REVIEW

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Interactions of metronidazole with other medicines: a brief review

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Metronidazole, a medicine discovered in the late 1950 s is mainly an antibiotic active against anaerobes and protozoa. There are numerous side effects of metronidazole. Some interactions with other medicines enhance its activity, and some cause the decrease in activity and plasma concentration. A short review of its side effects, mechanisms of action and interactions with other medicines is provided. As resistance towards metronidazole occurred, these mechanisms are described as well. The data presented in the review were selected on the basis of relevancy, citation and age of the used references.

1. Introduction

Metronidazole (2-(2-methyl-5-nitro-1*H*-imidazole-1-yl) ethanol) (Fig. 1) is a medicine from the nitroimidazole family, effective against anaerobes and protozoa. It was discovered in the late 1950 s when researchers at Rhone-Poulenc Research Laboratories in France were trying to create a synthetic product from a *Streptomyces* spp called azomycin that would have activity against *Trichomonas vaginalis* (Soares et al. 2012). It has an effect as antibiotic, amebicide and antiprotozoic medicine. It can be used orally (capsules and tablets), intravenously, topically (gel, cream, lotion) or intravaginally (gel or cream) (Kim et al. 2004).

Unionized metronidazole diffuses by selective absorption into anaerobes and sensitive protozoa (Fig. 2) (Viode et al. 1999).

Metronidazole shows almost complete absence of activity until it reaches host or microbial cells (Freeman et al. 1997; Lau et al. 1992). Reduction is the way for metronidazole activation, and reduction happens under strong reducing conditions (Goldman et al. 1986; Koch et al. 1997). The mechanism of action involves 4 phases: 1) entry into the bacterial cell; 2) reduction of the nitro group; 3) cytotoxic effect of the reduced product; 4) release of end products that are inactive (Muller 1983). Activated metronidazole causes damages of cells forming protein and DNA adducts (Goldman et al. 1986). DNA damages may be the causes of carcinogenicity of metronidazole in experimental animals; however, carcinogenicity of metronidazole in humans was not demonstrated (Falagas et al. 1998).

The compound is not active against viruses and fungi (Kim et al. 2004; Dunn at al. 2010; The European Agency for the evaluation of medicinal products 1997; Liu et al. 2000).

After oral administration, metronidazole is getting absorbed quickly and almost entirely from the gastrointestinal tract. Maximum serum concentration is being achieved after 1-2 h, and after 24 h is only present in traces. Rectal and vaginal administration gives as a result less drug adsorption and lower serum concentrations. Less than 20% of metronidazole bounds to serum proteins and gets distributed through the whole body. It reaches all tissues and liquids, including the cerebrospinal fluid.

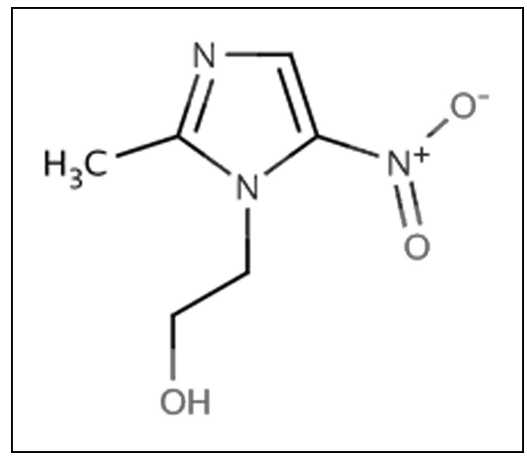

Fig. 1: Structure of metronidazole.

Metronidazole is getting metabolised in the liver. Main metabolites are produced as results of side chain oxidation and formation of glucuronides. Two main metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (active) and 1-acetic acid-2-methyl-5-nitroimidazole (inactive). Elimination of metabolites happens through the kidneys.

