Mepindolol Sulfate *(rINNM)* ⊗

LF-17895 (mepindolol); Mépindolol, Sulfate de; Mepindolol Sulphate *(BANM)*; Mepindololi Sulfas; SHE-222; Sulfato de mepindolol. 1-Isopropylamino-3-(2-methylindol-4-yloxy)propan-2-ol sulfate.

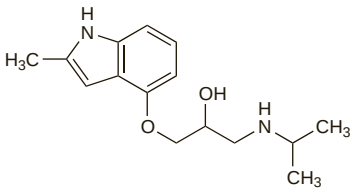
Мепиндолола Сульфат

$(C_{15}H_{22}N_2O_2)_2,H_2SO_4$ = 622.8.

CAS — 23694-81-7 (mepindolol); 56396-94-2 (mepindolol sulfate).

ATC — C07AA14.

ATC Vet — QC07AA14.



(mepindolol)

Profile

Mepindolol, the methyl analogue of pindolol, is a non-cardioselective beta blocker (p.1225). It is reported to possess intrinsic sympathomimetic activity. It has been given orally as the sulfate in the management of various cardiovascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Corindolan.

Multi-ingredient: ***Ger.:*** Corindocomb†.

Mersalyl Acid ⊗

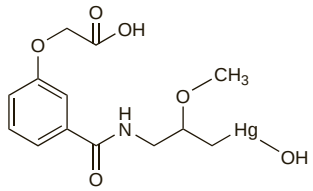
Acidum Mersalylicum; Mersal. Acid; Mersálico, ácido; Mersalylum Acidum. A mixture of {3-[2-(carboxymethoxy)benzamido]-2-methoxypropyl}hydroxymercury and its anhydrides.

$C_{13}H_{17}HgNO_6$ = 483.9.

CAS — 486-67-9.

ATC — C03BC01.

ATC Vet — QC03BC01.



Mersalyl Sodium ⊗

Mersalyl *(pINN)*; Mersalilo; Mersalylum; Mersalyyli. The sodium salt of mersalyl acid.

Мерсалил

$C_{13}H_{16}HgNNaO_6$ = 505.8.

CAS — 492-18-2.

ATC — C03BC01.

ATC Vet — QC03BC01.

Profile

Mersalyl acid, in the form of its salts, is a powerful diuretic that acts on the renal tubules, increasing the excretion of sodium and chloride, in about equal amounts, and of water. Organic mercurial diuretics were widely used before the introduction of thiazide and other diuretics but have now been almost completely superseded by these orally active drugs, which are both potent and less toxic. The most frequent adverse effects of mersalyl are stomatitis, gastric disturbance, vertigo, febrile reactions, and skin eruptions and irritation. Thrombocytopenia, neutropenia, and agranulocytosis have followed the use of mercurial diuretics. Intravenous injection may cause severe hypotension and cardiac arrhythmias and has been followed by sudden death.

Mersalyl acid was usually given by injection as the sodium salt with theophylline as this lessened the local irritant reaction and increased absorption. It was given by deep intramuscular injection after a test dose for hypersensitivity. Other organic mercurial diuretics include chlormerodrin, meralluride, mercaptomerin sodium, mercurophylline sodium, and merethoxylline procaine. They were mainly given by intramuscular injection or, for those which were less irritant, subcutaneous injection.

Metaraminol Tartrate *(BANM, rINNM)* ⊗

Hydroxynorephedrine Bitartrate; Metaradrine Bitartrate; Metaraminol Acid Tartrate; Metaraminol Bitartrate; Métaraminol, Tartrate de; Metaraminoli Tartras; Tartrato de metaraminol. (–)-2-Amino-1-(3-hydroxyphenyl)propan-1-ol hydrogen tartrate.

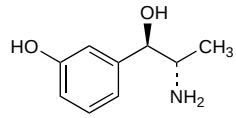
Метараминола Тартрат

$C_9H_{13}NO_2,C_4H_6O_6$ = 317.3.

CAS — 54-49-9 (metaraminol); 33402-03-8 (metaraminol tartrate).

ATC — C01CA09.

ATC Vet — QC01CA09.



(metaraminol)

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2008 (Metaraminol Tartrate). An odourless or almost odourless, white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 3.2 to 3.5.

USP 31 (Metaraminol Bitartrate). A 5% solution in water has a pH of between 3.2 and 3.5. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p.1407. The adverse effects of metaraminol primarily relate to its alpha-agonist action. Metaraminol has a longer duration of action than adrenaline or noradrenaline and therefore an excessive vasopressor response may cause a prolonged rise in blood pressure. Tissue necrosis can occur as a result of accidental extravasation during intravenous injection.

