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**COURSE CODE: PHA 306**

**DEPARTMENT: PHARMACOLOGY.**

**DRUG NAME**: Metronidazole.

**ANTI – BACTERIAL ACTIVITY**

Metronidazole is a potent bactericidal activity against obligate anaerobes (e.g. bacteroides, porphyromonas, prevotella, fusobacterium, peptostreptococcus, clostridum), many of which are associated with periodontitis, and various human parasites. It is bactericidal at very low concentrations, and its spectrum of activity encompasses of almost all anaerobic bacteria and some capnophillic organisms. It is highly active against gram-negative anaerobic bacteria, such as B. fragilis, and gram-positive anaerobic bacteria, such as C. difficile. Kill-curve studies demonstrate that there is a 2 – 5 log decrease in the number of colony forming units of B. fragellis and clostridium perfringens within one hour. Since metronidazole lacks any activity against aerobic bacteria, it must be combined with other agents, usually aminoglycosides, in the treatment of mixed infections involving anaerobic and aerobic bacteria.

**MECHANISM OF ACTION**

Metronidazole diffuses into the organism, inhibits protein synthesis by interacting with DNA and causing a loss of helical DNA structure and strand breakage. Therefore, it causes cell death in susceptible organisms. The mechanism of action of metronidazole occurs through a four-step process. Step one is the entry into the organism by diffusion across the cell membranes of anaerobic and aerobic pathogens. However, antimicrobial effects are limited to anaerobes. Step two involves reductive activation by intracellular transport proteins by altering the chemical structure of pyruvate-ferredoxin oxidoreductase. The reduction of metronidazole creates a concentration gradient in the cell that drives uptake of more drug and promotes free radical formation that is cytotoxic. Step three, interactions with intracellular targets, is achieved by cytotoxic particles interacting with host cell DNA resulting in DNA strand breakage and fatal destabilization of the DNA helix. Step four is the breakdown of cytotoxic products. Metronidazole is also cytotoxic to facultatively anaerobic bacteria like Helicobacter pylori and Gardnerella vaginalis, but the mechanism of action to these pathogens is not well understood.

**PHARMACOKINETICS**.

Absorption, fate, and excretion

Metronidazole is almost completely absorbed from the gastrointestinal tract (oral bioavailability approaches 100%) so that serum levels are essentially the same whether the drug is administered orally or intravenously. Food may delay peak serum levels of metronidazole but not the total amount absorbed. Metronidazole attains a peak blood level orally in 1 to 2 hours, has a wide volume of distribution, has excellent CNS penetration, has an elimination half-life of 8 hours, and is biotransformed into five metabolic products, all of which have anti-anaerobic activity. The pharmacokinetics of metronidazole are the same in pregnant and nonpregnant women, its metabolism is reduced in the presence of severe hepatic dysfunction, and its pharmacokinetics are not significantly altered with renal impairment.

**ADVERSE EFFECTS**

The primary adverse effects of metronidazole include confusion, peripheral neuropathy, metallic taste, nausea, vomiting, and diarrhea. Adverse events seen in greater than 10% of the population include headache (18%), vaginitis (15%), and nausea (10% to 12%). Adverse events affecting less than 10% of the population are metallic taste (9%), dizziness (4%), genital pruritus (5%), abdominal pain (4%), diarrhea (4%), xerostomia (2%), dysmenorrhea (3%), urine abnormality and neutropenia as well. Urinary tract infection (2%), bacterial infection (7%), candidiasis (3%), flu-like symptoms (6%), upper respiratory tract infection (4%), pharyngitis (3%), and sinusitis (3%). Rarely, there are reports of transient leukopenia

Metronidazole comes with a black box warning that it may be carcinogenic based on some animal studies in mice and rats. However the risks are considered low, and additional follow-up studies of patients treated do not reveal an increased incidence of cancer. As with any medication choice, physicians and patients must decide whether the benefit from therapy outweighs the potential risk. The use of metronidazole should be reserved for conditions approved by the FDA; it should not be used prophylactically or unnecessarily.

Additional warnings and precautions for metronidazole exist. Prolonged courses of the drug can cause severe neurological disturbances due to the risk of cumulative neurotoxicity. Monitor for neurologic sequela and discontinue therapy if any abnormal neurologic symptoms occur. Prolonged use may also result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis. There are reports of CDAD even after more than 2 months of postantibiotic treatment. Candidiasis infection may also be more prominent during metronidazole treatment.

* Gastrointestinal: abdominal discomfort, anorexia, nausea, vomiting, metallic taste, glossitis, hepatitis (rare), pancreatitis (rare)
* Neurologic: peripheral neuropathy, numbness, paraesthesia, ataxia, confusion, encephalopathy, tremors, seizures
* Hematologic: reversible leukopenia, thrombocytopenia
* Hypersensitivity: maculopapular rashes, urticaria, pruritus, bronchospasm, serum sickness