Metronidazole has an effect on: Bacteria (anaerobe Gram-negative bacilli (most of *Bacteroides* spp., *Fusobacterium* spp, *Veillonella* spp.; anaerobe Gram-positive bacilli (including *Clostridium* spp., *Peptostreptococcus* spp.)); protozoa (*Balantidium coli*, *Blastocystis hominis*, *Entamoeba histolytica*, *Giardia intestinalis*, *Trichomonas vaginalis*); facultative anaerobe *Gardnerella vaginalis*, some strains of *Campylobacter* spp., as well as *Helicobacter pylori*. It has also been used unspecifically in curing acute gingivitis and other dental infections; it is

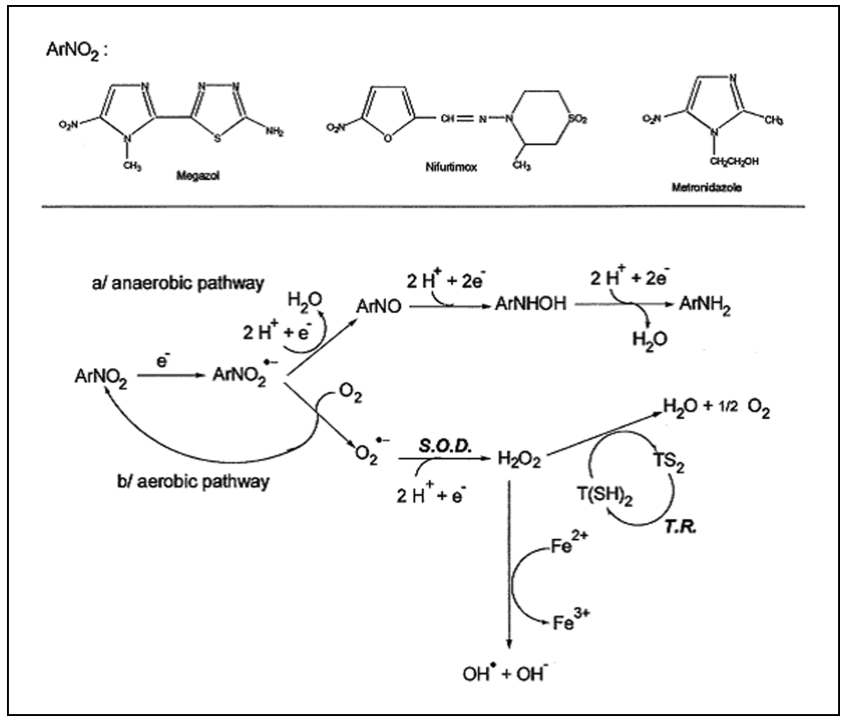

Fig. 2: Bioreductive pathway of aromatic nitrocompounds. SOD, superoxide dismutase (Viode et al. 1999).

applicable in treating Crohn's disease with intestinal or perianal appearance. In some treatment regimes (*Helicobacter pylori* eradication) it can be combined with other antibiotics, as well as bismuth or tetracyclines (Yousfi et al. 1996; Bell et al. 1996; Boixeda et al. 2002; Graham et al. 1997).

Common side effects of metronidazole in case of systemic therapy include vomiting, diarrhea and/or metal taste in the mouth. Sometimes, these effects include hypersensitive reactions (irritation, itching, fever, headache, dizziness, glossitis, stomatitis, dark urine and/or paresthesia). Metronidazole belongs to the B category of medicines regarding the risk towards pregnancy.

2. Mechanisms of metronidazole resistance

In order to understand the mechanisms of resistance, it is important to classify antibiotics based on their mechanism of action: 1) Agents that inhibit synthesis of bacterial cell walls (e.g. penicillins and cephalosporins); 2) Agents that interfere with the cell membrane of the microorganism, having an effect on permeability (e.g. some antifungal agents); 3) Agents that inhibit protein synthesis affecting the function of 30 S or 50 S ribosomal subunits (e.g. tetracyclines, macrolides and clindamycin); 4) Agents that block important metabolic steps of the microorganisms (e.g. sulphonamides and trimethoprim); 5) Agents that interfere with nucleic acid synthesis (e.g. metronidazole and quinolones) (Soares et al. 2012).

