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

Preparations

BP 2008: Methoxamine Injection.

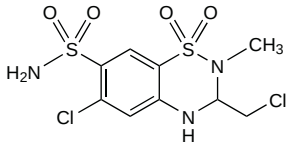
Proprietary Preparations (details are given in Part 3)
Irl.: Vasoxine†.

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.

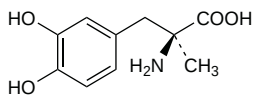
Multi-ingredient: ***Fr.:*** Isobar; ***Hong Kong:*** Enduronyl†; ***USA:*** Diutensen-R†.

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

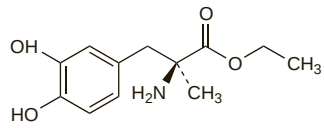
$C_{10}H_{13}NO_4,1/_2H_2O$ = 238.2.
CAS — 555-30-6 (anhydrous methyldopa); 41372-08-1 (methyldopa sesquihydrate).
ATC — C02AB01; C02AB02.
ATC Vet — QC02AB01; QC02AB01 (laevorotary); QC02AB02; QC02AB02 (racemic).



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,

and histopathological changes resembling those of viral hepatitis. Fever occurred in 28 of the 83 patients; rashes and eosinophilia occurred rarely. Symptoms usually began 1 to 4 weeks after the first dose of methyldopa. Clinically apparent jaundice occurred as early as 1 week and as late as 3 years after the start of therapy, although only 6 or 7 patients presented with jaundice later than 3 months. Liver damage was not dose-related and had features suggestive of an immunologically-mediated hypersensitivity reaction. The histological changes included chronic active hepatitis, massive fatal necrosis, and cirrhosis.

In a further analysis of 36 patients with liver damage due to methyldopa, hepatic injury tended to occur in 2 phases—acute and chronic.[2] Acute damage developed within a few months of starting treatment, and was considered to be an allergic reaction to methyldopa metabolites. The chronic form usually occurred at least a year after starting methyldopa, and was characterised by an accumulation of fat in the liver. Recovery after withdrawal of methyldopa was directly related to duration of exposure and degree of liver damage. There was also a suggestion of genetic predisposition, as acute methyldopa-induced liver damage occurred in 4 members of a family. Idiosyncratic metabolism of methyldopa in susceptible patients may be responsible for expression of an antigen on the surface of liver cells with which circulating antibodies react.[3]

See also Fever, below.

1. Rodman JS, *et al*. Methyldopa hepatitis: a report of six cases and review of the literature. *Am J Med* 1976; **60:** 941–8.
2. Sotaniemi EA, *et al*. Hepatic injury and drug metabolism in patients with alpha-methyldopa-induced liver damage. *Eur J Clin Pharmacol* 1977; **12:** 429–35.
3. Neuberger J, *et al*. Antibody mediated hepatocyte injury in methyldopa induced hepatotoxicity. *Gut* 1985; **26:** 1233–9.

Effects on mental function. Anecdotal reports have implicated methyldopa in disturbances of mental acuity including inability to concentrate, impaired calculating ability, and forgetfulness.[1-3] These have been confirmed to some extent by psychometric studies. Impaired verbal but not visual memory has been reported in 10 patients receiving methyldopa with a diuretic.[4] A crossover study in 16 patients also indicated impairment of cognitive function by methyldopa.[5]

1. Adler S. Methyldopa-induced decrease in mental activity. *JAMA* 1974; **230:** 1428–9.
2. Ghosh SK. Methyldopa and forgetfulness. *Lancet* 1976; **i:** 202–3.
3. Fernandez PG. Alpha methyldopa and forgetfulness. *Ann Intern Med* 1976; **85:** 128.
4. Solomon S, *et al*. Impairment of memory function by antihypertensive medication. *Arch Gen Psychiatry* 1983; **40:** 1109–12.
5. Johnson B, *et al*. Effects of methyldopa on psychometric performance. *J Clin Pharmacol* 1990; **30:** 1102–5.

