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Investigate The Safety Profile of Metronidazole, Exploring Potential Adverse Effects And Toxicity

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ABSTRACT

This analysis takes an in-depth look at the safety profile of metronidazole, a popular antibiotic that works well against anaerobic bacteria and parasites. The development of medicine over time, starting with the discovery of azomycin, demonstrated its ability to treat diseases, particularly trichomoniasis and giardiasis. The way metronidazole works is that it forms a cytotoxic intermediate intracellularly that damages the bacterial DNA, thereby clearing the anaerobic infection. The pharmacology of metronidazole encompasses diverse formulations, rapid absorption, and extensive tissue penetration. While generally well-tolerated, metronidazole presents considerations for dosage, duration, and patient-specific factors to minimize toxicity risks. Despite its efficacy, rare instances of resistance and adverse effects, such as neurotoxicity and hepatotoxicity, warrant cautious use.

This review delves into metronidazole-induced complications, including neurotoxicity, encephalopathy, and pancreatitis. Risk mitigation and monitoring strategies are outlined, emphasizing patient assessments, dosage adjustments, and organ function monitoring. Specific considerations for pregnant individuals and potential cytogenetic effects are also discussed.

In conclusion, while metronidazole remains a cornerstone in antimicrobial therapy, its judicious use requires an understanding of therapeutic benefits and associated risks. The review provides insights into metronidazole's intricate pharmacology, toxicity factors, and strategies for optimizing patient safety during clinical use. Ongoing research and vigilant clinical practices are crucial for ensuring the sustained efficacy of metronidazole across diverse medical contexts

Keywords: *Metronidazole, antimicrobial therapy, anaerobic bacteria, parasites, pharmacology, resistance, adverse effects, neurotoxicity, hepatotoxicity, drug interactions*

1. INTRODUCTION

Metronidazole (1-[2-hydroxyethyl]-2-methyl-5-nitroimidazole) is a nitroimidazole drug that works well against anaerobic microscopic organisms and a few parasites. The drug is extensively used because to its excellent oral bioavailability, tolerability, and ability to permeate a variety of tissues, including the central nervous system. Apart from treating infections caused by bacteria and protozoa, metronidazole is also commonly used to treat inflammatory bowel disease in humans and animals1

Metronidazole was initially developed in the 1950s during Rhone-Poulenc's search for a potent antitrichomonal drug to address vaginal trichomoniasis. According to preliminary studies, the active ingredient in the crude extract of Streptomyces bacteria, which effectively kills Trichomonas vaginalis, was identified as azomycin, an earlier discovered nitroimidazole antibiotic[2]. Metronidazole, a synthetic derivative of azomycin, proved to be extra effective against T. vaginalis and displayed fewer toxicity. Originally 8823 RP. It was later renamed metronidazole.

The beginning of the decade saw the discovery of the 5-nitroimidazole group, which was tested biologically, revealing both antiprotozoal and antibacterial properties. A significant breakthrough occurred in 1959 with the identification of trichomonacidal activity of 1-(2-hydroxy-ethyl)2-methyl-5-nitroimidazole, commonly known as metronidazole[3]. Metronidazole emerged as a successful remedy for trichomoniasis in both sexes and also demonstrated efficacy in treating infections caused by the protozoan Giardia.

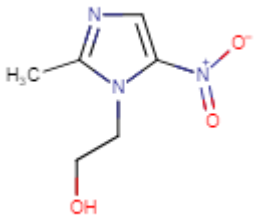

Fig. 1. **Molecular structure of Metronidazole**

Mechanism of Action Metronidazole

The capacity of metronidazole and other nitroimidazoles to intracellularly decrease the nitro group to produce nitroso-containing intermediates makes them prodrugs that are especially useful for anaerobic microscopic organisms. The mechanism of action of metronidazole involves its activation within the microbial cell, particularly by susceptible anaerobic organisms. The detailed breakdown of the steps in the mechanism:

Entry into the Cell: Metronidazole enters the microbial cell through passive diffusion[4].

Intracellular Activation: Once inside the cell, metronidazole undergoes reductive activation by intracellular transport proteins by altering the chemical structure of pyruvate-ferredoxin oxidoreductase[5]. This reduction is facilitated by electron transport proteins within the microbial cell.

Electron Transfer: The key step involves the transfer of electrons to the nitro group of metronidazole. This reduction process occurs under anaerobic conditions and is vital for activating the drug[6].

Formation of Reactive Intermediates: Reactive intermediates are created when the nitro group is reduced, including nitroso-free radicals. These reactive species are highly cytotoxic.

DNA Damage: The cytotoxic intermediates generated by metronidazole interfere with the microbial cell's DNA structure and function. They induce breaks in the DNA strands and disrupt the synthesis and repair processes[7].

Inhibition of Nucleic Acid Synthesis: Metronidazole disrupts the normal synthesis of nucleic acids (DNA and RNA) in the microbial cell by interacting with DNA structures and inhibiting the activity of enzymes involved in nucleic acid synthesis.

Cell Death: The cumulative effects of DNA damage, inhibition of nucleic acid synthesis, and disruption of other cellular processes lead to the death of the microbial cell.

Selective Toxicity: The reductive environment required for metronidazole activation is more prevalent in anaerobic microorganisms, making the drug selectively toxic to these pathogens. Aerobic cells typically lack the necessary reducing conditions for metronidazole activation.

