



Metronidazole

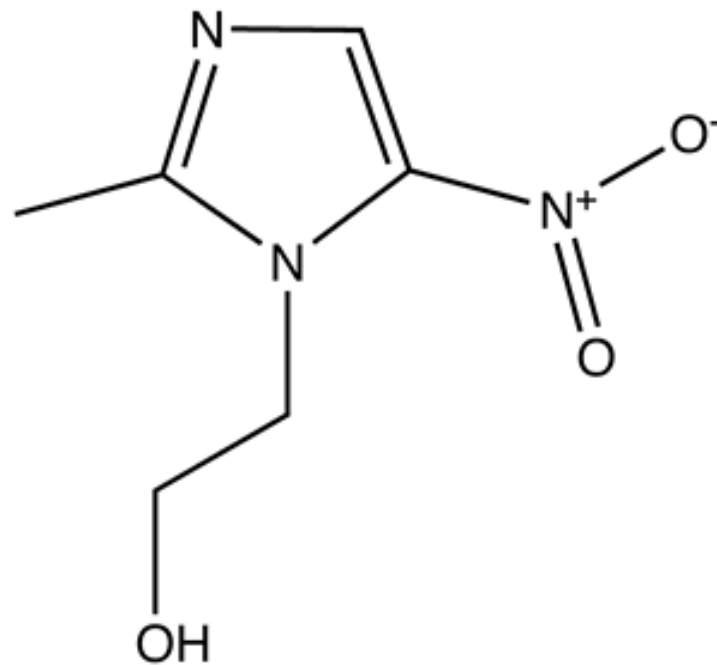
Diff than most of the drugs we covered -- developed as an anti-parasytic first

Pharmacy 407

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November, 2011

Metronidazole



A Nitroimidazole

Treats anaerobes, some parasites very well



Metronidazole (Flagyl)

Mechanism of Action

- 1) enters microbial cell
- 2) activated by reduction by nitroreductase
- 3) short-lived intermediates or free radicals
interact with DNA and possibly other
macromolecules → cell death
- 4) cytotoxic intermediates decompose (inactive)

MOA:

--> gets into the microbe and activated by nitroreductases
then forms short-lived free radicals which kill the DNA and macromolecules

Then the inactive cytotoxic intermediates decompose

It is BACTERIOCIDAL due to this MOA

Bacteriocidal



Resistance

Resistance Mechanisms

- ❑ ↓ uptake into cell
- ❑ ↓ nitroreductase activity
- ❑ may develop during during therapy
- ❑ Some resistance developing with *H. pylori*



Spectrum of Activity

Anaerobic Bacteria

- most including
 - ***B. fragilis*** (100% CHA 2006)
 - other **Bacteroides**
 - ***C. perfringens*** (100% CHA 2006)
 - ***C. difficile***
- ***H. pylori***
(as part of multidrug Rx) (11-70% resistant)
- ***Gardnerella vaginalis*** (Bacterial Vaginosa)
- limited activity *Propionibacterium acnes* To treat acne

A decorative graphic consisting of overlapping green and gold squares with a gold crosshair.

...Spectrum

Parasites

- ❑ *Trichomonas vaginalis*,
- ❑ *Giardia lamblia* (giardiasis)

Amoeba

- ❑ *Entamoeba histolytica*,
- ❑ **Aerobic bacteria inherently resistant**
(lack nitroreductase)

Kinetics

- absorbed extremely well orally, rectally and vaginally
- peaks similar to I.V. (not affected by food)
- Large Vd (80% body weight)
- distributes well to all tissues and fluids
including abscesses, bone, CSF, vaginal fluids
and seminal fluids Abscesses often invite anaerobes



Kinetics

- ❑ extensively metabolized
- ❑ 8 - 20% excreted unchanged in urine
- ❑ $t_{1/2}$ 6 - 8 hr
- ❑ dosage adjustment only if $CrCl < 10$ mL/min
- ❑ suggested ↓ dose 50% in hepatic failure



Adverse Effects

Peripheral neuropathy with prolonged therapy

- reversible

CNS toxicity

- rare, high dose, prolonged therapy
- caution if previous seizures
- D/C if any neurologic symptoms

Disulfiram effect with alcohol



...Adverse Effects

Dark Red-Brown Urine

- High doses
- metallic taste
 - Nausea, epigastric distress
 - Occasional dizziness, vertigo, paresthesias

Neutropenia - seldom, reversible, mild



Adverse Effects

???? mutagenicity, carcinogenicity, teratogenicity

NOPE! Class B

- Variable results in carcinogenic testing in rats and mice
- 1960s - 771 women received metronidazole & followed
 - • no association between metronidazole and cancer found

Summary:
No association
b/w metronidazole
and cancer

5222 user/nonusers followed for 12.6 yrs found no association between metronidazole and cancer

Reports (3) of
cancer in Crohn's
disease patients

Anecdotal report raises concerns in 3 cases Crohn's disease receiving metronidazole long term

- Risk Factor B in Pregnancy

About as safe as you get



Major Indications

Anaerobic infections & mixed infections

(500 mg q12h)

Surgical prophylaxis (bowel surgery)

(500 I.V. mg q12h)

C. difficile pseudomembranous colitis

(125 – 500 mg po x 10 -14 days)

Helicobacter pylori (as part of multi-drug regimen)



... Major Indications

Bacterial Vaginosis (*Gardnerella vaginalis*)

Trichomonas infections

(250 mg tid x 7 days) or (500 mg bid x 5 days) or (2g once)

Giardia lamblia gastro-enteritis

(750mg tid x 10 days) intestinal parasite

Amoebiasis (disseminated)

amoeba

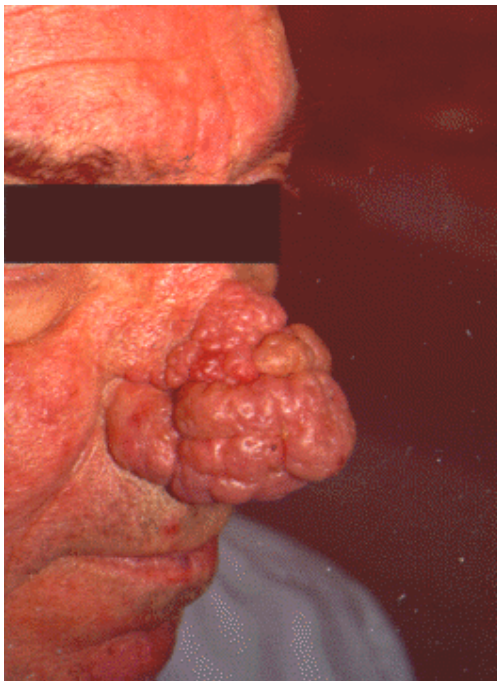
Topical gel/lotion for acne rosacea, fungating tumours

Rosacea

Different from normal acne --> usually affects tissue in the nose



Rosacea



No laughing matter.
W.C. Fields had advanced
rosacea, resulting in
rhinophyma.



Interactions

Alcohol → disulfiram effect

Disulfiram - confusion, psychosis

Interactions:

- ETOH: disulfiram rxn (confusion, psychosis, diarrhea)
- Warfarin: inc level (b/c CYP 2C9 inhibition)
- Li: inc. levels
- Busulfan: inc 5FU levels

Warfarin metabolism inhibited by metronidazole (CYP 2C9)

- avoid combination or monitor INR and ↓ dose if needed

↑ Lithium levels – avoid combination, if used together monitor lithium levels and adjust dose if needed

↑ Busulfan (Myleran), 5FU serum levels – avoid if possible