Interactions

As for Sympathomimetics, p.1407. The interactions of metaraminol relate to both its direct and indirect actions.

Pharmacokinetics

Metaraminol acts about 10 minutes after intramuscular injection with a duration of action of up to about 1 hour. Effects are seen 1 to 2 minutes after intravenous injection with a duration of action of about 20 minutes.

Uses and Administration

Metaraminol is a sympathomimetic (p.1408) with direct and indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity, the former being predominant. Metaraminol has an inotropic effect and acts as a peripheral vasoconstrictor, thus increasing cardiac output, peripheral resistance, and blood pressure. Coronary blood flow is increased and the heart rate slowed.

Metaraminol tartrate is used for its pressor action in **hypotensive states** such as those that may occur after spinal anaesthesia. Doses are expressed in terms of the base; metaraminol tartrate 9.5 mg is equivalent to about 5 mg of metaraminol. An intravenous infusion of 15 to 100 mg of metaraminol in 500 mL of glucose 5% or sodium chloride 0.9% may be used for maintaining the blood pressure, the rate of infusion being adjusted according to blood pressure response. Higher concentrations have been given. As the maximum effects are not immediately apparent, at least 10 minutes should elapse before increasing the dose and the possibility of a cumulative effect should be borne in mind. In an emergency an initial dose of 0.5 to 5 mg may be given by direct intravenous injection followed by an intravenous infusion as above.

Metaraminol tartrate has also been given by intramuscular or subcutaneous injection for the prevention of hypotension in doses equivalent to 2 to 10 mg of metaraminol. Subcutaneous injection increases the risk of local tissue necrosis and sloughing.

Priapism. Priapism[1,2] or prolonged penile erection may occur due to either decreased venous outflow (low-flow priapism) or increased arterial inflow (high-flow priapism). Low-flow priapism is a medical emergency since inflow is also impaired, leading to the development of ischaemia. It may be related to the use of drugs that cause smooth muscle relaxation, such as alpha blockers; intraluminal obstruction, such as in sickle-cell disease, may also be a cause. It is usually treated with corporal aspiration, followed if necessary by irrigation with a low dosage of a dilute solution of an alpha agonist such as metaraminol.

Intracavernosal metaraminol has been used successfully to treat drug-induced priapism,[3] as well as priapism associated with chronic myeloid leukaemia,[4] haemodialysis,[5] spinal block,[6] or fentanyl-induced general anaesthesia.[6] It may also be used to reverse the effects of alprostadil or papaverine given intracavernosally for the management of some types of erectile dysfunction, although this has been associated with fatal hypertensive crisis (see also Alprostadil, p.2184).

Alternative alpha agonists that have been used include intracavernosal phenylephrine,[7] and intracavernosal adrenaline, again in a low dosage and dilute solution. Phenylpropanolamine,[7] or pseudoephedrine,[8] given orally, have also been used. In patients with priapism due to sickle-cell disease, intracavernosal irrigation with a dilute adrenaline solution or intracavernosal injection of etilefrine have been used (see p.1205); oral etilefrine has been given for prophylaxis. Many other drugs have been tried or suggested, including baclofen, gabapentin, terbutaline, and, paradoxically, low doses of phosphodiesterase type-5 inhibitors such as sildenafil or tadalafil.[2] Surgery is usually favoured in low-flow priapism unresponsive to drug therapy.

In high-flow priapism, which is less of an emergency, embolisation of the source of abnormal inflow is the usual treatment.

1. Maan Z, *et al.* Priapism—a review of the medical management. *Expert Opin Pharmacother* 2003; **4:** 2271–7.
2. Yuan J, *et al.* Insights of priapism mechanism and rationale treatment for recurrent priapism. *Asian J Androl* 2008; **10:** 88–101.
3. Brindley GS. New treatment for priapism. *Lancet* 1984; **ii:** 220–1.
4. Stanners A, Colin-Jones D. Metaraminol for priapism. *Lancet* 1984; **ii:** 978.
5. Branger B, *et al.* Metaraminol for haemodialysis-associated priapism. *Lancet* 1985; **i:** 641.
6. Tsai SK, Hong CY. Intracavernosal metaraminol for treatment of intraoperative penile erection. *Postgrad Med J* 1990; **66:** 831–3.
7. Harmon WJ, Nehra A. Priapism: diagnosis and management. *Mayo Clin Proc* 1997; **72:** 350–5.
8. Millard RJ, *et al.* Risks of self-injection therapy for impotence. *Med J Aust* 1996; **165:** 117–18.