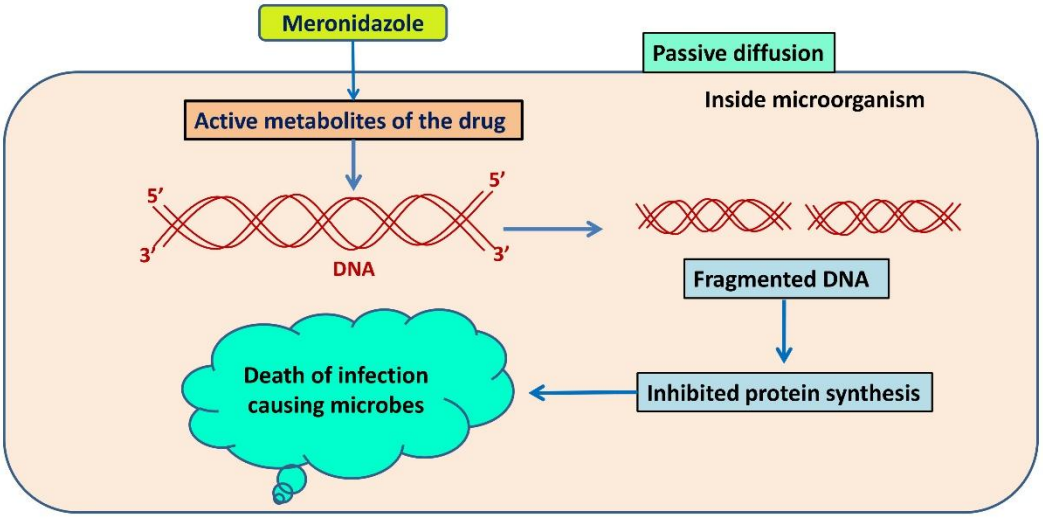

Fig. 2. **Mechanism of action of Metronidazole**

Metronidazole is active against Giardia (syn. G. duodenalis, G. lamblia, G. intestinalis) and Entamoeba histolytica in addition to T. vaginalis. Giardia seldom develops resistance, and clinical efficacy is typically more than 90%. However, in vitro testing has shown that clinical isolates had decreased metronidazole susceptibility[8,9], which is concerning.45,46 The trichomonad known to induce gastroenteritis, Dientamoeba fragilis, is active against nitroimidazoles in vitro[10].

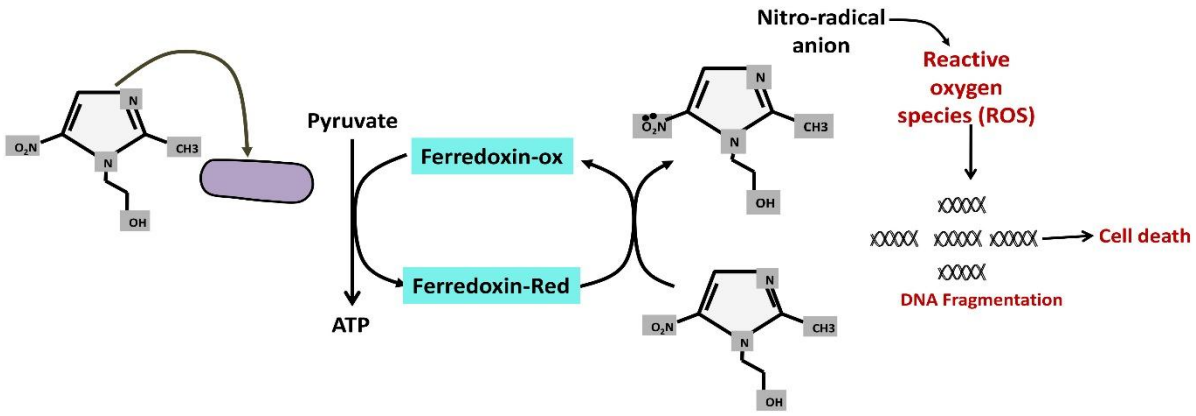

Fig. 3. **Cellular Mechanism of action of Metronidazole**

Pharmacology of Metronidazole

Metronidazole, a versatile antimicrobial agent, is commercially accessible in diverse formulations, spanning oral capsules,

tablets (both immediate and extended release), intravenous solutions, topical gels, creams, lotions, and vaginal gels[11,12]. Pharmacies commonly synthesize oral metronidazole suspension, despite the fact that it is not commercially available13. The product and indication determine the different dosing schedules, with an intravenous loading dose followed by maintenance doses recommended. The duration of therapy typically ranges from 1 to 10 days, contingent on the nature of the infection and the patient's condition, although caution is urged for durations surpassing 1 month due to potential adverse effects[14].

In terms of absorption, oral metronidazole exhibits rapid and near-complete absorption, with bioavailability approaching 100%. Rectal, topical, and vaginal administrations also result in substantial absorption. The range of peak serum values is 12–40 μg/mL, occurring within hours of administration. Metronidazole, characterized by its lipophilic nature and low protein binding, has a moderate to large volume of distribution, ensuring its penetration into various tissues, including inflamed cerebrospinal fluid, saliva, bile, and abscesses[15].

The pharmacological profile of metronidazole extends to specific populations, as it crosses the placental barrier and enters breast milk, emphasizing caution during the first trimester. Additionally, the drug undergoes oxidation as its primary elimination pathway, with active metabolites excreted in feces or urine. Hepatic diseases may necessitate dose adjustments, while patients with end-stage renal disease may experience altered drug half-life and clearance[16].

Metronidazole's efficacy is maintained across different dialysis modalities, with notable removal during conventional and continuous hemodialysis. Though renal dose adjustment is not universally recommended, caution is advised for long-term therapy. The pharmacological nuances of metronidazole, detailed here, provide a comprehensive understanding of its varied formulations, administration, absorption, distribution, metabolism, and elimination, catering to diverse patient needs and conditions.