Antimicrobial resistance can be: 1) intrinsic, 2) mutational and 3) acquired. Intrinsic resistance is referred to an inherent resistance to an antibiotic (naturally occurring feature of the microorganism). For example, certain oral bacteria like many streptococci have the absence of nitroreductases necessary to convert metronidazole to its active metabolites (Walker 1996).

Bacteria use three important ways to become resistant to antibiotics: 1) prevention the drug from reaching the target (Nikaido 2009; Nikaido 1994); 2) alteration of the target (Ince and Hooper 2003; Spratt 1994), and 3) inactivation of the antibiotic (Davies 1994; Robicsek et al. 2006).

Metronidazole is a cheap medicine and available without a prescription in the developing world. In developed countries the rate of resistance ranges from 10 to 50% (Reported in a European multicenter study in 1991) (Glupczynski 1992). It seems that the mechanism of metronidazole resistance in *H. pylori* is a null mutation in the *H. pylori rdxA* gene encoding an oxygen-insensitive NADPH nitroreductase (Goodwin et al. 1998). In other organisms, four genes (*nimA, nimB, nimC and nimD*) were found to be responsible for moderate to high levels of metronidazole resistance (Haggoud et al. 1994; Trinh et al. 1995; Trinh and Reysset 1997). They are situated on either the chromosome or a variety of plasmids (Soki et al. 2006) and can be transferred by conjugation or by transformation.

Among luminal parasites, metronidazole resistance is a slow developing process and it does not represent a clinically important issue. Several reasons may exist: 1) Luminal parasites are probably diploid, so change in a single gene is not sufficient to exert drug resistance (Yuh et al. 1997). 2) Luminal parasites posses few metabolic alternatives to POR, which is in charge for metronidazole activation. Trichomonads have cytosolic lactate dehydrogenase, which can substitute POR in parasites (high levels of metronidazole resistance in the lab) (Land and Johnson 1997). 3) Overexpression of ATP binding cassette (ABC) family transporters (known as "multidrug resistance" (*mdr*) gene products) causes resistance to some hydrophobic drugs, but not resistance to metronidazole (Borst and Ouellette 1995; Ghosh et al. 1996).

3. Interactions of medicines with metronidazole

Metronidazole contains a nitroimidazole ring which inhibits hepatic metabolism of many drugs which are getting metabolised with the CYP450 2C9 and/or CYP3A4 isoenzyme (Fig. 3).

This inhibition causes an increase in concentration of the drugs (CYP450 2C9 and/or CYP3A4 substrate) in plasma and thus it increases their effects, which, depending on the pharmacological effect of the drug, may causes harmful, even dangerous effects. Medicines that induce the hepatic metabolism of nitroimidazole (induction by certain microsomal enzymes) decrease the concentration of metronidazole in plasma and increase its