Preparations

BP 2008: Metaraminol Injection;
USP 31: Metaraminol Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fadamine; ***Austral.:*** Aramine; ***Braz.:*** Aramin; ***Gr.:*** Aramine†; Levicor†; ***Norw.:*** Aramine†; ***NZ:*** Aramine; ***Thai.:*** Aramine†; ***USA:*** Aramine.

Methoxamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metoxamina; Methoxamedrine Hydrochloride; Méthoxamine, Chlorhydrate de; Methoxamini Hydrochloridum. 2-Amino-1-(2,5-dimethoxyphenyl)propan-1-ol hydrochloride.

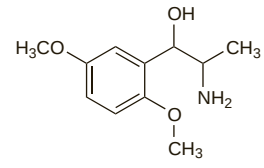
Метоксамина Гидрохлорид

$C_{11}H_{17}NO_3$,HCl = 247.7.

CAS — 390-28-3 (methoxamine); 61-16-5 (methoxamine hydrochloride).

ATC — C01CA10.

ATC Vet — QC01CA10.



(methoxamine)

Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Methoxamine Hydrochloride). Colourless crystals or white plate-like crystals or white crystalline powder; odourless or almost odourless. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. A 2% solution in water has a pH of 4.0 to 6.0.

Profile

Methoxamine is a sympathomimetic (p.1407) with mainly direct effects on adrenergic receptors. It has alpha-adrenergic activity entirely; beta-adrenergic activity is not demonstrable and beta-adrenoceptor blockade may occur at high doses. Methoxamine hydrochloride has been used parenterally for its pressor action in the management of hypotensive states, particularly in anaesthesia, and also in the management of paroxysmal supraventricular

tachycardia. It has also been used topically as a vasoconstrictor in the management of nasal congestion.

Preparations

BP 2008: Methoxamine Injection.

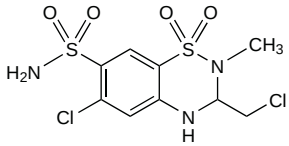
Proprietary Preparations (details are given in Part 3)
Irl.: Vasoxine†.

Methyclothiazide *(BAN, USAN, rINN)* ⊗

Méthyclothiazide; Methyclothiazidum; Meticlotiazida; Metyklotiatsidi; Metyklotiazid; NSC-110431. 6-Chloro-3-chloromethyl-3,4-dihydro-2-methyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Метиклотиазид

$C_9H_{11}Cl_2N_3O_4S_2$ = 360.2.
CAS — 135-07-9.
ATC — C03AA08.
ATC Vet — QC03AA08.



Pharmacopoeias. In *US.*
USP 31 (Methyclothiazide). A white or practically white crystalline powder, odourless or with a slight odour. Very slightly soluble to practically insoluble in water and in chloroform; soluble 1 in 92.5 of alcohol and 1 in 2700 of ether; freely soluble in acetone and in pyridine; sparingly soluble in methyl alcohol; very slightly soluble in benzene.

Profile

Methyclothiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (see p.1307). It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis starts in about 2 hours, reaches a peak at about 6 hours, and lasts for 24 hours or more.

In the treatment of oedema the usual initial dose is 2.5 to 5 mg daily, increasing to a maximum dose of 10 mg daily if necessary. In the treatment of hypertension the usual dose is 2.5 to 5 mg daily, either alone, or with other antihypertensives. Doses of up to 10 mg daily have been suggested, but this may not result in an increased hypotensive effect.

Children have been given a dose of 50 to 200 micrograms/kg daily.

Preparations

USP 31: Methyclothiazide Tablets.

Proprietary Preparations (details are given in Part 3)
Hong Kong: Enduron†; ***USA:*** Aquatensen†; Enduron.

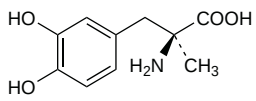
Multi-ingredient: ***Fr.:*** Isobar; ***Hong Kong:*** Enduronyl†; ***USA:*** Diutensen-R†.

Methyldopa *(BAN, USAN, rINN)*

Alpha-methyldopa; Méthyldopa; Methyldopum; Methyldopum Hydratum; Metildopa; Metyldopa; Metyylidopa; MK-351. (–)-3-(3,4-Dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate; (–)-2-Amino-2-(3,4-dihydroxybenzyl)propionic acid sesquihydrate.

Метилдопа

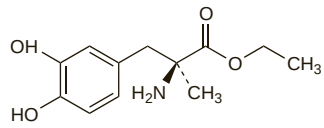
$C_{10}H_{13}NO_4,1/_2H_2O$ = 238.2.
CAS — 555-30-6 (anhydrous methyldopa); 41372-08-1 (methyldopa sesquihydrate).
ATC — C02AB01; C02AB02.
ATC Vet — QC02AB01; QC02AB01 (laevorotary); QC02AB02; QC02AB02 (racemic).