The drug demonstrates exceptional oral absorption, ranging from 98% to 100%, with rectal administration showing efficacy within the range of 59% to 94%. Vaginal formulations[17], including cream and gel, achieve absorption rates of 20% and 56%, respectively, while topical application results in a 2% absorption rate. Time to peak concentrations varies, with oral administration peaking at 1-2 hours, rectal at 3 hours, and topical formulations at 8-12 hours[18]. Peak serum concentrations following intravenous administration range from 25 to 40 μg/ml, with varying levels observed after different oral doses and topical applications.

The volume of distribution differs between adults (0.55 L/kg) and neonates (0.54-0.01 L/kg). Metronidazole exhibits notable penetration into various tissues and fluids, including cerebrospinal fluid (CSF), bile, epithelial lining fluid, saliva, abscesses, and peritoneal fluid, with concentrations approximating or exceeding serum levels. Metabolically, the drug undergoes oxidation and glucuronidation, primarily eliminated through the cytochrome P450 system.

Excretion of metronidazole involves both unchanged drug (5%-18%) and metabolites (60%-80%), with notable removal during hemodialysis (25%-45% over 4 hours) and peritoneal dialysis (10% over 75 hours). The drug exhibits minimal protein binding (<20%). In pregnancy, caution is advised, particularly in the first trimester (Category B), while lactating individuals should be aware of the drug's significant penetration into breast milk. This comprehensive insight into metronidazole's pharmacokinetics and pharmacodynamics aids clinicians in optimizing its therapeutic use across various clinical scenarios[19]

Metronidazole resistance

Metronidazole resistance in trichomonads, notably T. vaginalis, involves intricate steps and various contributing factors. Reports of resistance have surfaced, with some showing clinical insignificance due to resistance levels below therapeutically obtainable concentrations or non-anaerobic conditions. The presence of oxygen in cultures can elevate the redox potential, preventing drug reduction and leading to erroneous indications of resistance. Biochemical mechanisms, potentially related to carboxylation reactions in T. vaginalis, play a role. While truly resistant laboratory-developed organisms exist, they are cross-resistant to various nitroimidazoles. Notably, over two decades of metronidazole use has not yielded clinically significant resistant organisms, suggesting that a single-gene change conferring resistance may be incompatible with cell survival. Drug inactivation during treatment, often seen in refractory cases, involves the absorption of metronidazole by other organisms in the environment. Theoretical mechanisms of resistance, such as altered membrane permeability, pose challenges as nitroimidazoles enter cells passively. A more logical resistance mechanism may involve a mutation in enzymes of the pyruvate phosphoroclastic reaction, hindering nitro group reduction. Noteworthy is recent research inducing metronidazole resistance in Bacteroides, revealing reduced levels of pyruvate

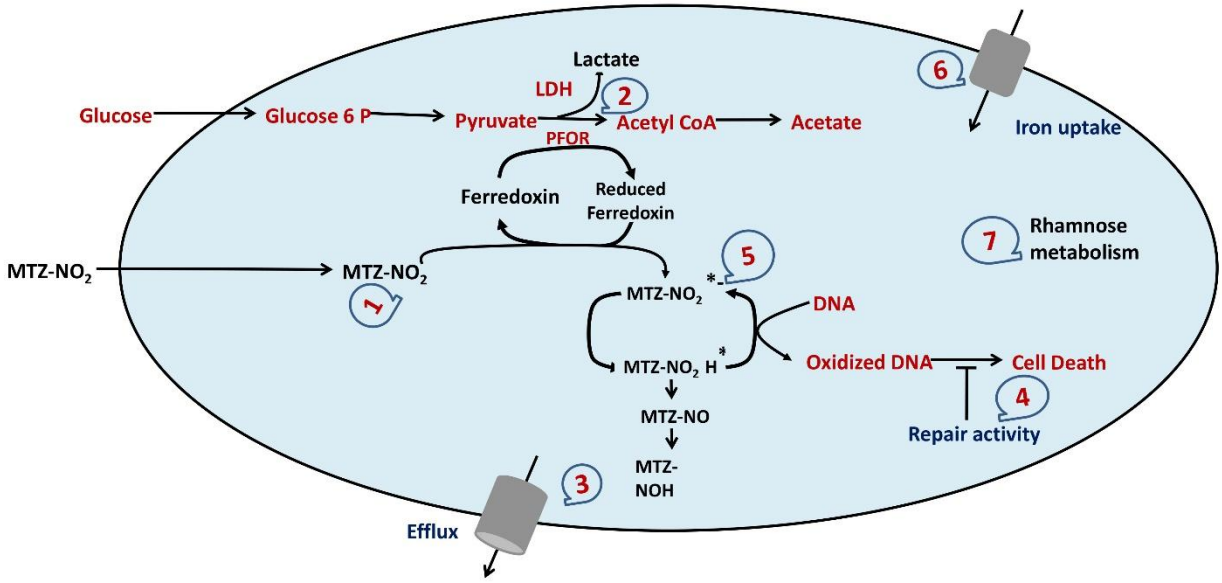

Fig. 4: Metronidazole resistance mechanism against Trichomoniasis

dehydrogenase. Continued exploration of resistance mechanisms is vital for developing effective strategies against emerging challenges in the clinical use of metronidazole[20,21,22].

