mothorax but the treatment is associated with pain and a high frequency of toxic effects.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Maladin.

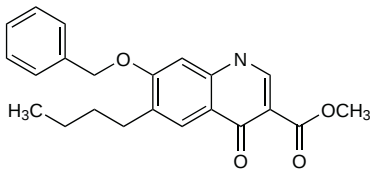
Methyl Benzoquate *(BAN)*

Nequinate *(USAN, pINN)*; AY-20385; ICI-55052; Néquinate; Nequinato; Nequinatum. Methyl 7-benzyloxy-6-butyl-1,4-dihydro-4-oxoquinoline-3-carboxylate.

Нехинат

$C_{22}H_{23}NO_4$ = 365.4.

CAS — 13997-19-8.



Profile

Methyl benzoquate is an antiprotozoal used in veterinary practice with clopidol (p.831) for the prevention of coccidiosis in poultry.

Metronidazole *(BAN, USAN, rINN)*

Bayer-5360; Metronidatsoli; Metronidazol; Metronidazolas; Métronidazole; Metronidazolum; NSC-50364; RP-8823; SC-10295. 2-(2-Methyl-5-nitroimidazol-1-yl)ethanol.

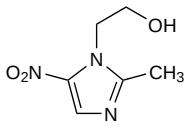
Метронидазол

$C_6H_9N_3O_3$ = 171.2.

CAS — 443-48-1.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Metronidazole). A white or yellowish, crystalline powder. Slightly soluble in water, in alcohol, in acetone, and in dichloromethane. Protect from light.

USP 31 (Metronidazole). White to pale yellow, odourless crystals or crystalline powder. It darkens on exposure to light. Sparingly soluble in water and in alcohol; slightly soluble in chloroform and in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. See below.

Metronidazole Benzoate *(BAN, rINNM)*

Benzoato de metronidazol; Benzoyl Metronidazole; Metronidatsolibentsoaatti; Metronidazolbensoat; Metronidazol-benzoát; Métronidazole, benzoate de; Metronidazoli benzoas; Metronidazolo benzoatas; RP-9712. 2-(2-Methyl-5-nitroimidazol-1-yl)ethyl benzoate.

Метронидазола Бензоат

$C_{13}H_{13}N_3O_4$ = 275.3.

CAS — 13182-89-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Metronidazole Benzoate). White or slightly yellowish, crystalline powder or flakes. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 31 (Metronidazole Benzoate). A white to slightly yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; very slightly soluble in solvent ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Metronidazole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de metronidazol; Métronidazole, Chlorhydrate de; Metronidazoli Hydrochloridum; SC-32642.

Метронидазола Гидрохлорид

$C_6H_9N_3O_3$,HCl = 207.6.

CAS — 69198-10-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

Incompatibility. Solutions of metronidazole hydrochloride have a low pH, usually of less than 2.0, before dilution and neutralisation for intravenous use. These undiluted solutions react with aluminium in equipment such as needles to produce reddish-brown discoloration, and a precipitate has been reported with ready-to-use preparations of metronidazole hydrochloride, although this occurred after contact for 6 hours or more.[1,2]

Several studies have assessed the compatibility of antibacterial injections and other drugs when added to metronidazole solution for intravenous infusion.[3-7] Results have varied according to the criteria applied and the preparations and conditions used. Physical incompatibilities due to the low pH of metronidazole injections appear to be more of a problem than chemical incompatibility. Regardless of these studies, it is generally recommended that other drugs should not be added to intravenous solutions of metronidazole or its hydrochloride. Specific information on the compatibility of individual formulations may be found in the manufacturers' literature.

