

**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.<sup>1</sup>

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-methyl-noradrenaline.

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<sub>2</sub> 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; Alufuzina; 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; Dopagy; **Indon.:** Dopamet; Medopa; **Ir.:** Aldomet; Meldopa; **Israel:** Aldomin; **Ital.:** Aldomet; Medopren; **Malaysia:** Aldomet; Dopamet; Dopegyt; **Mex.:** Aldomet; Amender; Biotenzol; Hipermessel; Prodop; Selin; Toparal; **Neth.:** Aldomet; **Norw.:** Aldomet; **NZ:** Prodopa; **Philipp.:** Aldomet; **Pol.:** Dopegyt; **Port.:** Aldomet; **Rus.:** Dopegyt (Aonerit); **S.Afr.:** Aldomet; Hy-Po-Tone; Normopress; **Singapore:** Dopegyt; **Spain:** Aldomet; **Swed.:** Aldomet; **Switz.:** Aldomet; **Thai.:** Aldomet; Dopamed; Dopasian; Dopegyt; Isomet; Medopa; Mefpa; Metpata; Servidopaj; Siamdopa; **Turk.:** Alfamet; **UK:** Aldomet; **Venez.:** Aldomet; Alfadopan; Almeapan;

**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.

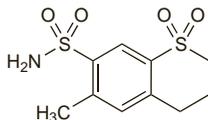
Метикран

$C_{10}H_{13}NO_4S_2 = 275.3$ .

CAS — 1084-65-7.

ATC — C03BA09.

ATC Vet — QC03BA09.



**Pharmacopeias.** 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; Metildigoxiini; Metildigoxina; Métildigoxine; Metildigoxinum; Metylidigoxiini. 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.

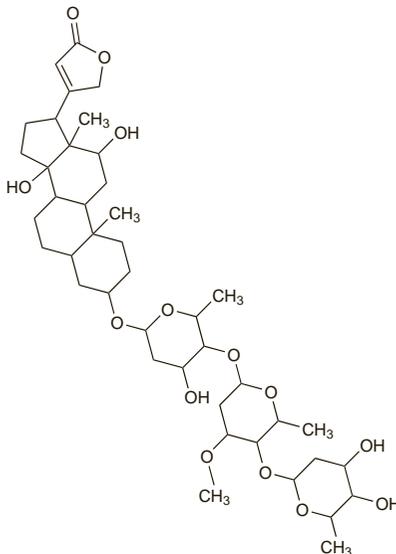
МетИЛДИГОКСИН

$C_{42}H_{66}O_{14} = 795.0$ .

CAS — 30685-43-9.

ATC — C01AA08.

ATC Vet — QC01AA08.



**Pharmacopeias.** 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.<sup>1</sup>

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.<sup>1</sup> Other studies have suggested<sup>2</sup> that dose reduction may be necessary in renal impairment when creatinine clearance is below 50 mL/minute per 1.48 m<sup>2</sup>.

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)

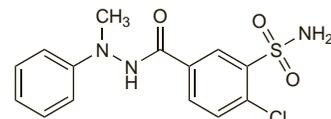
**Austria:** Lanitop; **Belg.:** Lanitop; **Braz.:** Lanitop; **Ger.:** Lanitop; **Hong Kong:** Lanitop; **Ital.:** Lanitop; **Jpn.:** Lanirapid; **Pol.:** Bemecor; **Medigox.:** Lanitop; **Spain:** Lanirapid; **Switz.:** Lanitop; **Venez.:** Lanitop.

### 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.

**Metirosine** (BAN, rINN)

L-588357-0; Metirosini; Metirosin; Metirosina; Métirosine; Metirosinum; Metirosine (USAN); MK-781. (-)- $\alpha$ -Methyl-L-tyrosine; 4-Hydroxy- $\alpha$ -methylphenylalanine.

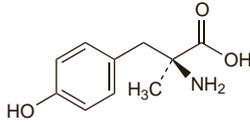
Метирозин

$C_{10}H_{13}NO_3 = 195.2$ .