Metronidazole Adverse Effect

Metronidazole, a widely used antibiotic, may induce cerebellar toxicity and neurotoxic effects. Common adverse reactions include metallic taste, confusion, nausea, vomiting, diarrhea, headache, ataxia, seizures, cochlear toxicity, and peripheral neuropathy. Neurological symptoms, ranging from headache and altered mental status to seizures and focal deficits, may occur. Neurotoxicity can lead to neuropathy, ataxic gait, dysarthria, seizures, and encephalopathy, presenting as a rare complication of metronidazole use. Discontinuation of metronidazole usually results in symptom improvement, with complete resolution upon cessation. The potential for neurotoxicity underscores the importance of cautious use and monitoring, especially in cases of prolonged or excessive administration[23].

Toxicokinetic:

Metronidazole, manifesting as crystalline structures of a pale-yellow hue and exhibiting restricted solubility in aqueous and alcoholic mediums, undergoes efficient absorption within the gastrointestinal tract. The compound achieves heightened concentrations within physiological compartments, including the plasma, bone, peripheral tissues, and the central nervous system (CNS). The pharmacokinetic profile reveals a discerned half-life of approximately 8 hours in mammalian plasma, with a variation spanning 3 to 13 hours in canines. Metronidazole undergoes hepatic biotransformation via processes of oxidation and glucuronide formation, primarily subject to excretion by the renal system. Noteworthy is its traceable presence in cerebrospinal fluid, saliva, and milk during periods of exposure[24].

Mechanism of Toxicity[25]: The mechanism of toxicity of metronidazole involves its capacity to interrupt nucleic acid synthesis, which enables it to exert specific antiparasitic and bactericidal actions. Moreover, when combined with ethanol, it can cause a disulfiram-like response that prevents aldehyde dehydrogenase from functioning.

Short-Term and Acute Toxicity:

Animal Research: Symptoms of an overdose in animals can include vomiting, nystagmus, decreased appetite, and ataxia**.**

Studies on Humans: No known acute fatal dose has been administered to humans. Ataxia, emesis, and nausea are typical side effects. When used in conjunction with ethanol, a disulfiram-type response may occur, causing symptoms like headache, dyspnea, flushing, nausea, and low blood pressure.

Long-Term Toxicology:

Research on Animals: Long-term studies in rats and mice show an increased risk of tumor growth.

Human Studies: In humans, chronic exposure can cause symptoms as parenthesis, nausea, headaches, anorexia, emesis, metallic tastes, and numbness in the extremities. There have been reports of neurological side effects, such as vertigo, sleeplessness, and dizziness. Moreover, the white blood cell count may be reversibly suppressed**.**

Drug Interaction Concerns:

Metronidazole has the potential to enhance the effects of oral anticoagulants, resulting in heightened physiological responses. Co-administration with disulfiram may precipitate acute psychosis and confusion. Heightened concentrations of lithium and cyclosporine have been documented in association with metronidazole utilization. It is imperative to meticulously contemplate these potential detrimental effects and drug interactions during the prescription or administration of metronidazole to proactively address and mitigate any associated risks.

Metronidazole-induced neurotoxicity

Metronidazole-induced neurotoxicity is an underappreciated phenomenon associated with the use of metronidazole, a commonly prescribed medication for anaerobic and protozoal infections. Although considered uncommon, it can lead to adverse effects involving the central nervous system (CNS). The exact mechanism of metronidazole-induced neurotoxicity remains unclear, and its incidence may be underestimated[26].

Clinical presentations of metronidazole-induced neurotoxicity encompass various syndromes, with common CNS features including ataxia, dysarthria, and altered mental status. Less frequent manifestations such as seizures, encephalopathy, and cerebellar dysfunction have also been reported. Peripheral neuropathy associated with metronidazole-induced neurotoxicity presents as diminished sensation, numbness, and neuropathic pain, often coexisting with CNS abnormalities in approximately one-third of cases[27].

The main risk factors are treatment time and dose; however, symptoms can appear early and at low dosages. According to reports, the typical time of treatment until symptoms appear is 6-7 weeks, although symptoms may appear a few days after treatment begins. Due to long-term exposure, patients receiving protracted metronidazole medication for ailments such as large undrained abscesses, osteomyelitis, and inflammatory bowel disease are more susceptible to neurotoxicity28.

Radiologically, up to 90% of patients with CNS involvement exhibit characteristic lesions on MRI, commonly seen on T2-weighted FLAIR sequences. These lesions often involve the dentate nuclei, callosal splenium, and dorsal pons. Discontinuation of metronidazole typically results in symptom improvement, with most patients experiencing complete resolution upon cessation. Radiologic resolution, either complete or near-complete, occurs in approximately 75% of cases, typically within a time frame of about 2 weeks[29].

Hematologic and Hepatic Adverse Effects of Metronidazole

Hepatotoxicity[30,31]

Even though metronidazole is used extensively, there are very few cases of hepatotoxicity, and long-term case series do not consistently relate the medication to acute liver failure or drug-induced liver damage. Serum aminotransferases can be raised in response to parenterally administered metronidazole at higher dosages or in cases of overdose; these events are usually self-limiting and exhibit minor symptoms. Metronidazole-induced acute liver damage that is clinically noticeable is an uncommon occurrence. Ornidazole, a different synthetic nitroimidazole that is sold in Europe, has been linked to multiple instances of drug-induced liver injury, which is defined by a hepatocellular pattern of injury and a few day or week latency period.

