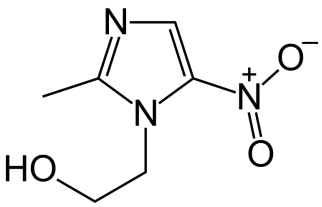
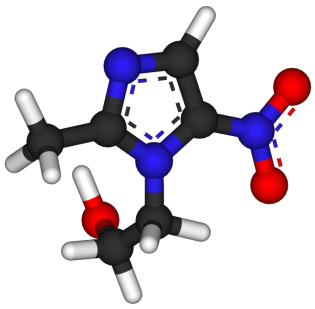
Metronidazole

Metronidazole





Systematic (IUPAC) name	
2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol	
Identifiers	
CAS number	443-48-1 [1]
ATC code	A01 AB17 [2], D06 BX01 [3], G01 AF01 [4], J01 XD01 [5], P01 AB01 [6], QP51 AA01 [7]
PubChem	CID 4173 [8]
DrugBank	APRD00631 [9]
ChemSpider	4029 [10]
Chemical data	
Formula	$C_6H_9N_3O_3$
Mol. mass	171.15 g/mol
Physical data	
Melt. point	159–163 °C (318–325 °F)
Pharmacokinetic data	
Bioavailability	100% (oral) 59–94% (rectal)
Metabolism	Hepatic
Half-life	6–7 hours
Excretion	Renal (60-80%), biliary (6–15%)
Therapeutic considerations	
Pregnancy cat.	B(US) B2 (Au)
Legal status	Prescription Only (S4) (AU) POM (UK) ℞-only (US)
Routes	oral, topical, rectal, IV, vaginal

✓ **(what is this?) (verify)** [11]

Metronidazole (INN) (pronounced /mɛtrəˈnaɪdəzoʊl/) is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal.[12] It is the drug of choice for first episodes of mild-to-moderate *Clostridium difficile* infection.[13] It is marketed by Pfizer under the trade name **Flagyl** in the US, by Sanofi-Aventis globally under the same tradename **Flagyl**, in **Pakistan** it is also available with the brand name of **Nidagyl** manufactured and marketed by **Star Laboratories**.

Metronidazole is also used as a gel preparation in the treatment of the dermatological conditions such as rosacea (**Rozex** and **MetroGel** by Galderma) and fungating tumours (**Anabact**, Cambridge Healthcare Supplies).

Mechanism of action

Metronidazole, taken up by diffusion, is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it is non-enzymatically reduced by reacting with reduced ferredoxin, which is generated by pyruvate oxido-reductase. This reduction causes the production of toxic products to anaerobic cells, and allows for selective accumulation in anaerobes.

The metronidazole metabolites are taken up into bacterial DNA, and form unstable molecules. This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria.[14]

Indications

Systemic metronidazole is indicated for the treatment of:

Bacterial

- Bacterial vaginosis, commonly associated with overgrowth of *Gardnerella* species and coinfective anaerobes (Mobiluncus, Bacteroides), in symptomatic patients
- Pelvic inflammatory disease in conjunction with other antibiotics such as ofloxacin, levofloxacin, or ceftriaxone
- Anaerobic bacterial infections such as *Bacteroides fragilis, spp*, *Fusobacterium spp*, *Clostridium spp*, *Peptococcus spp*, *Peptostreptococcus spp*, *Prevotella spp*, or any other anaerobes in intra-abdominal abscess, peritonitis, empyema, pneumonia, aspiration pneumonia, lung abscess, diabetic foot ulcer, meningitis and brain abscess, bone and joint infections, septicemia, endometritis, tubo-ovarian abscess, or endocarditis
- Pseudomembranous colitis due to *Clostridium difficile*
- *Helicobacter pylori* eradication therapy, as part of a multi-drug regimen in peptic ulcer disease

Protozoal

Amoebiasis: Infections caused by *Entamoeba histolytica*. Giardiasis: infection of the small intestine caused by the ingestion of infective cysts of a single-celled organism called *Giardia lamblia*. Giardiasis occurs worldwide with a prevalence of 20–30% in developing countries. The Centers for Disease Control and Prevention reports that in the US Giardia infects over 2.5 million people annually. There are multiple modes of transmission including person-to-person, water-borne, and venereal. Person-to-person transmission accounts for a majority of Giardia infections and is usually associated with poor hygiene and sanitation. Water-borne transmission is common in United States Giardia epidemics, which are often associated with the ingestion of unfiltered water (contaminated). Venereal transmission happens through fecal-oral contamination. Additionally, diaper changing and inadequate hand washing are risk factors for transmission from infee epidemics of Giardia have developed through the contamination of food by infected food-handlers.