DEPRESSION. Depression has been associated with methyldopa therapy, although the exact relationship is unclear.[1] One review[2] reported the incidence to be 3.6% and suggested that depression was more common in patients with a previous history.

1. Patten SB, Love EJ. Drug-induced depression. *Drug Safety* 1994; **10:** 203–19.
2. Paykel ES, *et al*. Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol* 1982; **2:** 14–39.

Effects on the nervous system. Involuntary choreoathetotic movements resembling those of Huntington's chorea began in a 59-year-old man with cerebrovascular disease after an increase of his methyldopa dose from 1 to 1.5 g daily. He recovered when the drug was withdrawn.[1] In another report methyldopa was associated with the development of bilateral choreiform movements in a patient without cerebrovascular disease but with chronic renal failure.[2]

1. Yamadori A, Albert ML. Involuntary movement disorder caused by methyldopa. *N Engl J Med* 1972; **286:** 610.
2. Neil EM, Waters AK. Generalized choreiform movements as a complication of methyldopa therapy in chronic renal failure. *Postgrad Med J* 1981; **57:** 732–3.

Effects on sexual function. Methyldopa has been associated with numerous cases of sexual dysfunction. In males failure to maintain erection, decreased libido, impaired ejaculation, and gynaecomastia have occurred, while in females decreased libido, painful breast enlargement, and delayed or absent orgasm have been reported.[1] The reported incidence varies and there is some evidence[2] that sexual dysfunction may be underreported: while only 2 of 30 men receiving methyldopa spontaneously reported erection failure the actual incidence on questioning was 16 of 30.

1. Stevenson JG, Umstead GS. Sexual dysfunction due to antihypertensive agents. *Drug Intell Clin Pharm* 1984; **18:** 113–21.
2. Alexander WD, Evans JI. Side effects of methyldopa. *BMJ* 1975; **2:** 501.

Fever. In a report of 78 cases of methyldopa-induced fever,[1] fever occurred 5 to 35 days after the first exposure to methyldopa in 77 patients and one day after recommencing methyldopa in the remaining patient. Rigors, headache, and myalgia were common accompanying symptoms, but eosinophilia and skin rashes were not seen. The majority of patients did not appear seriously ill, but 4 patients presented with symptoms of septic shock. Biochemical evidence of liver damage was found in 61% of patients but jaundice was uncommon. In the majority of patients, symptoms were relieved within 48 hours of stopping the drug.

1. Stanley P, Mijch A. Methyldopa: an often overlooked cause of fever and transient hepatocellular dysfunction. *Med J Aust* 1986; **144:** 603–5.

Lupus erythematosus. The incidence of antinuclear antibodies was 13% in 269 hypertensive patients taking methyldopa (irrespective of other medication), compared with 3.8% in 448 hypertensive patients not taking methyldopa.[1] However, methyldopa-induced lupus has been reported[2] only rarely.

1. Wilson JD, *et al*. Antinuclear antibodies in patients receiving non-practolol beta-blockers. *BMJ* 1978; **1:** 14–16.
2. Dupont A, Six R. Lupus-like syndrome induced by methyldopa. *BMJ* 1982; **285:** 693–4.

Overdosage. Ingestion of methyldopa 2.5 g produced coma, hypothermia, hypotension, bradycardia, and dry mouth in a 19-year-old man.[1] His serum-methyldopa concentration 10 hours after ingestion was 19.2 micrograms/mL compared with serum concentrations of about 2 micrograms/mL in patients receiving therapeutic doses of methyldopa. He recovered after treatment with intravenous fluids.