Hepatitis-Like Syndrome[32]

Metronidazole has been linked to a hepatitis-like sickness with a brief incubation time, however these occurrences are far less frequent. Uncommon symptoms include fever, rash, eosinophilia, and autoimmune traits. Acute liver injury has been known to recur fatally in a few cases when metronidazole exposure occurs. Surprisingly, reports of metronidazole hepatotoxicity in individuals with Cockayne syndrome—a rare genetic disorder characterized by insufficiency or absence of an essential enzyme for nucleotide excision repair in DNA—have been made on multiple occasions. In these instances, jaundice began to manifest within a short latency period of one to seven days, exhibiting a severe course with a high mortality rate and an enhanced enzyme pattern in the hepatic pattern.

Metronidazole-Induced Pancreatitis[33]

Some literature indicates that certain arrhythmias associated with the use of metronidazole are often associated with concurrent ingestion of other drugs due to their effects on drug metabolism. However, Induced Pancreatitis presents a unique case involving an 18-year-old male who developed ventricular fibrillation without pre-existing medical conditions or additional medication intake after attempting to end his life by taking an overdose of metronidazole. felt. This event, which has not been previously reported, raises questions about potentially rare and serious adverse effects of metronidazole that require further investigation. The presented case underlines the importance of continued research to increase our understanding of the safety profile of metronidazole and the identification of potential unusual complications.

Metronidazole-Induced Encephalopathy

Experimental studies indicate possible effects on brain monoamines, binding to neuronal RNA in rats, and modulation of GABA receptors in canine studies[34,35]. Clinical manifestations such as encephalopathy, reduced consciousness, and ataxia during metronidazole treatment should prompt prompt consideration of metronidazole-induced encephalopathy[36]. This suspicion may also arise in pre-existing non-epileptic patients presenting with multifocal myoclonus or seizures without evidence or risk factors for epilepsy[37]. The diagnosis is confirmed by ruling out alternative conditions and observing typical symmetric lesions on brain MRI, particularly in the dentate nucleus and posterior pons. Although initial MRIs may be negative, subsequent imaging often reveals typical bilateral changes. In the presented case, the diagnosis of metronidazole-induced encephalopathy was established several weeks after symptom onset, with significant improvement seen after 2–3 days of metronidazole discontinuation. While irreversible deficits and death have been reported, most cases demonstrate reversible clinical and MRI abnormalities, underscoring the critical importance of early identification for optimal patient outcomes[38].

Reproductive Toxicity:

Studies have explored the impact of metronidazole on reproductive health, particularly in pregnant women[29]. The drug can cross the placental barrier, reaching the developing fetus. Although the majority of evidence does not suggest a significant increase in the risk of congenital abnormalities or adverse pregnancy outcomes with standard therapeutic doses, caution is advised, especially during the first trimester when organogenesis occurs[40]. Limited studies have reported conflicting results, necessitating careful consideration of risks and benefits when prescribing metronidazole to pregnant women[41].

This study explores the impact of high-dose metronidazole (500 mg/kg/day) on male reproductive and hematopoietic parameters in mice[42]. The findings reveal significant decreases in testes and epididymides weights, hormonal disruption, and adverse effects on sperm parameters after 1 and 2 months of administration[43]. Metronidazole-induced anemia, characterized by decreased erythrocyte and leukocytic counts, and reduced mitotic index were observed after one month. Genotoxic effects persisted with increased chromosomal aberrations and micronuclei. The study underscores potential risks associated with elevated metronidazole doses, necessitating further research for refined safety considerations in clinical use[44].

Cytogenetic Toxicity[45]:

The potential cytogenetic effects of metronidazole have been investigated, focusing on its impact on chromosomes and genetic material. Some studies have suggested that metronidazole might induce chromosomal aberrations in certain cell types. However, the clinical significance and relevance of these findings remain debated, and the majority of evidence indicates that metronidazole does not pose a significant genotoxic risk at therapeutic doses in humans.

Factors Influencing Metronidazole Toxicity

The toxicity of metronidazole, and 5-nitroimidazole drug, can be influenced by various physiological and other factors. Some of the key factors include:

Dosage and Duration of Treatment[46]: The toxicity of metronidazole is often dose-dependent. Higher doses or prolonged use beyond recommended durations can increase the risk of adverse effects.

Individual Variation[54]: There may be individual variations in drug metabolism and sensitivity, leading to differences in the manifestation and severity of toxicity.

Liver Function: Metronidazole is metabolized in the liver, and individuals with impaired liver function may experience increased drug levels and potential toxicity.

Renal Function: Although metronidazole is primarily eliminated through the liver, renal function can play a role in drug clearance. Impaired renal function may affect drug excretion.

Age: Elderly individuals may be more susceptible to drug toxicity due to changes in drug metabolism and elimination associated with aging.

Drug Interactions: Metronidazole can interact with other drugs, potentially enhancing or reducing its toxicity. For example, interactions with drugs that affect liver enzymes may influence metronidazole metabolism.

Underlying Health Conditions[47]: Pre-existing health conditions, such as neurological disorders or blood disorders, may exacerbate the toxicity of metronidazole.

Pregnancy and Lactation: Metronidazole use during pregnancy, particularly in the first trimester, has been associated with potential risks. The drug can also be excreted in breast milk.

Alcohol Consumption: Concurrent use of metronidazole and alcohol should be avoided, as it can lead to a disulfiram-like reaction, causing symptoms such as nausea, vomiting, and headache.

Genetic Factors: Genetic polymorphisms can influence drug metabolism and response. Individuals with specific genetic

variations may metabolize metronidazole differently.

Immune System Status[45]: Individuals with compromised immune systems, such as those with HIV or undergoing immunosuppressive therapy, may be more vulnerable to certain adverse effects.