CAS — 672-87-7 (metirosine); 620-30-4 (racemetirosine).

ATC — C02KB01.

ATC Vet — QC02KB01.



NOTE. The term  $\alpha$ -methyltyrosine ( $\alpha$ -MPT;  $\alpha$ -MT;  $\alpha$ -methyl-*p*-tyrosine) is used below since although metirosine, the (-)-isomer, is the active form the manufacturers state that some racemate (racemetirosine; ( $\pm$ )- $\alpha$ -methyl-DL-tyrosine) is produced during synthesis but that the material supplied contains mainly (-)-isomer with a small amount of (+)-isomer.

The code name MK-781, applied to earlier investigational material, may have described a racemate or a preparation containing a smaller proportion of (-)-isomer than the product now available commercially.

Potency of the proprietary preparation (*Demser*) is expressed in terms of metirosine.

**Pharmacopoeias.** In *US*.

**Adverse Effects**

Sedation occurs in almost all patients receiving  $\alpha$ -methyltyrosine. Other adverse effects include extrapyramidal symptoms, such as trismus and frank parkinsonism; anxiety, depression, and psychic disturbances including hallucinations, disorientation, and confusion; and diarrhoea, which may be severe. Crystalluria, transient dysuria, and haematuria have been seen in a few patients. There have also been occasional reports of slight swelling of the breast, galactorrhoea, nasal congestion, decreased salivation, gastrointestinal disturbances, headache, impotence or failure of ejaculation, and hypersensitivity reactions. Eosinophilia, raised serum aspartate aminotransferase, and peripheral oedema have been reported rarely.

**Neuroleptic malignant syndrome.** Neuroleptic malignant syndrome occurred after the use of the dopamine-depleting drugs tetrabenazine and  $\alpha$ -methyltyrosine in a patient with Huntington's chorea.<sup>1</sup>

1. Burke RE, *et al.* Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. *Neurology* 1981; **31**: 1022-6.

**Precautions**

To minimise the risk of crystalluria, patients receiving  $\alpha$ -methyltyrosine should have a fluid intake sufficient to maintain a urine volume of at least 2 litres daily and their urine should be examined regularly for the presence of crystals.

$\alpha$ -Methyltyrosine has sedative effects and patients should be warned of the hazards of driving a motor vehicle or operating machinery while receiving the drug. Symptoms of psychic stimulation and insomnia may occur when  $\alpha$ -methyltyrosine is withdrawn.

When  $\alpha$ -methyltyrosine is used pre-operatively in patients with phaeochromocytoma, blood pressure and the ECG should be monitored continuously during surgery as the danger of hypertensive crises and arrhythmias is not eliminated. Concomitant  $\alpha$ -blockade (e.g. with phentolamine) may be required; a beta blocker or lidocaine may be needed for the management of arrhythmias. Blood volume must be maintained during and after surgery, particularly if an  $\alpha$ -blocker is used, to avoid hypotension.

**Interactions**

The sedative effects of  $\alpha$ -methyltyrosine may be potentiated by alcohol and other CNS depressants. Use with phenothiazines or haloperidol may exacerbate extrapyramidal effects.

**Pharmacokinetics**

$\alpha$ -Methyltyrosine is well absorbed from the gastrointestinal tract and is excreted mainly unchanged by the kidneys. A plasma half-life of 3.4 to 7.2 hours has been reported. Less than 1% of a dose may be excreted as the metabolites  $\alpha$ -methyl-dopa,  $\alpha$ -methyl-dopamine,  $\alpha$ -methylnoradrenaline, and  $\alpha$ -methyltyramine.

**Uses and Administration**

$\alpha$ -Methyltyrosine is an inhibitor of the enzyme tyrosine hydroxylase, and consequently of the synthesis of catecholamines. It is used to control the symptoms of excessive sympathetic stimulation in patients with phaeochromocytoma (p.1179) and decreases the frequency and severity of hypertensive attacks and related symptoms in most patients. It may be given for pre-operative preparation, or for long-term management in those for whom surgery is contra-indicated or who have malignant phaeochromocytoma.