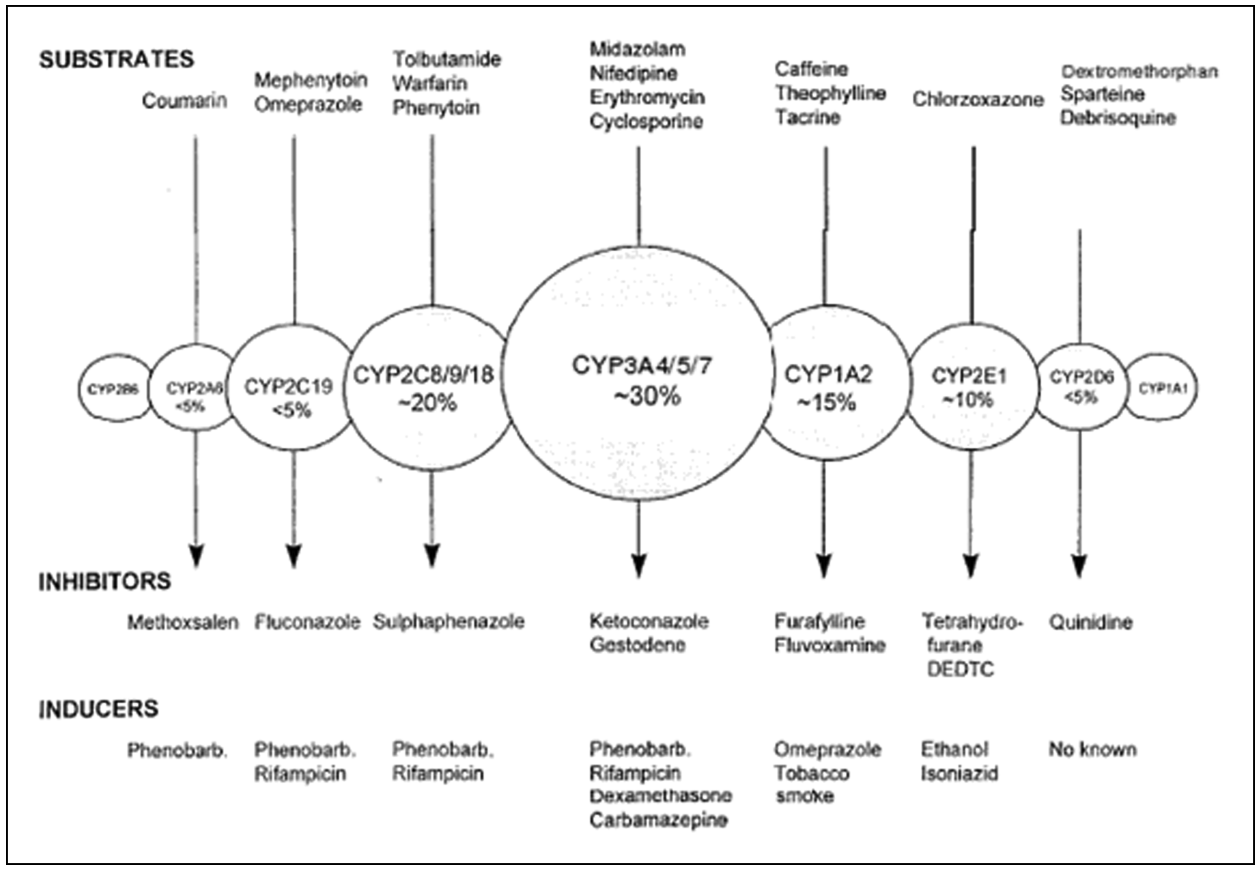

Fig. 3: Schematic representation of human hepatic P450 enzymes with model substrates, inhibitors and inducers. The size of the circles is approximately proportional to the relative amounts in human liver (Elizondo and Ostrosky-Wegman 1996).

elimination. Barbiturates are belonging to this class and a particularly important interaction is that with phenobarbital. Some medicines reduce the activity of microsomal enzymes in the of lever, *e.g.* cimetidine, which can extend the elimination half-life and decrease the plasma clearance of metronidazole (Elizondo and Ostrosky-Wegman 1996). Particular medicines can increase side effects of metronidazole: e.g. those also causing peripheral neuropathy. Alcohol, as well as disulfiram, when combined with metronidazole can cause unwanted psycho-physical effect, and also there are cases of severe toxicity. Taking lithium preparations concomitantly can cause serious toxic effects by a still unknown mechanism. Many drugs, depending on their structures can exhibit specific interactions with metronidazole. Mechanisms of many interactions are still incompletely understood.

*3.1. Allopurinol (*1*)*

The risk of peripheral neuropathy is increased when two drugs causing this effect are uses in combination. Effects are dose-dependent, therefore, recommended doses should not be exceeded. Dose reduction or even immediate cessation must be considered in patients showing symptoms of peripheral neuropathy (Llanos-Cuentas et al. 1997).

