

# Therapeutic uses of metronidazole and its side effects: an update

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**Abstract.** – **OBJECTIVE:** Metronidazole is an antibiotic widely used in different medical conditions such as trichomoniasis, amoebiasis, and giardiasis among others. Its use has been associated with toxicity; however, it is not well characterized. In this review, we discuss the different therapeutic uses of metronidazole and its side effects in order to aid future investigation in this field.

**MATERIALS AND METHODS:** Relevant information, original research articles, clinical trials, and reviews were collected from PubMed to know the state of the art of the different therapeutic uses of metronidazole and the reported side effects.

**RESULTS:** Metronidazole was used by the first time in 1959, to treat an infection caused by *Trichomonas vaginalis*; subsequently, new therapeutic properties were discovered. Nowadays, Metronidazole is used to treat infections caused by *Bacteroides*, *Fusobacteria* and *Clostridia*, rosacea, oral and dental infections, bone and joint infections, gynecologic infections, endocarditis, septicemia, and respiratory tract infections. It also can be used to treat Crohn's disease or even like prophylaxis, before surgical procedures. Metronidazole is well tolerated with mild to moderate side effects such as nausea, abdominal pain, and diarrhea. Nevertheless, serious neurotoxicity, optic neuropathy, peripheral neuropathy, and encephalopathy have been reported in rare cases. Their genotoxic effects observed in animal models are controversial in humans.

**CONCLUSIONS:** The therapeutic use of metronidazole had increased worldwide. Even though it is widely used, metronidazole has been associated with neurotoxicity and genotoxicity; however, its side effects are not well established. Conversely, its veterinary use is restricted in some countries because of its tumor association. Subsequently, further studies are needed to discover the secure use of metronidazole and describe new usages for this drug.

*Key Words:*

Metronidazole, Therapeutic uses, Side effects.

## Introduction

Metronidazole is a synthetic antibiotic derivatized from azomycin, a nitroimidazole produced by the genera *Actinobacteria* and *Proteobacteria*. In 1959, this compound was used for trichomoniasis treatment, an infection caused by the protozoan *Trichomonas vaginalis*. Further, metronidazole has been effective against dysentery and liver abscess produced by the intestinal protozoan parasite, *Entamoeba histolytica*. It also was efficacious against *Giardia lamblia*, another intestinal parasite that causes malabsorption and epigastric pain<sup>1</sup>. Metronidazole is available as orally, intravenously, vaginally and rectally presentations, although the most clinically used is the oral presentation. Its oral dosage forms of 250 or 500 mg are rapidly absorbed and distributed almost to the entire body. The liver is the main organ responsible for metabolizing metronidazole, where this is hydroxylated, acetylated and or conjugated with glucuronides. The metabolites are finally excreted mainly by the kidneys<sup>2-4</sup>.

Metronidazole was introduced in 1959 for trichomoniasis treatment; however, subsequently, new pharmacological properties were uncovered<sup>5</sup>. Due to the high cost and long time needed for research and development of novel therapeutic molecules, exploring new uses of existing drugs is a possible solution to treat infectious diseases<sup>6,7</sup>. In this review, we recapitulate the current clinical uses of metronidazole and discuss their side effects.

## Pharmacodynamics

The mechanism of action of metronidazole has not been fully elucidated. However, its nitro group reduction by anaerobic organisms appears to be responsible for the cytotoxic and antimicrobial effects. The mechanism described for this drug is summarized here:

Metronidazole crosses the membrane of the cell target by passive diffusion; then, its nitro group is reduced to nitro radicals by ferredoxin or flavodoxin.

The selectivity of metronidazole for anaerobic or microaerophilic microorganisms is due to the redox potential of their electron transport components, which are responsible for nitro group reduction and generate toxic metabolites.

These metabolites such as N-(2-hydroxyethyl) oxamic acid and acetamide can react with DNA and form adducts with guanosine<sup>1,5</sup>.