1. Shnaps Y, *et al*. Methyldopa poisoning. *J Toxicol Clin Toxicol* 1982; **19:** 501–3.

Retroperitoneal fibrosis. A 60-year-old patient developed retroperitoneal fibrosis and a positive direct Coombs' test associated with methyldopa given in a daily dose of 750 mg with bendroflumethiazide 2.5 mg for about 5 years.[1]

1. Iversen BM, *et al*. Retroperitoneal fibrosis during treatment with methyldopa. *Lancet* 1975; **ii:** 302–4.

Treatment of Adverse Effects

Withdrawal of methyldopa or reduction in dosage causes the reversal of many adverse effects. If overdosage occurs, the benefit of gastric decontamination is uncertain, but patients who present within 1 hour may be given activated charcoal. Treatment is largely symptomatic, but if necessary, intravenous fluid infusions may be given to promote urinary excretion, and vasopressors given cautiously. Atropine may be given for bradycardia. Severe hypotension may respond to placing the patient in the supine position with the feet raised.

Methyldopa is dialysable.

Precautions

Methyldopa should be used with caution in the elderly, and in patients with hepatic or renal impairment or with a history of haemolytic anaemia, liver disease, or depression. Care is also advisable in patients with parkinsonism. It should not be given to patients with active liver disease or depression and it is not recommended for phaeochromocytoma.

It is advisable to make periodic blood counts and to perform liver function tests at intervals during the first 6 to 12 weeks of treatment or if the patient develops an unexplained fever. Patients taking methyldopa may produce a positive response to a direct Coombs' test; if blood transfusion is required, prior knowledge of a positive direct Coombs' test reaction will aid crossmatching.

Methyldopa may cause sedation; if affected, patients should not drive or operate machinery.

Breast feeding. Methyldopa is distributed into breast milk in small amounts.[1] In a study[2] of 3 breast-feeding women, concentrations of free methyldopa in the breast milk were found to be between 19 and 30% of those in the plasma after a 500-mg dose. Detectable levels were found in the plasma of only 1 infant and adverse effects were seen in none. It was estimated that the amount of methyldopa a breast-fed infant would receive would be about 0.02% of the maternal dose. In another study[3] over a 3-month period no adverse effects were found in a breast-feeding infant whose mother was taking methyldopa, although the drug was detectable in the infant's urine. The American Academy of Pediatrics considers[4] that methyldopa is therefore usually compatible with breast feeding.

1. Jones HMR, Cummings AJ. A study of the transfer of α-methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; **6:** 432–4.
2. White WB, *et al*. Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants. *Clin Pharmacol Ther* 1985; **37:** 387–90.
3. Hauser GJ, *et al*. Effect of α-methyldopa excreted in human milk on the breast-fed infant. *Helv Paediatr Acta* 1985; **40:** 83–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/09/05)

Porphyria. Methyldopa has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Methyldopa is commonly used in the management of hypertension during pregnancy (p.1171). There is little evidence of adverse effects on fetal development. However, it crosses the placenta[1] and reduced blood pressure has been reported in infants born to mothers receiving the drug.[2] There has also been a report of tremor in 7 infants associated with maternal methyldopa use in pregnancy.[3] Depressed noradrenaline concentrations in the CSF were noted in the 3 infants examined leading to successful treatment of the other 4 infants with atropine: tremor was abolished in 2 and substantially reduced in the other 2.

1. Jones HMR, Cummings AJ. A study of the transfer of α-methyldopa to the human foetus and newborn infant. *Br J Clin Pharmacol* 1978; **6:** 432–4.
2. Whitelaw A. Maternal methyldopa treatment and neonatal blood pressure. *BMJ* 1981; **283:** 471.
3. Bódis J, *et al*. Methyldopa in pregnancy hypertension and the newborn. *Lancet* 1982; **ii:** 498–9.

Interactions

The hypotensive effects of methyldopa are potentiated by diuretics, other antihypertensives, and drugs with hypotensive effects. However, there have been reports of paradoxical antagonism of the hypotensive effects by tricyclic antidepressants, antipsychotics, and beta blockers. Sympathomimetics may also antagonise the hypotensive effects.