Risk Mitigation and Monitoring Strategies[46,47,48]

Risk mitigation and monitoring strategies are essential when using metronidazole to ensure patient safety and optimize therapeutic outcomes. Several key measures can be implemented to minimize risks and monitor patients effectively during metronidazole therapy:

Patient Assessment: Conduct a thorough patient assessment before prescribing metronidazole. Consider factors such as age, hepatic and renal function, immune status, and the presence of any underlying medical conditions.

Dosage Adjustment: Adjust the dosage of metronidazole based on individual patient characteristics, especially in those with hepatic or renal impairment. Consider lower doses or extended dosing intervals as necessary.

Duration of Treatment: Limit the duration of metronidazole treatment to the shortest effective course. Prolonged use may increase the risk of adverse effects and the development of resistance.

Patient Education: Provide patients with clear and comprehensive information about metronidazole, including potential side effects, the importance of completing the prescribed course, and any specific instructions (e.g., taking with food).

Monitoring Liver Function: Regularly monitor hepatic function through liver function tests, especially in patients with pre-existing liver conditions. If signs of hepatic dysfunction appear, consider discontinuing metronidazole.

Renal Function Monitoring: Monitor renal function, particularly in patients with compromised kidney function. Adjust the dosage accordingly to prevent drug accumulation.

Neurological Monitoring: Exercise caution in patients with a history of neurological disorders. Monitor for signs of neurological toxicity, such as peripheral neuropathy or seizures.

Immunocompromised Patients: Take extra precautions when prescribing metronidazole to immunocompromised individuals. Monitor for potential complications and consider alternative treatment options if necessary.

Pregnancy and Lactation: Assess the risks and benefits of metronidazole use during pregnancy and lactation. Consider alternative therapies when possible, and if metronidazole is deemed necessary, closely monitor the mother and infant.

Adverse Event Reporting: Encourage healthcare providers and patients to report any adverse events promptly. Establish a system for reporting and documenting adverse reactions for continuous evaluation.

Drug Interactions: Be vigilant about potential drug interactions, especially with other medications that affect hepatic enzymes. Adjust metronidazole dosages or consider alternative therapies as needed.

Resistant Strain Surveillance: Monitor for the development of metronidazole-resistant strains, especially in settings with high antibiotic use. Consider susceptibility testing when clinically relevant.

2. CONCLUSION:

Metronidazole, a widely used nitroimidazole drug, exhibits a favorable safety profile when used appropriately for bacterial and parasitic infections. Its mechanism of action involves intracellular activation, leading to the formation of reactive intermediates that disrupt microbial DNA and inhibit nucleic acid synthesis. The drug's pharmacology includes diverse formulations, rapid absorption, and extensive tissue penetration. Despite its efficacy, certain factors, such as metronidazole resistance, adverse effects, and toxicity, warrant careful consideration. Metronidazole resistance, though uncommon, poses a concern, especially with decreased susceptibility observed in some clinical isolates. Understanding resistance mechanisms is crucial for addressing emerging challenges. Adverse effects include neurotoxicity, hematologic effects, and rare occurrences like metronidazole-induced encephalopathy, pancreatitis, and hepatotoxicity. These adverse effects emphasize the importance of vigilant monitoring and adherence to recommended dosages and durations.

Toxicokinetic evaluations highlight metronidazole's distribution, metabolism, and excretion, underscoring the need for dose adjustments in specific populations. Metronidazole-induced neurotoxicity, although rare, can manifest with CNS and peripheral symptoms, necessitating prompt recognition and discontinuation. Hepatotoxicity is rare but may be severe in individuals with certain genetic disorders. Unusual complications, such as induced arrhythmias and encephalopathy, warrant further investigation to enhance our understanding of metronidazole's safety profile. Reproductive toxicity studies emphasize caution during pregnancy, particularly in the first trimester. High-dose exposures in animal studies indicate potential risks to male reproductive and hematopoietic parameters.

Factors influencing metronidazole toxicity range from dosage and duration to individual variations, liver and renal function, age, drug interactions, and genetic factors. Risk mitigation and monitoring strategies, including thorough patient assessments,

dosage adjustments, and vigilant monitoring of liver and renal functions, are pivotal for optimizing therapeutic outcomes.

In conclusion, metronidazole remains a valuable antimicrobial agent, but its use requires careful consideration of potential risks and benefits. Continued research into its safety profile and monitoring strategies will contribute to its judicious and effective clinical application.

REFERENCES

[1] Jolles GE. Origins and anti-infective activities of metronidazole. In: Finegold SM, Conference IM, eds. Metronidazole: Proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada, May 26-28, 1976. Excerpta Med.; 1977.

[2] Maeda K. A new antibiotic, azomycin. J Antibiot (Tokyo). 1953;6(4):182. CRID: 1572261551093773440; NII Article ID :10027192787.

[3] Cosar C, Julou L. Activity of (Hydroxy-2'Ethyl)-1 Methyl-2 Nitro-5 Imidazole (8823, RP) in Experimental Trichomonas vaginalis Infections. Ann Inst Pasteur (Paris). 1959;96(2):238-41. CABI Record Number: 19592702329.

[4] Edwards DI. Nitroimidazole drugs-action and resistance mechanisms I. Mechanism of action. Journal of Antimicrobial Chemotherapy. 1993 Jan 1;31(1):9-20. https://doi.org/10.1093/jac/31.1.9.

[5] Edwards DI. Reduction of nitroimidazoles in vitro and DNA damage. Biochemical pharmacology. 1986 Jan 1;35(1):53-8. https://doi.org/10.1016/0006-2952(86)90554-X.