Trichomoniasis: infection caused by *Trichomonas vaginalis*, which is a common cause of vaginitis and is the most frequently presenting new infection of the common sexually transmitted diseases.[15]

A small number of infected individuals experience an abrupt onset of abdominal cramps, explosive, watery diarrhea, vomiting, foul flatus, and fever which may last for 3–4 days before proceeding into a more sub-acute phase. The majority of infected persons develop gradual symptoms that become recurrent or resistant.

In both the acute and insidious onsets of symptoms, stools become greasy and malodorous but do not contain blood or pus because giardiasis does not involve dysenteric symptoms. Watery diarrhea may cycle with soft stools and constipation. Upper GI symptoms including nausea, early satiety, bloating, substernal burning, egg-smelling halitosis, and acid indigestion may be exacerbated by eating and are generally present in the absence of soft stools.

Treatment with metronidazole

Adult dosage: 250 mg three times a day for 5 days. Alternative: 2000 mg one time only

Pediatric dosage: 15 mg per kilogram of body weight per dose, 3 times per day, for 5 days

Nonspecific

- Prophylaxis for those undergoing potentially contaminated colorectal surgery or appendectomies and may be combined with neomycin
- Acute gingivitis and other dental infections (TGA approved, non-U.S. Food and Drug Administration (FDA) approved)
- Crohn's disease with colonic or perianal involvement (non-FDA approved) – believed to be more effective in combination with ciprofloxacin
- Topical metronidazole is indicated for the treatment of rosacea, and in the treatment of malodorous fungating wounds.[16]

Prevention of preterm births

A 2005 study found "Metronidazole therapy before 32 weeks was associated with an increased risk of preterm birth", possibly as a result of "changes in the vaginal flora… seen with vaginal clindamycin or oral metronidazole therapy."[17]

Metronidazole has also been used in women to prevent preterm birth associated with bacterial vaginosis, amongst other risk factors including the presence of cervicovaginal fetal fibronectin (fFN). A randomised controlled trial demonstrated that metronidazole was ineffective in preventing preterm delivery in high-risk pregnant women and, conversely, the incidence of preterm delivery was actually higher in women treated with metronidazole.[18]

Lamont has argued that Metronidazole is not the right antibiotic to administer in these circumstances and was often administered too late to be of use. Clindamycin administered early in the second trimester to women who test positive for bacterial vaginosis seems to be more effective.[19]

Adverse effects

Common adverse drug reactions (≥1% of patients) associated with systemic metronidazole therapy include: nausea, diarrhea, and/or metallic taste in the mouth. Intravenous administration is commonly associated with thrombophlebitis. Infrequent adverse effects include: hypersensitivity reactions (rash, itch, flushing, fever), headache, dizziness, vomiting, glossitis, stomatitis, dark urine, and/or paraesthesia.[16]

High doses and/or long-term systemic treatment with metronidazole is associated with the development of leukopenia, neutropenia, increased risk of peripheral neuropathy and/or CNS toxicity.[16]

Metronidazole is listed by the US National Toxicology Program (NTP) as reasonably anticipated to be a human carcinogen. Although some of the testing methods have been questioned, it has been shown to cause cancer in

experimental animals.[20] Yet, metronidazole was shown to be safe in humans.[20] [21] It appears to have a fairly low potential for cancer risk and under most circumstances the benefits of treatment outweigh the risk. Metronidazole is listed as a possible carcinogen according to the WHO International Agency for Research on Cancer (IARC).[22]

Because metronidazole is an important drug in treatment of human pathogens including C. difficile, metronidazole is banned in the EU and the USA for veterinary use in the feed of animals and is banned for use in any food animals in the USA.[23] [24]

Earlier studies suggested a relation between metronidazole and various birth defects. Those studies are nowadays considered flawed and more recent studies "do not support a significant increased risk for birth defects or other adverse effects on the fetus."[25]

Common adverse drug reactions associated with topical metronidazole therapy include local redness, dryness, and/or skin irritation; and eye watering (if applied near eyes).[16]

Interaction with alcohol

Consuming ethanol (alcohol) while using metronidazole has long been thought to have a disulfiram-like reaction with effects that can include nausea, vomiting, flushing of the skin, tachycardia (accelerated heart rate), and shortness of breath,[26] however there are studies calling that notion into question.[27] Consumption of alcohol should be avoided by patients during systemic metronidazole therapy and for at least 48 hours after completion of treatment.[16] However, the mechanism of this reaction in the clinical setting has recently been questioned by some authors,[28] [29] and a possible central toxic serotonin reaction for the alcohol intolerance suggested.[30]

Stevens-Johnson syndrome with mebendazole

Metronidazole alone rarely causes Stevens-Johnson syndrome but is reported to occur at high rates when combined with mebendazole.[31]

Potentially fatal serotonin syndrome

It is important to note that Serotonin Syndrome is not fully understood. The complex drug interaction can happen after a couple days or take up to months. The exact mechanism is not known, a theory of serotonin dysfunction helps explain how the syndrome presents and how it is to be treated. Signs and symptoms are muscle rigidity, headache, elevated blood pressure, and changes in blood chemistry. The only direct treatment is to discontinue the offending drugs. Recently, there have been reported cases of SSRI/SNRI antidepressant drugs and metronidazole induced serotonin syndrome,[30] [32] this information is not included on the metronidazole patient information leaflet. SSRI and SNRI antidepressants include Prozac, Lexapro, Celexa, Zoloft, Effexor, Cymbalta, etc.