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Methyldopa). Colourless or almost colourless crystals or a white to yellowish-white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; freely soluble in dilute mineral acids. Protect from light.
USP 31 (Methyldopa). A white to yellowish-white odourless fine powder which may contain friable lumps. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in ether; very soluble in 3N hydrochloric acid. Protect from light.

Methyldopate Hydrochloride *(BANM, USAN)*

Cloridrato de Metildopato; Metildopato, hidrocloruro de. The hydrochloride of the ethyl ester of anhydrous methyldopa; Ethyl (–)-2-amino-2-(3,4-dihydroxybenzyl)propionate hydrochloride.
$C_{12}H_{17}NO_4,HCl$ = 275.7.
CAS — 2544-09-4 (methyldopate); 2508-79-4 (methyldopate hydrochloride).



(methyldopate)

Pharmacopoeias. In *Br.* and *US.*
BP 2008 (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 3.0 to 5.0. Protect from light.
USP 31 (Methyldopate Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; slightly soluble in chloroform; practically insoluble in ether. A 1% solution in water has a pH of between 3.0 and 5.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. A haze developed over 3 hours when methyldopate hydrochloride 1 mg/mL was mixed with amphotericin B 200 micrograms/mL in glucose; crystals were produced with methohexital sodium 200 micrograms/mL in sodium chloride, and a haze developed when they were mixed in glucose. A crystalline precipitate occurred with tetracycline hydrochloride 1 mg/mL in glucose, and with sulfadiazine sodium 4 mg/mL in glucose or sodium chloride.[1]

1. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28:** 228–40.

Adverse Effects

The adverse effects of methyldopa are mostly consequences of its pharmacological action. The incidence of adverse effects overall may be as high as 60% but most are transient or reversible. Drowsiness is common, especially initially and after an increase in dosage. Dizziness and lightheadedness may be associated with orthostatic hypotension; nausea, headache, weakness and fatigue, and decreased libido and impotence have also been reported quite often.

The mental and neurological effects of methyldopa have included impaired concentration and memory, mild psychoses, depression, disturbed sleep and nightmares, paraesthesias, Bell's palsy, involuntary choreoathetotic movements, and parkinsonism.

As well as orthostatic hypotension, methyldopa is often associated with fluid retention and oedema, which responds to diuretics but may rarely progress to heart failure. Angina pectoris may be aggravated. Bradycardia, syncope, and prolonged carotid sinus hypersensitivity have been reported. Intravenous methyldopate has been associated with a paradoxical rise in blood pressure.

Methyldopa may produce gastrointestinal disturbances including nausea and vomiting, diarrhoea, constipation, and rarely pancreatitis and colitis. A black or sore tongue, and inflammation of the salivary glands, have occurred, and dry mouth is quite common.

A positive Coombs' test may occur in 10 to 20% of all patients on prolonged therapy but only a small proportion develop haemolytic anaemia. Thrombocytopenia and leucopenia, notably granulocytopenia, have occurred and warrant prompt withdrawal. Other hypersensitivity effects have included myocarditis, fever, eosinophilia, and disturbances of liver function. Hepatitis may develop, particularly in the first 2 or 3 months of therapy, and is generally reversible on stopping, but fatal hepatic necrosis has occurred. Antinuclear antibodies may develop and cases of a lupus-like syndrome have been reported.

Other adverse effects that have been reported in patients taking methyldopa include rashes, lichenoid and granulomatous eruptions, toxic epidermal necrolysis, a flu-like syndrome (of fever, myalgia, and mild arthralgia), nocturia, uraemia, nasal congestion, and retroperitoneal fibrosis. Hyperprolactinaemia may occur, with breast enlargement or gynaecomastia, galactorrhoea, and amenorrhoea.

Methyldopa may occasionally cause urine to darken on exposure to the air because of the breakdown of the drug or its metabolites.

◊ Reviews.

1. Furhoff A-K. Adverse reactions with methyldopa—a decade's reports. *Acta Med Scand* 1978; **203:** 425–8.
2. Lawson DH, *et al*. Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96:** 572–9.