### **Antibiotic and Antiparasitic Uses**

Metronidazole is usually, very effective to treat infections caused by anaerobic or microaerophilic microorganisms, such as *Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*, *Clostridium difficile*, *Helicobacter pylori*, among others<sup>1</sup>.

### **Amoebiasis**

Amoebiasis is an infection caused by the protozoan *Entamoeba histolytica* that can result in amebic colitis or amebic liver abscess. Optimal treatment, usually effective for intestinal or hepatic infections by *E. histolytica*, includes three daily oral doses of 750 mg of metronidazole for 5 or 10 days<sup>8-10</sup>.

### **Giardiasis**

*Giardia lamblia* is the most common intestinal parasite as the etiological agent of diarrheal around the world; its treatment is based on 250 mg of the drug thrice daily for 5 to 7 days<sup>11</sup>.

### **Trichomoniasis**

*Trichomonas vaginalis* is a protozoan parasite responsible for one of the most sexually transmitted diseases, and its management includes a 2 g single dose of metronidazole. However, if the single dose fails, the treatment can be administered during 7 days<sup>12,13</sup>.

### **Bacterial Vaginosis**

Metronidazole is useful to treat some bacterial infections. 500 mg are administered orally twice a day for a week. There is a second scheme consisting of a single dose of 2 g of metronidazole, mainly used to treat *Gardnerella vaginalis*. A gel presentation of 0.75% metronidazole, administered intravaginally twice a day for five days is also effective for bacterial vaginosis<sup>13,14</sup>.

### **Helicobacter Pylori**

*H. pylori* causes peptic ulcers disease and it is associated with stomach cancer. Metronidazole

in combination with bismuth and tetracycline for two weeks is highly effective for *H. pylori* eradication. Dosage may vary from 200 to 500 mg three or five times daily. Metronidazole also has been combined with bismuth and amoxicillin or with acid suppression regimens<sup>15-17</sup>.

### **Clostridium Difficile**

*C. difficile* colitis is a major cause of nosocomial infections, causing morbidity and mortality in patients. Its treatment is based on oral metronidazole, 500 mg three times a day for 10-14 days<sup>18-20</sup>.

### **Anaerobic Infections**

Metronidazole is also effective against anaerobic bacteria (for example, *Bacteroides fragilis*) in combination with other antibiotics such as cefazolin, cefuroxime, ceftriaxone, quinolone, ceftazidime, cefepime, carbapenems, piperacillin or tazobactam depending on the infection type. Metronidazole dosage varies in anaerobic infections; however, 500 mg administered intravenously every 8 h is the most common dose used<sup>13,21</sup>.

### **Crohn's Disease**

Crohn's disease is a chronic inflammatory bowel disease, which has been hypothesized, is the result of an abnormal immune response to the gut microbiome in susceptible subjects. Metronidazole is used for the treatment of Crohn's disease and its effectiveness has been evaluated in several clinical trials, suggesting that metronidazole has therapeutic benefits against the symptoms, such as perianal discharge and pain. However, controlled clinical trials are needed to establish the efficacy of metronidazole for Crohn's disease<sup>13,22</sup>.

### **Surgical Prophylaxis**

Infections after surgical procedures contribute to higher rates of mortality; however, a single dose of 500 mg metronidazole reduces the risk of postoperative anaerobic infections when is used as a prophylactic treatment in appendicitis, but also is used in prophylactic treatment in surgical procedures for the colon, head, and neck<sup>13,23-24</sup>.

### **Rosacea**

Rosacea is a cutaneous disease of uncertain etiology characterized by flushing, erythema, papules, pustules and telangiectasia that affect the cheeks, nose, eyes, chin and forehead<sup>26</sup>. There are various treatments available for rosacea, but topical metronidazole gel and azelaic acid appear to be effective and safe according to multiple

clinical trials. 200 mg of metronidazole, administered orally twice a day for 12 weeks, is efficacious when tetracycline is not effective in rosacea treatment<sup>25-27</sup>.