There may be an interaction between methyldopa and MAOIs and care is required if they are given together. Caution is also needed with catechol-*O*-methyltransferase inhibitors, such as entacapone, since they might reduce the metabolism of methyldopa.

Patients receiving methyldopa may require lower doses of general anaesthetics.

Alpha blockers. Urinary incontinence occurred when methyldopa was given with *phenoxybenzamine* in a patient who had undergone bilateral lumbar sympathectomy.[1]

1. Fernandez PG, *et al*. Urinary incontinence due to interaction of phenoxybenzamine and α-methyldopa. *Can Med Assoc J* 1981; **124:** 174–5.

Antipsychotics. Antipsychotics may enhance the hypotensive effects of methyldopa but a paradoxical increase in blood pressure has also been reported. A woman with SLE taking *trifluoperazine* up to 15 mg daily and prednisone up to 120 mg daily was given methyldopa up to 2 g and triamterene for high blood pressure.[1] Her blood pressure rose further to 200/140 mmHg. After stopping trifluoperazine blood pressure returned to 160/100 mmHg.

In another report, 2 patients with essential hypertension who had been taking methyldopa for 3 years and 18 months respectively developed symptoms of dementia within days of taking *haloperidol* for anxiety.[2] In both patients the symptoms resolved rapidly on stopping haloperidol.

1. Westervelt FB, Atuk NO. Methyldopa-induced hypertension. *JAMA* 1974; **227:** 557.
2. Thornton WE. Dementia induced by methyldopa with haloperidol. *N Engl J Med* 1976; **294:** 1222.

Cephalosporins. A pustular pruritic eruption occurred after use of *cefazolin* by a patient taking methyldopa.[1] A previous similar case involved use of *cefradine* with methyldopa.

1. Stough D, *et al*. Pustular eruptions following administration of cefazolin: a possible interaction with methyldopa. *J Am Acad Dermatol* 1987; **16:** 1051–2.

Digoxin. Syncope associated with carotid sinus hypersensitivity has been reported to be possibly enhanced by methyldopa in a patient taking digoxin and chlortalidone.[1] In another report,[2] sinus bradycardia developed in 2 patients taking methyldopa and digoxin.

1. Bauernfeind R, *et al*. Carotid sinus hypersensitivity with alpha methyldopa. *Ann Intern Med* 1978; **88:** 214–15.
2. Davis JC, *et al*. Sinus node dysfunction caused by methyldopa and digoxin. *JAMA* 1981; **245:** 1241–3.

Iron. After results in healthy subjects indicated that the absorption of methyldopa was reduced by 73% and 61% respectively when taken with a dose of *ferrous sulfate* or *ferrous gluconate*, 5 hypertensive patients taking methyldopa were also given ferrous sulfate 325 mg three times daily for 2 weeks.[1] All patients experienced a rise in systolic pressure, and 4 had a rise in diastolic pressure, amounting to more than 15/10 mmHg in some patients after 2 weeks. Blood pressure fell again when the ferrous sulfate was stopped.

1. Campbell N, *et al*. Alteration of methyldopa absorption, metabolism, and blood pressure control caused by ferrous sulfate and ferrous gluconate. *Clin Pharmacol Ther* 1988; **43:** 381–6.

Levodopa. For reference to a mutual interaction between methyldopa and levodopa, see Antihypertensives, under Levodopa, Interactions, p.807.

Lithium. For reference to the development of lithium toxicity when given with methyldopa, see p.405.

Sympathomimetics. A 31-year-old man whose hypertension was well controlled with methyldopa and oxprenolol suffered a severe hypertensive episode when he took a preparation containing *phenylpropanolamine* for a cold.[1]

1. McLaren EH. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxprenolol. *BMJ* 1976; **2:** 283–4.

Pharmacokinetics

After oral use methyldopa is variably and incompletely absorbed, apparently by an amino-acid active transport system. The mean bioavailability has been reported to be about 50%. It is extensively metabolised and is excreted in urine mainly as unchanged drug and the *O*-sulfate conjugate. It crosses the blood-brain barrier and is decarboxylated in the CNS to active alpha-methylnoradrenaline.

