory cytokines.[39]

CONCLUSION

According to studies, NTZ is a new broad spectrum antiparastic chemical agent that works against many different types of intestinal protozoa, helminths, and anaerobic bacteria. It is now licensed to treat infections due to Cryptosporidium species in children and adults, as well as infections due to G. intestinalis. The drug has a limited number of potential side effects and only has to be treated for a short period of time. In spite of this, there is still a need for more studies to be conducted on its molecular mechanisms of action, bioavailability, and drug interactions in order to determine whether or not it can be utilized safely across a variety of patient populations.

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