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bisaillon S, Sarrazin R. Compatibility of several antibiotics or hydrocortisone when added to metronidazole solution for intravenous infusion. *J Parenter Sci Technol* 1983; **37:** 129–32.
4. Gupta VD, Stewart KR. Chemical stabilities of hydrocortisone sodium succinate and several antibiotics when mixed with metronidazole injection for intravenous infusion. *J Parenter Sci Technol* 1985; **39:** 145–8.
5. Gupta VD, *et al.* Chemical stabilities of cefamandole nafate and metronidazole when mixed together for intravenous infusion. *J Clin Hosp Pharm* 1985; **10:** 379–83.
6. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; **15:** 187–96.
7. Nahata MC, *et al.* Stability of metronidazole and ceftizoxime sodium in ready-to-use metronidazole bags stored at 4 and 25° C. *Am J Health-Syst Pharm* 1996; **53:** 1046–8.

Adverse Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastrointestinal disturbances, especially nausea and an unpleasant metallic taste. Vomiting, and diarrhoea or constipation may also occur. A furred tongue, glossitis, and stomatitis may be associated with an overgrowth of *Candida*. There have been rare reports of antibiotic-associated colitis associated with metronidazole, although it is also used in the treatment of this condition.

Weakness, dizziness, ataxia, headache, drowsiness, insomnia, and changes in mood or mental state such as depression or confusion have also been reported. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures have been associated with high doses of metronidazole or prolonged treatment.

Temporary moderate leucopenia and thrombocytopenia may occur in some patients receiving metronidazole. Skin rashes, urticaria, and pruritus occur occasionally and erythema multiforme, angioedema, and anaphylaxis have been reported rarely. Other adverse effects include urethral discomfort and darkening of the urine. Raised liver enzyme values, cholestatic hepatitis, and jaundice have occasionally been reported. Thrombophlebitis may follow intravenous use of metronidazole.

Studies have shown metronidazole to be mutagenic in bacteria and carcinogenic in some *animals*.

Carcinogenicity and mutagenicity. Metronidazole is mutagenic in bacterial assays, and its hydroxy metabolite even more so, but studies of mammalian cells *in vitro* and *in vivo* have not consistently demonstrated a mutagenic effect. Similarly, there is no uniformity in the limited data concerning genotoxicity in humans,[1] and although metronidazole has been classified as a carcinogen in *animals*, the evidence of human carcinogenicity is ambiguous. There was no appreciable increase in the incidence of cancer in a retrospective study of 771 patients given metronidazole for vaginal trichomoniasis,[2] nor in another similar study of 2460 patients.[3] The first study[2] did show an excess of cases of lung cancer, although all 4 were in women who were smokers. Subsequent follow-up[4] to 1984, covering a period of 15 to 25 years, still showed an excess of lung cancer cases even after allowing for smoking status. However, this follow-up also continued to show no significant increase overall in cancer-related morbidity or mortality. Follow-up[5] of the patients from the second study for 11 to 15 years to 1984 also showed no increase in the overall incidence of cancers nor did it confirm any increase in lung cancer.

Risks to the fetus are discussed under Pregnancy in Precautions, below.

1. Bendesky A, *et al.* Is metronidazole carcinogenic? *Mutat Res* 2002; **511:** 133–44.
2. Beard CM, *et al.* Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 1979; **301:** 519–22.
3. Friedman GD. Cancer after metronidazole. *N Engl J Med* 1980; **302:** 519.
4. Beard CM, *et al.* Cancer after exposure to metronidazole. *Mayo Clin Proc* 1988; **63:** 147–53.
5. Friedman GD, Selby JV. Metronidazole and cancer. *JAMA* 1989; **261:** 866.

Effects on the blood. Adverse haematological effects associated with metronidazole therapy include a report of bone marrow aplasia, with leucopenia and markedly reduced erythropoiesis and granulopoiesis,[1] aplastic anaemia,[2] and the haemolytic-uraemic syndrome.[3]

1. White CM, *et al.* Bone marrow aplasia associated with metronidazole. *BMJ* 1980; **280:** 647.
2. Raman R, *et al.* Metronidazole induced aplastic anaemia. *Clinician* 1982; **46:** 464–8.
3. Powell HR, *et al.* Haemolytic-uraemic syndrome after treatment with metronidazole. *Med J Aust* 1988; **149:** 222–3.