The elimination is biphasic with a half-life of about 1.7 hours in the initial phase; the second phase is more prolonged. Clearance is decreased and half-life prolonged in renal impairment. Plasma protein binding is reported to be minimal. Methyldopa crosses the placenta; small amounts are distributed into breast milk.

Uses and Administration

Methyldopa is an antihypertensive that is thought to have a mainly central action. It is decarboxylated in the CNS to alpha-methylnoradrenaline, which is thought to stimulate alpha$_2$ adrenoceptors resulting in a reduction in sympathetic tone and a fall in blood pressure. It may also act as a false neurotransmitter, and have some inhibitory actions on plasma renin activity. Methyldopa reduces the tissue concentrations of dopamine, noradrenaline, adrenaline, and serotonin.

Methyldopa is used in the management of hypertension (p.1171), although other drugs with fewer adverse effects are generally preferred. Methyldopa may, however, be the treatment of choice for hypertension in pregnancy. Oedema and tolerance sometimes associated with methyldopa therapy may be reduced when it is given with a thiazide diuretic.

Methyldopa is given orally as the sesquihydrate, but doses are usually expressed in terms of anhydrous methyldopa. Methyldopa sesquihydrate 1.13 g is equivalent to about 1 g of anhydrous methyldopa. For hypertensive crises, methyldopa has been given intravenously as methyldopate hydrochloride.

When methyldopa is given orally its effects reach a maximum in 4 to 6 hours after a single dose, although the maximum hypotensive effect may not occur until the second or third day of continuous treatment; some effect is usually apparent for 48 hours after withdrawal of methyldopa. When given intravenously the hypotensive effect may be obtained within 4 to 6 hours and last for 10 to 16 hours. It lowers the standing, and to a lesser extent the supine, blood pressure.

In hypertension, the usual initial adult oral dose is 250 mg of methyldopa two or three times daily for 2 days; this is then adjusted, not more frequently than every 2 days according to response, up to a usual maximum dose of 3 g daily. The usual maintenance dosage is 0.5 to 2 g of methyldopa daily. In the elderly an initial dose of 125 mg twice daily has been used; this dose may be increased gradually if necessary, but should not exceed 2 g daily.

An initial dose for children is 10 mg/kg daily in 2 to 4 divided doses, increased as necessary to a maximum of 65 mg/kg or 3 g daily, whichever is less.

Preparations

BP 2008: Methyldopa Tablets; Methyldopate Injection;
USP 31: Methyldopa and Chlorothiazide Tablets; Methyldopa and Hydrochlorothiazide Tablets; Methyldopa Oral Suspension; Methyldopa Tablets; Methyldopate Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Aldomet; Dopagrand; Dopatral; ***Austral.:*** Aldomet; Hydopa; ***Austria:*** Aldometil; ***Belg.:*** Aldomet; ***Braz.:*** Aldomet; Aldotensin; Alfuzina; Angimet; Cardiodopa†; Dimipress; Dopametil; Ductomet; Etildopanan; Kindomet; Metil-DT; Metilbio†; Metilcord†; Metilpress; Metilprod; Pressodopa†; Tensioval; Tildomet; ***Canad.:*** Aldomet†; Nu-Medopa; ***Chile:*** Aloset†; ***Cz.:*** Dopegyt; ***Denm.:*** Aldomet; ***Fr.:*** Aldomet; ***Ger.:*** Dopegyt; Presinol; ***Gr.:*** Aldomet; ***Hong Kong:*** Aldomet; Dopamet; Dopegyt; ***Hung.:*** Dopegyt; ***India:*** Alphadopa; Dopagyt; ***Indon.:*** Dopamet; Medopa; ***Irl.:*** Aldomet; Meldopa†; ***Israel:*** Aldomin; ***Ital.:*** Aldomet; Medopren†; ***Malaysia:*** Aldomet†; Dopamet†; Dopegyt; ***Mex.:*** Aldomet; Amender; Biotenzol†; Hipermessel; Prodop†; Selm; Toparal; ***Neth.:*** Aldomet; ***Norw.:*** Aldomet; ***NZ:*** Prodopa; ***Philipp.:*** Aldomet; ***Pol.:*** Dopegyt; ***Port.:*** Aldomet; ***Rus.:*** Dopegyt (Допегит); ***S.Afr.:*** Aldomet; Hy-Po-Tone; Normopress; ***Singapore:*** Dopegyt; ***Spain:*** Aldomet; ***Swed.:*** Aldomet; ***Switz.:*** Aldomet; ***Thai.:*** Aldomet; Dopamed; Dopasian; Dopegyt; Isomet; Medopa; Mefpa; Metpata; Servidopa†; Siamdopa; ***Turk.:*** Alfamet; ***UK:*** Aldomet; ***Venez.:*** Aldomet; Alfadopan†; Almepan†.