3.2. Antibiotics

The speed of metronidazole taken up by bacterial cells incubated with amoxicillin was higher than that of cells incubated with the nitroimidazole alone. This phenomenon can explain the *in vitro* synergistic interaction between metronidazole and amoxicillin against *Aggregatibacter actinomycetemcomitans* (Pavicic et al. 1994; Pavicic et al. 1991).

Chloramphenicol can cause peripheral neuropathy (Kasten 1999). Co-administration of nitrofurantoin and metronidazole also increases the risk of peripheral neuropathy, because both compounds can cause this effect (Graham et al. 2001).

In an *in vitro* investigation of ranitidine, bismuth citrate has been shown synergistic effects with metronidazole against *Helicobacter* spp. (Lopez-Brea et al. 1998).

Co-administration of rifampicin can decrease the plasma concentration of the nitroimidazole. It is suggested that rifamicin induces the metabolism of nitroimidazole *via* hepatic microsomal enzymes. Similar interactions can be shown for rifabutin (mycobutin) and rifapentine.

The macrolide antibiotic azithromycin, alone or in the combination with metronidazole has been shown to possess similar response rates to comparative agents (metronidazole plus doxycycline plus cefoxitin plus probenecid or doxycycline plus amoxicillin-clavulanate) in the treatment of pelvic inflammatory disease (Bevan et al. 2003).

3.3. Anticonvulsants

Barbiturates can decrease significantly plasma concentrations and pharmacological effects of nitroimidazoles. Obviously barbiturates induce nitroimidazole metabolism by barbiturates *via* hepatic microsomal enzymes. In patients taking barbiturates, the pharmacological response to metronidazole must be followed and may need dose adjustment (Eradiri et al. 1998).

Phenytoin can speed up the elimination of metronidazole (induction of microsomal enzymes of liver (CYP2C9)) which results in reduction of plasma levels.

Metronidazole inhibits the metabolism of carbamazepine and increases its levels in blood. Concomitant use may lead to severe consequences (Spina et al. 1996).

3.4. H_1-Antihistamines

Cisapride and terfenadine are substrates of CYP3A4 enzyme. Inhibition of this enzyme by metronidazole leads to its accumulation, which can cause ventricular arrhythmias (Gomez-Moreno et al. 2009).

3.5. Anti-inflammatory drugs

Co-administration with inhibitors of CYP2C9 and/or 3A4 like metronidazole can increase the plasma concentration valdecoxib which is getting metabolised by this isoenzyme (Davies and Saleh 2000).
Celecoxib is primarily getting metabolized by the CYP2C9 isoenzyme; so there is an opportunity of increased plasma concentrations and extended and/or increased pharmacological effects (Yagiela et al. 2010).

3.6. Anticoagulants

Metronidazole increases the anticoagulant effect of warfarin, causing reduction or inhibition of its metabolism. It is suggested that metronidazole inhibits the CYP2C9 isoenzyme responsible for the metabolic clearance of the more active *S*(-) enantiomer of warfarin. Therefore, this combination must be avoided.
Similarly, metronidazole increases the anticoagulant effect of other coumarin anticoagulants as well (acenocoumarol, dicoumarol) (Dunn et al. 2010; Gomez-Moreno et al. 2009; Gulseth 2007).

3.7. Antirheumatic drugs and medicines for arthritis

Medicines which include complexes with gold (auranofin, aurothioglucose) increase the risk of peripheral neuropathy if they are in use together with metronidazole (Tejman-Yarden et al. 2013). Colchicine or probenecid (Proben-C) can additionally increase the risk of peripheral neuropathy during co-administration with metronidazole, because both of them are causing the same event (Rossignal 2010).