[6] Tocher JH, Edwards DI. The interaction of reduced metronidazole with DNA bases and nucleosides. International Journal of Radiation Oncology* Biology* Physics. 1992 Jan 1;22(4):661-3. https://doi.org/10.1016/0360-3016(92)90498-7.

[7] Muller M, Lindmark DG, McLaughlin J. Mode of action of metronidazole on anaerobic microorganisms. In: Finegold SM, ed. Metronidazole. Amsterdam: Excerpta Medica 1977:12-9. CABI Record Number: 19780848037

[8] Farthing MJ. Giardiasis. Gastroenterology Clinics. 1996 Sep 1;25(3):493-515. DOI:https://doi.org/10.1016/S0889-8553(05)70260-0.

[9] Lau AH, Lam NP, Piscitelli SC, Wilkes L, Danziger LH. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. Clinical pharmacokinetics. 1992;23(5):328-64. https://doi.org/10.2165/00003088-199223050-00002.

[10] Goldstein EJ, Citron DM, Vreni Merriam C, Warren Y, Tyrrell KL. Comparative in vitro activities of ertapenem (MK-0826) against 1,001 anaerobes isolated from human intra-abdominal infections. Antimicrobial agents and chemotherapy. 2000 Sep 1;44(9):2389-94. DOI: https://doi.org/10.1128/aac.44.9.2389-2394.2000.

[11] Freeman CD, Klutman NE, Lamp KC. Metronidazole: a therapeutic review and update. Drugs. 1997;54(5):679-708. https://doi.org/10.2165/00003495-199754050-00003.

[12] Lau AH, Lam NP, Piscitelli SC, Wilkes L, Danziger LH. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. Clinical pharmacokinetics. 1992;23(5):328-64. https://doi.org/10.2165/00003088-199223050-00002.

[13] Allen Jr LV, Erickson III MA. Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. American journal of health-system pharmacy. 1996 Sep 1;53(17):2073-8. https://doi.org/10.1093/ajhp/53.17.2073.

[14] Sprandel KA, Schriever CA, Pendland SL, Quinn JP, Gotfried MH, Hackett S, Graham MB, Danziger LH, Rodvold KA. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin at 750 milligrams and various doses of metronidazole in healthy adult subjects. Antimicrobial agents and chemotherapy. 2004 Dec;48(12):4597-605. DOI: https://doi.org/10.1128/aac.48.12.4597-4605.2004.

[15] Plaisance KI, Quintiliani R, Nightingale CH. The pharmacokinetics of metronidazole and its metabolites in critically ill patients. Journal of Antimicrobial Chemotherapy. 1988 Feb 1;21(2):195-200. https://doi.org/10.1093/jac/21.2.195.

[16] Somogyi A, Kong C, Sabto J, Gurr FW, Spicer WJ, McLean AJ. Disposition and removal of metronidazole in patients undergoing haemodialysis. European journal of clinical pharmacology. 1983;25(5):683-687. https://doi.org/10.1007/BF00542359.

[17] Ralph ED, Clarke JT, Libke RD, Luthy RP, Kirby WM. Pharmacokinetics of metronidazole as determined by bioassay. Antimicrobial Agents and Chemotherapy. 1974 Dec;6(6):691-6. DOI:

https://doi.org/10.1128/aac.6.6.691.

[18] Ings RM, McFadzean JA, Ormerod WE. The fate of metronidazole and its implications in chemotherapy. Xenobiotica. 1975 Jan 1;5(4):223-35. https://doi.org/10.3109/00498257509052069

[19] Placidi GF, Masuoka D, Alcaraz A, Taylor JA, Earle R. Distribution and metabolism of 14C-metronidazole in mice. Archives Internationales de Pharmacodynamie et de Therapie. 1970; 188:168-79. CABI Record Number: 19712203098.

[20] Ralph ED, Clarke DA. Inactivation of metronidazole by anaerobic and aerobic bacteria. Antimicrobial Agents and Chemotherapy. 1978 Sep;14(3):377-83. DOI: https://doi.org/10.1128/aac.14.3.377.

[21] Edwards DI ED, Thompson EJ, Tomusange J, Shanson D. Inactivation of metronidazole by aerobic organisms. J Antimicrob Chemother 1979; 5:315-6. DOI: 10.1093/jac/5.3.315

[22] McCalla DR. Biological effects of nitrofurans. Journal of Antimicrobial Chemotherapy. 1977 Sep 1;3(5):517-20. https://doi.org/10.1093/jac/3.5.517

[23] Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clinical pharmacokinetics. 1999 May; 36:353-73. PMID: 10384859 DOI: 10.2165/00003088-199936050-00004

[24] Lala VG, Bobat B, Haagensen M, Kathan P, Mahomed A. Metronidazole-induced encephalopathy. SA Journal of Radiology. 2021;25(1). doi: 10.4102/sajr. v25i1.2016. PMID: 33824746; PMCID: PMC8008077.

[25] Edwards DI. Mechanisms of selective toxicity of metronidazole and other nitroimidazole drugs. Sexually Transmitted Infections. 1980 Oct 1;56(5):285-90. PMID: 7000306; PMCID: PMC1045807. https://doi.org/10.1136/sti.56.5.285

[26] Sørensen CG, Karlsson WK, Amin FM, Lindelof M. Metronidazole-induced encephalopathy: a systematic review. Journal of neurology. 2020 Jan; 267:1-3. DOIhttps://doi.org/10.1007/s00415-018-9147-6

[27] Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity: a systematic review. Clinical neuropharmacology. 2011 Nov 1;34(6):241-7. DOI: 10.1097/WNF.0b013e3182334b35

[28] Patel L, Batchala P, Almardawi R, Morales R, Raghavan P. Acute metronidazole-induced neurotoxicity: an update on MRI findings. Clinical Radiology. 2020 Mar 1;75(3):202-8. https://doi.org/10.1016/j.crad.2019.11.002

[29] Appleby DH, Vogtland HD. Suspected metronidazole hepatotoxicity. Clinical pharmacy. 1983 Jul 1;2(4):373-4. PMID: 6883967.