External links

- Metronidazole monograph [33]
- Merck manuals [34]
- [35]
- U.S. National Library of Medicine: Drug Information Portal - Metronidazole [36]

References

[1] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?term=443-48-1&rn=1
[2] http://www.whocc.no/atc_ddd_index/?code=A01AB17
[3] http://www.whocc.no/atc_ddd_index/?code=D06BX01
[4] http://www.whocc.no/atc_ddd_index/?code=G01AF01
[5] http://www.whocc.no/atc_ddd_index/?code=J01XD01
[6] http://www.whocc.no/atc_ddd_index/?code=P01AB01

[7] http://www.whocc.no/atcvet/atcvet_index/?code=QP51AA01
[8] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=4173
[9] http://www.drugbank.ca/cgi-bin/show_drug.cgi?CARD=APRD00631
[10] http://www.chemspider.com/Chemical-Structure.4029
[11] http://en.wikipedia.org/w/index.php?&diff=cur&oldid=307210613
[12] Merck Manual for Professionals (http://www.merck.com/mmpe/lexicomp/metronidazole.html)
[13] The Society for Healthcare Epidemiology of America and the Infectiouslogy]. Accessed Mar. 22, 2010 9:00am.
[14] Eisenstein, Barry I.; Schaechter, Moselio (2007). "DNA and Chromosome Mechanics" (http://books.google.com/books?id=1Zl70SLDU3oC&pg=PA28). in Schaechter, Moselio; Engleberg, N. Cary; DiRita, Victor J. et al.. *Schaechter's mechanisms of microbial disease*. Hagerstwon, MD: Lippincott Williams & Wilkins. p. 28. ISBN 978-0-7817-5342-5. .
[15] Associated Press, Abstinence students still having sex (http://www.msnbc.msn.com/id/18093769/), MSNBC, April 16, 2007. Retrieved March 12, 2008.
[16] Rossi, Simone, ed (2006). *Australian Medicines Handbook 2006*. Adelaide: Australian Medicines Handbook Pty Ltd. ISBN 978-0-9757919-2-9. OCLC 224831213.
[17] Carey JC, Klebanoff MA (2005). "Is a change in the vaginal flora associated with an increased risk of preterm birth?". *American Journal of Obstetrics and Gynecology* **192** (4): 1341–6; discussion 1346–7. doi:10.1016/j.ajog.2004.12.069. PMID 15846235.
[18] Shennan A, Crawshaw S, Briley A, *et al.* (2006). "A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study". *BJOG* **113** (1): 65–74. doi:10.1111/j.1471-0528.2005.00788.x. PMID 16398774.
[19] Lamont RF (2005). "Can antibiotics prevent preterm birth--the pro and con debate". *BJOG* **112** (Suppl 1): 67–73. doi:10.1111/j.1471-0528.2005.00589.x. PMID 15715599.
[20] "Metronidazole CAS No. 443-48-1" (http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s112metr.pdf) (PDF). *Report on Carcinogens, Eleventh Edition*. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. . Retrieved 2009-12-11.
[21] *Flagyl 375 U.S. Prescribing Information* (http://www.pfizer.com/pfizer/download/uspi_flagyl_375.pdf) Pfizer (PDF)
[22] "Agents Classified by the IARC Monographs, Volumes 1–100" (http://monographs.iarc.fr/ENG/Classification/index.php) (PHP). *International Agency for Research on Cancer (IARC)*. World Health Organization. May 2010. . Retrieved 2010-06-06.
[23] "Metronidazole Summary Report EMEA/MRL/173/96-FINAL" (http://www.emea.europa.eu/pdfs/vet/mrls/017396en.pdf) (PDF). *Committee for Medicinal Products for Veterinary Use (CVMP)*. European Medicines Agency. July 1997. . Retrieved 2009-12-11.
[24] "FDA's prohibited drug list" (http://www.farad.org/eldu/prohibit.html). *Food Animal Residue Avoidance and Depletion Program (FARAD)*. USA Food and Drug Administration. 2010. . Retrieved 2010-06-06.
[25] OTIS: Metronidazole (Flagyl®) and Pregnancy (http://www.otispregnancy.org/pdf/Flagyl.pdf)
[26] Cina SJ, Russell RA, Conradi SE (1996). "Sudden death due to metronidazole/ethanol interaction". *The American Journal of Forensic Medicine and Pathology* **17** (4): 343–6. doi:10.1097/00000433-199612000-00013. PMID 8947362.
[27] Gupta NK, Woodley CL, Fried R (1970). "Effect of metronidazole on liver alcohol dehydrogenase". *Biochemical Pharmacology* **19** (10): 2805–8. doi:10.1016/0006-2952(70)90108-5. PMID 4320226.
[28] Williams CS, Woodcock KR (2000). "Do ethanol and metronidazole interact to produce a disulfiram-like reaction?". *The Annals of Pharmacotherapy* **34** (2): 255–7. doi:10.1345/aph.19118. PMID 10676835. "the authors of all the reports presumed the metronidazole-ethanol reaction to be an established pharmacologic fact. None provided evidence that could justify their conclusions".
[29] Visapää JP, Tillonen JS, Kaihovaara PS, Salaspuro MP (2002). "Lack of disulfiram-like reaction with metronidazole and ethanol". *The Annals of Pharmacotherapy* **36** (6): 971–4. doi:10.1345/aph.1A066. PMID 12022894.
[30] Karamanakos PN, Pappas P, Boumba VA, *et al.* (2007). "Pharmaceutical agents known to produce disulfiram-like reaction: effects on hepatic ethanol metabolism and brain monoamines". *International Journal of Toxicology* **26** (5): 423–32. doi:10.1080/10915810701583010. PMID 17963129.
[31] Chen KT, Twu SJ, Chang HJ, Lin RS (2003). "Outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with mebendazole and metronidazole use among Filipino laborers in Taiwan" (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1447769). *American Journal of Public Health* **93** (3): 489–92. doi:10.2105/AJPH.93.3.489. PMID 12604501. PMC 1447769.
[32] Karamanakos PN (2008). "The possibility of serotonin syndrome brought about by the use of metronidazole" (http://www.minervamedica.it/index2.t?show=R02Y2008N11A0679). *Minerva Anestesiologica* **74** (11): 679. PMID 18971895. .
[33] http://www.wedgewoodpharmacy.com/monographs/metronidazole.asp
[34] http://www.merck.com/mmpe/lexicomp/metronidazole.html
[35] http://www.patient.co.uk/showdoc/30003224/
[36] http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Metronidazole