3.8. Antiviral drugs

Amprenavir (against HIV) should not be used in combination with metronidazole, because amprenavir preparations contain propylene glycol. Metronidazole blocks the degradation of propylene glycol in the liver which leads to the accumulation of propylene glycol in the blood followed by stiffness, rapid heartbeat or altered kidney function.
Didanosine and pegylated interferon alfa-2a (Pegasys) can additionally increase the risk of peripheral neuropathy during the co-administration with metronidazole, because both drugs exert this side effect (Karalleidde et al. 2010).
Co-administration with inhibitors of CYP450 2C19, 2C9, and/or 3A4 (e.g. metronidazole) can increase plasma concentration of etravirine, which is a substrate of these isoenzymes.
Indinavir, nelfinavir, ritonavir and saquinavir are CYP3A4 substrates, while metronidazole is an inhibitor, so concomitant application can cause accumulation of these medicines (Gomez-Moreno et al. 2009).

3.9. Bosentan

Co-administration of metronidazole which inhibits CYP450 and 3A4 can increase concentration of bosentan, which is metabolised through these isoenzymes (Gallant 2012).

3.10. Calcium channel blockers

Felodipine, nifedipine, amlodipine, verapamil and diltiazem are CYP 3A4 substrates and metronidazole can cause inhibition of their metabolisms and accumulation. The consequence is hypersensitivity which causes severe hypotension and edema (Gomez-Moreno et al. 2009).

3.11. Cyclophosphamide

There is a reported case of encepalopathy with hallucinations and paralysis in children having received metronidazole and cyclophosphamide. There is no established mechanism, but it is believed that the reaction is connected with toxic metabolites of cyclophosphamide (Tannock 1980).

3.12. Ciprofloxacin (34)

Two independent trials conducted in Italy and Great Britain showed that a combination of metronidazole and ciprofloxacin is highly efficient for the treatment of recurrent and refractory pouchitis (Mimura et al. 2002).

3.13. Ergot alkaloids

Application of ergotamine with potential inhibitors CYP3A4 (metronidazole) increases the risk of ergotamine toxicity *i. e.* ergotism (which is manifested by squizing of limbs, peripheral vasospasm), because of the increase in concentration of ergot derivatives (Achilles and Wu 2009).

3.14. Estrogen oral contraceptives

The effectiveness of oral contraceptives containing estrogen can be decreased if it is used together with antibiotics (Joshi et al. 1980).

3.15. Phenazone (antipyrine)

In a trial conducted with volunteers, phenazone and metronidazole were administered together. There was no change in pharmacokinetics of phenazone. Urine excretion of main oxidative metabolites of phenazone (4-hydroxyphenasone, 3-hydroxymethylphenasone and norphenasone) was not changed in the presence of metronidazole (Staiger et al. 1984).

3.16. H_2-Blockers

Cimetidine decreases the activity of microsomal enzymes in the liver, so administration together with metronidazole can extend the elimination half-life and decrease the plasma clearance of metronidazole (Graham et al. 1997).

3.17. Chemotherapy drugs

Application of 5-fluorouracil together with metronidazole can increase the toxicity of fluorouracil. The suggested mechanism includes the reduction of 5-FU clearance in the presence of the nitroimidazole.
Carboplatin, docetaxel, oxaliplatin, fludarabine, nitrofurantoin, vinorelbine, nelarabine, and cisplatin together with metronidazole can increase the risk of peripheral neuropathy (Stewart et al. 1997).

3.18. Lipid lowering drugs

Atorvastatine, cerivastatin, lovastatin, simvastatin are getting metabolized under the influence of CYP3A4 enzyme, which metronidazole inhibits. Consequences are accumulation of medicines against hypercholesterolemia resulting in myalgia, rhabdomyolysis and decreased kidney function. Kidney tubules may be blocked by musculoskeletal degradation products (Gomez-Moreno et al. 2009).

3.19. Cholestyramine

Cholestyramine can bind and decrease the oral bioavailability of nitroimidazoles. However, an *in vitro* study shows that there is no physico-chemical interaction between metronidazole and cholestyramine when they are mixed in solution at pH 7.38 in different ratios (Hill et al. 1986).

