

How is Metronidazole Used?

Introduction

Metronidazole Indication and Mechanism of action

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa. It has a radio-sensitizing effect and has been tried in the treatment of malignant neoplasms. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of Metronidazole has been reduced (Sean C Sweetman, 2011). Metronidazole has activity against several protozoa including: *Balantidium coli*, *Blastocystis hominis*, *Entamoeba histolytica*, *Giardia intestinalis* (*Giardia lamblia*) and *Trichomonas vaginalis*. Anaerobic bacteria which are typically sensitive are gram-negative anaerobes belonging to the *bacteroides* and *fusobacterium* spp. and Gram-positive anaerobes such as *Peptococcus niger*, *Peptostreptococcus*, *Clostridium* spp. and susceptible strains of *Eubacterium*. Metronidazole is bactericidal and also has activity against the facultative anaerobes *Gardnerella vaginalis*, *Helicobacter pylori* and against some spirochaetes.

Metronidazole is considered to be a prodrug that needs to be activated by susceptible organisms. The mechanism of action is not entirely clear, but is thought to involve reduction by bacteria 'nitroreductase' to an unstable intermediate which interacts with DNA, effectively preventing further replication. According to (Alexander, 2013) the active agent diffuses into the susceptible organism, interact with the DNA to cause a loss of helical DNA structure and strand breakage resulting in inhibition of protein synthesis and cell death.

Metronidazole is used in the treatment of susceptible anaerobic bacterial and protozoal infections in the following conditions: Amebiasis, symptomatic and asymptomatic Trichomoniasis; skin and skin structure infections, bone and joint infections, CNS infections, endocarditis, gynaecologic infection, intra-abdominal infections (as part of combination regimen), respiratory tract infections (lower), systemic anaerobic infections; treatment of antibiotic-associated pseudomembranous colitis; as a part of multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; surgical prophylaxis (colorectal); useful as single agent or in combination with Amoxicillin, Amoxicillin/Clavulanic acid, or Ciprofloxacin in the treatment of periodontitis associated with the presence of *Actinobacillus actinomycetemcomitans*.

Dosage

Infants and children:

Amebiasis: Oral: 35-50 mg/kg/day in divided doses every 8 hours or 10 days

Trichomoniasis: Oral: 15-30mg/kg/day in divided doses every 8 hours or 7 days

Giardiasis: Oral: 15mg/kg/day in divided doses every 8 hours for 5 days. Maximum dose 750mg/24hr

Other Parasitic Infections: Oral: 15-30mg/kg/day in divided doses every 8 hours

Anaerobic infections: Oral: 15-30mg/kg/day in divided doses every 8 hours, I.V.: 30mg/kg/day in divided doses every 6 hours. Maximum dose: 4g/24hours

Neonates: Oral/I.V.: < 7 days: <1.2kg: 7.5mg/kg/dose Q48hr, 1.2-2kg: 7.5mg/kg/dose Q24hr, ≥ 2kg: 15mg/kg/day in divided doses every 12 hours.

Neonates: Oral/I.V.: > 7 days: < 1.2 kg: 7.5 mg/kg Q24hr, 1.2-2kg: 15mg/kg/day in divided doses every 12 hours, ≥ 2kg: 30mg/kg/day in divided doses every 12 hours

***Clostridium difficile* (antibiotic-associated colitis):** Oral: 30mg/kg/day divided every 6 hours for 7 to 10 days. Maximum dose: 2g/day

***Helicobacter pylori* Infection (used in combination with Amoxicillin and Bismuth subsalicylate):** Oral: 15-20mg/kg/day divided every 12 hours for 4 weeks

Adults:

Anaerobic infections (diverticulitis intra-abdominal, peritonitis, cholangitis, or abscess): Oral, I.V. 500mg every 6-8 hours, not to exceed 4g/day. Note Initial: 1g I.V. loading dose may be administered.

Amebiasis: Oral: 500-750mg every 8 hours for 5-10 days

Antibiotic-associated pseudomembranous colitis: Mild to moderate infection: Oral: 500mg 3 times/day for 10-14 days.

Severe complicated infection I.V.: 500mg 3 times/day with oral Vancomycin (recommended agent) for 10-14 days

***Helicobacter pylori* eradication:** oral 250-500mg with meals and at bedtime for 14 days; requires combination therapy with at least one other antibiotic and an acid suppressing agent (proton pump inhibitor or H₂ inhibitor)

Intra-abdominal infection, complicated, community acquired, mild to moderate (in combination with cephalosporin or fluoroquinolone) I.V.: 500mg every 8-12 hours or 1.5g every 24 hours for 4-7 days (provided source controlled)

Bacterial vaginosis or vaginitis due to *Gardnerella*, *Mobiluncus*: Oral: 500mg twice daily (regular release) or 750mg once daily (extended release) for 7 days

Pelvic Inflammatory Disease: Oral 500mg twice daily for 14 days (in combination with cephalosporin or Doxycycline)

Periodontitis treatment (monotherapy or combination) associated with the presence of *Actinobacillus actinomycetemcomitans*: Oral 250mg-500mg every 8 hour for 8-10 days used in addition to scaling and root planning

Trichomoniasis: Oral: 250mg every 8 hours for 7 days or 375mg twice daily for 7 days or 2g as a single dose or 1g twice daily for 2 doses (on the same day) mg/kg 1 hour prior to surgery; followed by 7.5mg/kg 6 and 12 hours after initial dose.

Urethritis: Oral 2g as a single dose with Azithromycin

Surgical prophylaxis (colorectal): I.V.: 15

Elderly: Used lower end of dosing recommendations for adult, do not administer as a single dose.

Metronidazole IV to Oral Use and Switch of I.V to Oral formulation

According to (Anthem, 2015) certain Intravenous (IV) drugs have documented clinical efficacy that is bio-equivalent to the oral (PO) route of administration. When this is the case, and a stable individual requires long term drug therapy, then PO administration is generally preferred. The use of the oral route of drug administration is considered medically necessary if both of the following are met:

- There is clear, well documented evidence that the IV and oral preparations of the drug are bio-equivalent
- Individual can tolerate enteral intake, including via oral, nasogastric or percutaneous endoscopic gastrostomy (PEG) tube routes

The use of the IV route of administration is considered medically necessary if both of the following are met:

- The efficacy of the IV form is required
- The individual cannot tolerate enteral medication administration. Examples include, but are not limited to: gastrointestinal malabsorption and bowel obstruction

Examples of bio-equivalent IV and oral medication include, but are not limited to:

- Fluoroquinolone antibiotics: Ciprofloxacin, Levofloxacin, Moxifloxacin
- Other Antibiotics: Clarithromycin, Linezolid, Sulfamethoxazole/Trimethoprim, Fluconazole, Metronidazole
- Proton Pump Inhibitors: Lansoprazole, Pantoprazole

The intravenous administration of medication that have oral preparation which are bio—equivalent and the individual can tolerate oral intake is considered not medically necessary.

If the intravenous formulation was started it is important that the clinician make all necessary steps to switch/discontinue the IV dosing and commence appropriate oral dose once the patient is clinically stable. This can reduce the length of hospitalization and lower associated costs. While the intravenous medications may be more bioavailable and have greater effects, some oral drugs produce serum levels comparable to those of the parenteral form as listed above.

References

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