Effects on the ears. A review of reports of ototoxicity notified to the Australian Adverse Drug Reactions Advisory Committee revealed a number of cases of deafness associated with the use of metronidazole.[1]

1. Anonymous. Drug-induced ototoxicity. *WHO Drug Inf* 1991; **5:** 12.

Effects on the eyes. Myopia which developed in a patient after 11 days of oral metronidazole for trichomoniasis had resolved 4 days after withdrawal of treatment, but recurred when she resumed treatment.[1]

Optic neuropathies have also occurred.[2,3] In one report, retrobulbar or optic neuritis was seen in 7 patients given oral metronidazole.[2] Dosage varied from 0.75 to 1 g daily and duration of treatment from 7 days to a year. Abnormalities included defects in colour vision, decreased vision, and scotomas. Vision improved on withdrawal of metronidazole, although there was a residual deficit in 2 patients.

1. Grinbaum A, *et al.* Transient myopia following metronidazole treatment for Trichomonas vaginalis. *JAMA* 1992; **267:** 511–12.
2. Putnam D, *et al.* Metronidazole and optic neuritis. *Am J Ophthalmol* 1991; **112:** 737.
3. McGrath NM, *et al.* Reversible optic neuropathy due to metronidazole. *Clin Experiment Ophthalmol* 2007; **35:** 585–6.

Effects on the gastrointestinal tract. ***ANTIBIOTIC-ASSOCIATED COLITIS.*** Reports of pseudomembranous colitis associated with the use of metronidazole.

1. Thomson G, *et al.* Pseudomembranous colitis after treatment with metronidazole. *BMJ* 1981; **282:** 864–5.
2. Daly JJ, Chowdary KVS. Pseudomembranous colitis secondary to metronidazole. *Dig Dis Sci* 1983; **28:** 573–4.

Effects on the liver. Severely elevated liver enzyme values, consistent with a drug-induced hepatitis, occurred in a patient given metronidazole hydrochloride 500 mg every 6 hours intravenously for 4 days. He was also receiving cefapirin sodium and tobramycin sulfate.[1] A case of reversible hepatotoxicity caused by an overdose of metronidazole 12.5 g has also been reported.[2]

1. Appleby DH, Vogtland HD. Suspected metronidazole toxicity. *Clin Pharm* 1983; **2:** 373–4.
2. Lam S, Bank S. Hepatotoxicity caused by metronidazole overdose. *Ann Intern Med* 1995; **122:** 803.

Effects on the nervous system. ***ASEPTIC MENINGITIS.*** A 42-year-old man had 3 episodes of aseptic meningitis during treatment with oral metronidazole as part of an eradication regimen for *Helicobacter pylori* infection.[1] On each occasion his symptoms resolved spontaneously when eradication treatment was stopped and recurred when treatment was restarted. The aseptic meningitis was attributed to the metronidazole and the patient later tolerated an eradication treatment regimen containing a proton-pump inhibitor and a macrolide.

1. Khan S, *et al.* Metronidazole-induced aseptic meningitis during Helicobacter pylori eradication therapy. *Ann Intern Med* 2007; **146:** 395–6.

CEREBELLAR TOXICITY. Ataxia and dysarthria have been reported in 2 patients taking oral metronidazole plus intravenous cefepime or oral levofloxacin.[1] Symptoms occurred about one month after starting treatment and resolved 2 to 5 weeks after stopping metronidazole.

1. Woodruff BK, *et al.* Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med* 2002; **346:** 68–9.

CONVULSIONS. Reports of convulsions associated with metronidazole therapy (usually in high doses or in patients with renal impairment).

1. Halloran TJ. Convulsions associated with high cumulative doses of metronidazole. *Drug Intell Clin Pharm* 1982; **16:** 409.