3.20. Immunosuppressive medicines

Azathioprine in combination with metronidazole effectively reduced perianal irritation in dogs, as well as intensity and the extent of damage of tissues before operation. Combined application of the described immunosuppressive and antimicrobial therapy, which was followed by operation, minimized the potential morbidity connected with aggressive application (Tisdall et al. 1999).

Co-administration with metronidazole can increase the concentration of ciclosporin in blood. The suggested mechanism is an inhibition of the CYP3A4 mediated hepatic metabolism of ciclosporin.

Theoretically, antibiotics can reduce the bioavailability of mycophenolic acid and its derivatives (e.g. mycophenolate mofetil) because they are changing gut flora. It is believed that antimicrobial medicines can affect enterohepatic recirculation of mycophenolic acid by the decrease of bacterial hydrolytic enzymes in gastrointestinal tract which are responsible for the regeneration of mycophenol (Biller 2008).

Combination therapy of metronidazole and prednisone was investigated in antiinflammatory treatment of the intestine in dogs. The results show that oral monotherapy with prednisone was equally effective as the combination of prednisone and metronidazole (Gulseth 2007).

Nitroimidazoles can increase plasma levels of tacrolimus. An interaction with metronidazole is reported, the suggested mechanism is inhibition of the CYP3A4 mediated hepatic metabolism of tacrolimus (Upcroft et al. 1999).

There is a possibility of the decrease of chemotaxis and causing of false negative results by the investigation of leukocytes marked with indium In-III (Gnarpe et al. 1978).

3.21. Proton-pump inhibitor

On the basis of experiments, it was concluded that omeprazole has a negligible influence on plasma and saliva's pharmacokinetics of metronidazole (or its hydroxymetabolite), but it has an important effect on the pharmacokinetics of metronidazole in gastric juice (Jessa et al. 1997).

3.22. Laboratory tests

Metronidazole can affect some biochemical analysis of serum, e.g. tests of aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides and hexokinase glucose. All samples in which interference was reported interference include enzymatic coupling of samples for oxidation-reduction of nicotinamide adenine dinucleotide ($NAD^+ \leftrightarrow NADH$). The reason is a similarity in absorption peaks NADH (340 nm) and metronidazole (322 nm) on pH = 7 (Graham et al. 2001).

3.23. Tinidazole

There is an additional risk of peripheral neuropathy after co-administration of the two nitroimidazoles: metronidazole and tinidazole (Fallah et al. 2007).

4. Conclusion

Metronidazole is an antibiotic from the nitroimidazole class with indications against anaerobes and protozoa. It shows interactions with various medicines, so that its concentration can be decreased below therapeutic levels. On the other hand, metronidazole can decrease or increase the concentration of other medicines.

Some antibiotics (rifampicin, mycobutin, rifapentine), barbiturates and prednisone can decrease the concentration and pharmacological effects of metronidazole, on the contrary, the H_2-blocker cimetidine increases its concentration.

Metronoidazole decreases the concentration of estrogen containing oral contraceptives and increases the concentration of warfarin and other coumarin anticoagulants, some antivirals (ritonavir, lopinavir, saquinavir), benzodiazepines, calcium channel blockers, drugs against hypercholesterolemia, ergot alkaloids, H_1-antihistamines, busulfan, and 5-fluorouracil.

Interaction mechanisms are various, but most often, blocking or induction of drug metabolising enzymes in the liver is involved. Mechanisms of some interactions are still unclear. Some undesired effects of metronidazole and other drugs are additive. Other nitroimidazoles, allopurinol, chloramphenicol, isoniazid, some antirheumatic drugs which contain gold complexes can, like metronizadole, cause peripheral neuropathy. Thus, co-administration increases risk and severity of those reactions.

Amoxicillin and ranitidine show, in some therapies, synergism with metronidazole.

Metronidazole increases the risk from lithium toxicity. Rarely, very serious forms of toxicity are possible.

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