Article Sources and Contributors

Metronidazole *Source*: http://en.wikipedia.org/w/index.php?oldid=380723318 *Contributors*: AZDub, Aghochikyan, Alex.tan, Andrew.e.gibson, Andrew73, Andrewr47, Antonello41, Anubis1975, Anypodetos, Arcadian, ArcadianOnUnsecuredLoc, ArnoldReinhold, Axl, Beetstra, Binky, Bryan Derksen, CanisRufus, Carlo Banez, Casforty, Chem-awb, Chris Capoccia, Clawed, Clay1039, Conti, Copperman, CranialNerves, Cybrspunk, Cycleskinla, D3, Danelo, Darkskystargazer, Davidruben, Diberri, Donaldlindmark, Doug Flournoy, Dozols, Duk, EhJJ, Epolk, Etnenisridhar, FirstPrinciples, Fvasconcellos, Giorgiogp2, Grec3000, HamburgerRadio, Hariva, HazyM, Indon, JForget, Jac16888, Jeeves, Johnathonm, Joyous!, Kariteh, Kbreit, Kilbad, Kwamikagami, Lanternix, Lewisbasic, Lizardxy, Mackant1, Maestrosync, Materialscientist, McDogm, Mecanismo, Mkontkow, Mmalik, MuZemike, Myredroom, Nbauman, Neparis, Newellc, Oliver.cie, Onco p53, Pagz9, Pamon, Paul, Peterl, Philculmer, Philip Trueman, Pol098, Reinderien, Rich Farmbrough, Rotcaeroib, RyanCross, Sbmehta, Shoy, Snow64, Techelf, Tossh eng, Tristanb, Tyrol5, Uthbrian, Vberger, Wimt, Xenonice, Xiephoire, Zhuuu, 190 anonymous edits

Image Sources, Licenses and Contributors

file:Metronidazole.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Metronidazole.svg *License*: Public Domain *Contributors*: Benjah-bmm27, Fvasconcellos, NEUROtiker

file:Metronidazole 3D 1w3r.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Metronidazole_3D_1w3r.png *License*: Public Domain *Contributors*: Fvasconcellos

File:Yes check.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Yes_check.svg *License*: Public Domain *Contributors*: User:Gmaxwell, User:WarX

License