Effects on the blood. An analysis of drug-induced blood dyscrasias reported to the Swedish Adverse Drug Reaction Committee for the 10-year period 1966 to 1975 showed that haemolytic anaemia attributable to methyldopa had been reported on 69 occasions and had caused 3 deaths. This represented the vast majority of all the reports of drug-induced haemolytic anaemia.[1] However, the actual incidence of haemolytic anaemia in patients receiving methyldopa is quite low; data from the Boston Collaborative Drug Surveillance Program indicated that only 2 of 1067 patients receiving methyldopa developed haemolytic anaemia,[2] an incidence of about 0.2%. The proportion of patients with a positive Coombs' test is much higher, being variously reported[3-5] at 10 to 20%. It has been suggested that the high incidence of autoantibody formation may be due to inhibition of suppressor T-cells by methyldopa[4] while the relatively low incidence of resultant haemolysis may be due to drug-associated impairment of the reticuloendothelial system which would normally clear the antibody-sensitised cells from the circulation.[5]

1. Böttiger LE, *et al*. Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205:** 457–61.
2. Lawson DH, *et al*. Adverse reactions to methyldopa with particular reference to hypotension. *Am Heart J* 1978; **96:** 572–9.
3. Carstairs K, *et al*. Methyldopa and haemolytic anaemia. *Lancet* 1966; **i:** 201.
4. Kirtland HH, *et al*. Methyldopa inhibition of suppressor-lymphocyte function: a proposed cause of autoimmune hemolytic anemia. *N Engl J Med* 1980; **302:** 825–32.
5. Kelton JG. Impaired reticuloendothelial function in patients treated with methyldopa. *N Engl J Med* 1985; **313:** 596–600.

Effects on the gastrointestinal tract. ***COLITIS.*** There has been a report of 6 cases of colitis associated with methyldopa.[1] An auto-immune mechanism was proposed.

1. Graham CF, *et al*. Acute colitis with methyldopa. *N Engl J Med* 1981; **304:** 1044–5.

DIARRHOEA. Severe chronic diarrhoea was associated with methyldopa over periods of 2 and 7 years;[1,2] it stopped in both cases on withdrawal of the drug.

1. Quart BD, Guglielmo BJ. Prolonged diarrhea secondary to methyldopa therapy. *Drug Intell Clin Pharm* 1983; **17:** 462.
2. Gloth FM, Busby MJ. Methyldopa-induced diarrhea: a case of iatrogenic diarrhea leading to request for nursing home placement. *Am J Med* 1989; **87:** 480–1.

PANCREATITIS. Increases in serum- and urinary-amylase activity accompanied by fever and suggestive of pancreatitis were associated with methyldopa in 2 patients,[1] one of whom had symptoms of severe pancreatitis. Symptoms reappeared on rechallenge in both patients. A further report of acute pancreatitis in a patient who had recently begun methyldopa therapy (with a diuretic) also confirmed a recurrence of symptoms on rechallenge.[2] In contrast to the acute form, chronic pancreatitis is not generally attributable to drug use.[3] However, a case of florid chronic pancreatitis, with exocrine and endocrine insufficiency and heavy calcification over 30 months, associated with 2 periods of methyldopa treatment, has been reported.[4] Symptoms in this patient, who was also receiving a thiazide, included severe diabetic ketoacidosis.

1. van der Heide H, *et al*. Pancreatitis caused by methyldopa. *BMJ* 1981; **282:** 1930–1.
2. Anderson JR, *et al*. Drug-associated recurrent pancreatitis. *Dig Surg* 1985; **2:** 24–6.
3. Banergee AK, *et al*. Drug-induced acute pancreatitis. *Med Toxicol Adverse Drug Exp* 1989; **4:** 186–98.
4. Ramsay LE, *et al*. Methyldopa-induced chronic pancreatitis. *Practitioner* 1982; **226:** 1166–9.

Effects on the heart. Sudden death in a number of patients receiving methyldopa has been associated with myocarditis (often with hepatitis and pneumonitis).[1,2] The effect is thought to be due to hypersensitivity. Hypersensitivity myocarditis is generally marked by ECG changes, a slight rise in cardiac enzymes, cardiomegaly, and persistent sinus tachycardia, along with peripheral blood eosinophilia, and most patients will recover within days if the drug is withdrawn in time.[3]

1. Mullick FG, McAllister HA. Myocarditis associated with methyldopa therapy. *JAMA* 1977; **237:** 1699–1701. Correction. *ibid.*; **238:** 399.
2. Seeverens H, *et al*. Myocarditis and methyldopa. *Acta Med Scand* 1982; **211:** 233–5.
3. Anonymous. Myocarditis related to drug hypersensitivity. *Lancet* 1985; **ii:** 1165–6.

Effects on the liver. In a report of 6 cases of hepatitis in patients taking methyldopa, including a review of 77 cases from the literature,[1] most patients presented with symptoms including malaise, fatigue, anorexia, weight loss, nausea, and vomiting,