[30] Lam S, Bank S. Hepatotoxicity caused by metronidazole overdose. Annals of internal medicine. 1995 May 15;122(10):803. https://doi.org/10.7326/0003-4819-122-10-199505150-00023.

[31] Hunaut T, Boulagnon-Rombi C, Thorn H, Doco-Fenzy M, Thiéfin G. Hepatotoxicity of metronidazole in Cockayne syndrome: a clinical report. European Journal of Medical Genetics. 2022 Jan 1;65(1):104388. DOI: 10.1016/j.ejmg.2021.104388. Epub 2021 Nov 9. PMID: 34768013.

[32] Elgassim MA, Saied AS, Mustafa MA, Abdelrahman A, AlJaufi I, Salem W, Elgassim MA. A Rare Case of Metronidazole Overdose Causing Ventricular Fibrillation. Cureus. 2022 May 4;14(5). DOI: 10.7759/cureus.24728. PMID: 35676987; PMCID: PMC9166500.

[33] Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. British medical journal. 1977 Sep 9;3(2)(6087):610-11. doi: 10.1136/bmj.2.6087.610

[34] Evans J, Levesque D, Knowles K, Longshore R, Plummer S. Diazepam as a treatment for metronidazole toxicosis in dogs: a retrospective study of 21 cases. Journal of veterinary internal medicine. 2003 May;17(3):304-10. https://doi.org/10.1111/j.1939-1676.2003.tb02452.x.

[35] Ahmed A, Loes DJ, Bressler EL. Reversible magnetic resonance imaging findings in metronidazole-induced encephalopathy. Neurology. 1995 Mar;45(3):588-9. https://doi.org/10.1212/WNL.45.3.588.

[36] Onder H. A case of MRI negative metronidazole-induced encephalopathy and recovery of electroencephalography at follow-up. Journal of Neurology Research. 2016 Sep 7;6(4):81-4. doi: http://dx.doi.org/10.14740/jnr386w.

[37] Hobbs K, Stern-Nezer S, Buckwalter MS, Fischbein N, Finley Caulfield A. Metronidazole-induced encephalopathy: not always a reversible situation. Neurocritical care. 2015 Jun; 22:429-36. https://doi.org/10.1007/s12028-014-0102-9.

[38] Kazy Z, Puhó E, Czeizel AE. Teratogenic potential of vaginal metronidazole treatment during pregnancy.

European Journal of Obstetrics & Gynecology and Reproductive Biology. 2005 Dec 1;123(2):174-8. https://doi.org/10.1016/j.ejogrb.2005.03.016.

[39] Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G, Poston L. General obstetrics: A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: The PREMET Study. BJOG: An International Journal of Obstetrics & Gynaecology. 2006 Jan;113(1):65-74. https://doi.org/10.1111/j.1471-0528.2005.00788.x

[40] Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. American journal of obstetrics and gynecology. 1995 Feb 1;172(2):525-9. https://doi.org/10.1016/0002-9378(95)90567-7.

[41] Grover JK, Vats V, Srinivas M, Das SN, Jha P, Gupta DK, Mitra DK. Effect of metronidazole on spermatogenesis and FSH, LH and testosterone levels of pre-pubertal rats. Indian J. Exp. Biol. 2001; 39: 1152–60.DOI: http://nopr.niscpr.res.in/handle/123456789/17523

[42] Patanelli DJ. Suppression of fertility in the male. Handbook of physiology. 1975; 5:245-58.

[43] McClain RM, Downing JC, Edgcomb JE. Effect of metronidazole on fertility and testicular function in male rats. Toxicological Sciences. 1989 Apr 1;12(3):386-96. https://doi.org/10.1093/toxsci/12.3.386

[44] El-Nahas AF, El-Ashmawy IM. Reproductive and cytogenetic toxicity of metronidazole in male mice. Basic & clinical pharmacology & toxicology. 2004 May;94(5):226-31. https://doi.org/10.1111/j.1742-7843.2004.pto940505.

[45] Urtasun RC, Rabin HR, Partington J. Human pharmacokinetics and toxicity of high-dose metronidazole administered orally and intravenously. Surgery. 1983 Jan 1;93(1):145-8. DOI: https://doi.org/10.5555/uri:pii:003960608390291X

[46] Jain KK, Jain KK. Basics of personalized medicine. Textbook of Personalized Medicine. 2009:1-27. https://doi.org/10.1007/978-1-4419-0769-1_4.

[47] Lee HC, Kim YE, Ma HI. Metronidazole-Induced Craniocervical Myoclonus with Reversible Bilateral Dentate Nucleus Lesions. J Mov Disord. 2017 Jan;10(1):67-68. doi: 10.14802/jmd.16021. Epub 2017 Jan 18. PMID: 28122422; PMCID: PMC5288659. doi: 10.14802/jmd.16021

[48] Gelderman AH, Bartgis IL, Keister DB, Diamond LS. A comparison of genome sizes and thermal-denaturation-derived base composition of DNAs from several members of Entamoeba (histolytica group). J Parasitol. 1971 Aug;57(4):912–916. https://doi.org/10.2307/3277827