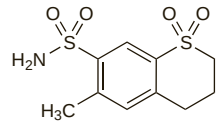
Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Aldoretic; ***Braz.:*** Hydromet; ***Canad.:*** Apo-Methazide; PMS-Dopazide; Supres†; ***Gr.:*** Hydromet†; ***Ital.:*** Medozide; Saludopin; ***Port.:*** Aldoretic†; ***USA:*** Aldoclor; Aldoril†.

Meticrane *(rINN)* ⊗

Méticrane; Meticrano; Meticranum; SD-17102. 6-Methylthiochroman-7-sulphonamide 1,1-dioxide.

Метикран

$C_{10}H_{13}NO_4S_2$ = 275.3.
CAS — 1084-65-7.
ATC — C03BA09.
ATC Vet — QC03BA09.



Pharmacopoeias. In *Jpn*.

Profile

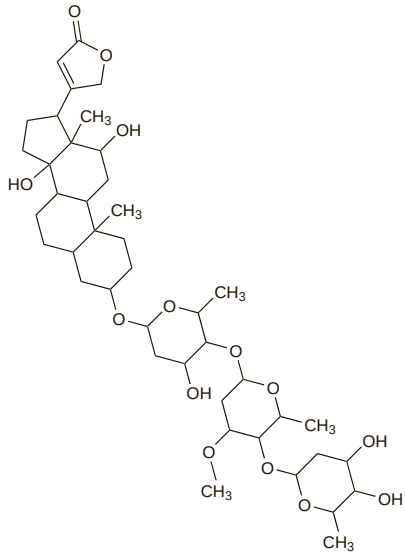
Meticrane is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used in the treatment of hypertension.

Metildigoxin *(BAN, rINN)*

Medigoxin; β-Methyl Digoxin; β-Methyldigoxin; Metildigoksiini; Metildigoxina; Métildigoxine; Metildigoxinum; Metyylidigoksiini. 3β-[(*O*-2,6-Dideoxy-4-*O*-methyl-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide.

Метилдигоксин

$C_{42}H_{66}O_{14}$ = 795.0.
CAS — 30685-43-9.
ATC — C01AA08.
ATC Vet — QC01AA08.



Pharmacopoeias. In *Chin.* In *Jpn.* as $C_{42}H_{66}O_{14}$, / C_3H_6O.

Adverse Effects, Treatment, and Precautions

As for Digoxin, p.1259.

Interactions

As for Digoxin, p.1261.

Calcium-channel blockers. For a report of an interaction between metildigoxin and *diltiazem*, see Calcium-channel Blockers, under Interactions of Digoxin, p.1262.

Pharmacokinetics

Metildigoxin is rapidly and almost completely absorbed from the gastrointestinal tract and at steady state has a half-life of 36 to 47.5 hours. Demethylation to digoxin occurs. About 60% of an oral or intravenous dose is excreted in the urine as unchanged drug and metabolites over 7 days.