### **Adverse Effects of Metronidazole**

Metronidazole is well tolerated with mild to moderate side effects such as nausea, abdominal pain, and diarrhea. Serious neurotoxicity, optic neuropathy, peripheral neuropathy, and encephalopathy have been reported in rare cases. Metronidazole neurotoxicity is not fully elucidated. Rao and colleagues suggested that the free radicals damage nerves, while Alston, proposed the formation of a thiamine analog derived from the metronidazole that may result in a nutrition deficiency-like neuropathy. On the other hand, Scholars proposed that the union of metronidazole and its metabolites to RNA provokes the inhibition of protein synthesis and axonal degeneration of nerve fiber<sup>13,28-31</sup>.

Peripheral neuropathy is uncommon with short term-use of metronidazole (4 weeks). Yet, the risk of peripheral neuropathy increases when the dose is higher than 42 g; however, this effect is reversible when discontinuing the drug therapy. Cerebellar dysfunction, visual impairment, vestibulotoxicity, cochleotoxicity, ataxic gait, dysarthria, and seizures also have been reported when metronidazole is used<sup>32-34</sup>.

### **Genotoxicity of Metronidazole**

Metronidazole induces single and double DNA strand breaks, especially in AT clusters. It also forms adducts and GC-CG transversions. The clastogenic effect is related to its hydroxylated derivatives formed during its biotransformation by cytochrome P450<sup>35-36</sup>.

For the mouse micronucleus test and chromosomal aberration in bone marrow cells, metronidazole showed a dose-dependent effect, inducing cytogenetic damage in both models, but did not show alteration in the rate of polychromatic/normochromic erythrocytes as a measure of its cytotoxic effect<sup>37</sup>. In combination with miconazole, metronidazole was tested for its teratogenic effect on mice, showing strong potentiation for the production of skeletal defects when administered together<sup>38</sup>.

Few studies have been done on human genotoxicity; metronidazole and its analogues did not induce sister chromatid exchanges in human lymphocytes with or without S9 mixture, indicating that the drug only induced DNA minor ruptures while its cytotoxic effect was observed only un-

der metabolic activation<sup>39</sup>. Also, it has been reported, that metronidazole can induce an increase in chromosomal aberrations and chromatid and isochromatic breaks in the cell of patients treated with therapeutic doses of metronidazole<sup>40</sup>.

In a study<sup>41</sup> where patients were treated with metronidazole 4 hours before surgery to remove colon tumors, a high concentration of the drug and its hydroxyl metabolite were found inside the lesion and metastatic tumors, but not in healthy tissue.

In carcinogenesis, its role is controversial because metronidazole can induce genotoxic effects in human cells *in vitro* and *in vivo*; however, it has been established with a carcinogenic role in mice and rats. According to the IARC (International Agency for Research on Cancer), there is evidence to consider metronidazole as an animal carcinogen, but insufficient evidence in humans<sup>42</sup>. More studies are needed for clarifying the role of metronidazole in human cancers.

## **Conclusions**

Metronidazole was first described in 1959 as a therapeutic agent to treat *Trichomonas vaginalis* infection; over time, metronidazole has been used against *Giardia lamblia*, *Entamoeba histolytica*, *Clostridium difficile*, *Helicobacter pylori* and anaerobic bacteria. Metronidazole is also used to treat Crohn's disease, rosacea, and as a prophylactic after a surgical procedure. A lot of work must be performed to elucidate new uses of metronidazole; however, some more studies are also needed to find alternatives or variations of this drug because of the increase of metronidazole-resistant microorganisms.

Metronidazole is widely used to treat a variety of infections due to its high efficacy compared with others drugs; however, their side effects must be considered. Genotoxicity and neurotoxicity studies on humans should be done to clarify the role of metronidazole in human health.

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### **Conflict of Interest**

The Authors declare that they have no conflict of interest.

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