Hepatic impairment. Hepatic demethylation of metildigoxin was reduced in 12 patients with cirrhosis of the liver compared with 12 healthy subjects. This resulted in a reduction in metildigoxin clearance, a smaller volume of distribution, and a significantly higher serum concentration.[1]

1. Rameis H, *et al*. Changes in metildigoxin pharmacokinetics in cirrhosis of the liver: a comparison with β-acetyldigoxin. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 145–51.

Renal impairment. For reference to the pharmacokinetics of metildigoxin in patients with renal impairment, see under Uses and Administration, below.

Uses and Administration

Metildigoxin is a cardiac glycoside with positive inotropic activity. It has actions similar to those of digoxin (p.1263) and may be used in the treatment of some cardiac arrhythmias (p.1160) and in heart failure (p.1165).

The onset of action of metildigoxin is more rapid than that of digoxin. When metildigoxin is given orally an effect may appear within 5 to 20 minutes and a maximum effect on the myocardium may be seen in 15 to 30 minutes. The duration of action is similar to or a little longer than that of digoxin; therapeutic plasma concentrations are also similar. In stabilised patients on oral therapy a dose of 300 micrograms of metildigoxin is as effective as 500 micrograms of digoxin.

Metildigoxin may be given orally or intravenously. Initial oral doses of 100 to 600 micrograms daily may be given depending upon whether rapid or slow digitalisation is desired; digitalisation is usually performed over about 2 to 4 days and the larger doses are given in divided daily doses. Similar doses may also be given intravenously. Oral maintenance therapy is continued with 50 to 300 micrograms daily in divided doses.

Dosage should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Fairly good non-linear correlation was found between creatinine clearance and metildigoxin half-life in a study of 15 patients with chronic renal impairment, including 8 undergoing haemodialysis, and 4 patients with heart failure and unimpaired renal function. The mean elimination half-life was 5.62 days in patients undergoing dialysis (clearance essentially 0 mL/minute) and 3.41 days in the other patients with chronic renal impairment (clearance 15 to 50 mL/minute) compared with 1.49 days in patients with normal renal function (clearance 62 to 96 mL/minute). It was recommended that patients undergoing dialysis should be given 30 to 50% of the usual dose initially.[1] Other studies have suggested[2] that dose reduction may be necessary in renal impairment when creatinine clearance is below 50 mL/minute per 1.48 m^2.

1. Trovato GM, *et al*. Relationship between β-methyl-digoxin pharmacokinetic and degree of renal impairment. *Curr Ther Res* 1983; **33:** 158–64.
2. Tsutsumi K, *et al*. Pharmacokinetics of beta-methyldigoxin in subjects with normal and impaired renal function. *J Clin Pharmacol* 1993; **33:** 154–60.

Preparations

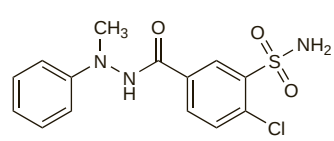
Proprietary Preparations (details are given in Part 3)

Austria: Lanitop; ***Belg.:*** Lanitop; ***Braz.:*** Lanitop†; ***Ger.:*** Lanitop; ***Gr.:*** Lanitop; ***Hong Kong:*** Lanitop; ***Ital.:*** Lanitop; ***Jpn:*** Lanirapid; ***Pol.:*** Bemecor; Medigox; ***Port.:*** Lanitop; ***Spain:*** Lanirapid; ***Switz.:*** Lanitop†; ***Venez.:*** Lanitop.

Metipamide ⊗

Metipamid; Metipamidum; VÚFB-14429. 3-(Aminosulfonyl)-4-chlorobenzoic acid 2-methyl-2-phenylhydrazide.

$C_{14}H_{14}ClN_3O_3S$ = 339.8.
CAS — 85683-41-6.



Profile

Metipamide is a diuretic structurally related to indapamide (p.1314); it is used as an antihypertensive.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Hypotylin.