In the management of phaeochromocytoma,  $\alpha$ -methyltyrosine is given orally in a dose of 250 mg four times daily, increased daily by 250 mg or 500 mg to a maximum of 4 g daily in divided doses. The optimum dose, achieved by monitoring clinical symptoms and catecholamine excretion, is usually in the range of 2 to 3 g daily and when used pre-operatively it should be given for at least 5 to 7 days before surgery. The use of  $\alpha$ -blockers may also be necessary.

$\alpha$ -Methyltyrosine is not effective in controlling essential hypertension.

$\alpha$ -Methyltyrosine has also been tried in patients with schizophrenia.

**Preparations**

**USP 31:** Metirosine Capsules.

**Proprietary Preparations** (details are given in Part 3)

**USA:** Demser.

**Metolazone** (BAN, USAN, rINN) ⊗

Metolatsoni; Metolazon; Metolazona; Métolazone; Metolazonum; SR-720-22. 7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3- $\alpha$ -tolylquinazolinone-6-sulphonamide.

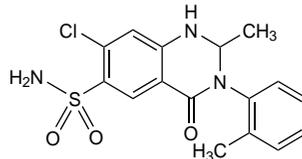
МетОлазон

$C_{16}H_{16}ClN_3O_3S = 365.8$ .

CAS — 17560-51-9.

ATC — C03BA08.

ATC Vet — QC03BA08.



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

**Ph. Eur. 6.2** (Metolazone). A white or slightly yellowish, crystalline powder. It exhibits polymorphism. Very slightly soluble in water and dichloromethane; sparingly soluble in methyl alcohol; slightly soluble in ethyl acetate. Protect from light.

**USP 31** (Metolazone). Store in airtight containers. Protect from light.

**Adverse Effects and Treatment**

As for Hydrochlorothiazide, p.1307. Metolazone has also been reported to cause palpitations, chest pain, and chills.

**Effects on the blood.** Profound neutropenia was seen in a 58-year-old woman within 10 days of starting treatment with metolazone.<sup>1</sup> Neutropenia persisted for a further 10 days after metolazone was withdrawn. No other haematological abnormalities were seen.

1. Donovan KL. Neutropenia and metolazone. *BMJ* 1989; **299**: 981.

**Effects on the nervous system.** Two patients had acute muscle cramps with impairment of consciousness and epileptiform movements after taking metolazone 5 mg (single dose) or 2.5 mg daily for 3 days.<sup>1</sup>

1. Fitzgerald MX, Brennan NJ. Muscle cramps, collapse, and seizures in two patients taking metolazone. *BMJ* 1976; **1**: 1381-2.

**Precautions**

As for Hydrochlorothiazide, p.1309.

**Interactions**

As for Hydrochlorothiazide, p.1309. Severe electrolyte disturbances may occur when metolazone and furosemide are used together.

**ACE inhibitors.** Deterioration in renal function occurred in a 65-year-old woman when metolazone 5 mg [daily] was added to captopril, furosemide, spironolactone, and digoxin for heart failure.<sup>1</sup> An interaction between captopril and metolazone was suspected and both drugs were stopped with a subsequent return to normal renal function. It was suggested that natriuresis and a fall in blood pressure caused by the diuretic may have compromised an already low renal perfusion pressure when autoregulatory mechanisms were blocked by captopril.

1. Hogg KJ, Hillis WS. Captopril/metolazone induced renal failure. *Lancet* 1986; **1**: 501-2.

**Antidiabetics.** Hypoglycaemia occurred in a patient with type 2 diabetes mellitus controlled with glibenclamide 40 hours after starting therapy with metolazone 5 mg daily.<sup>1</sup> Studies of protein

binding *in vitro* did not reveal any evidence of displacement of glibenclamide from binding sites.

1. George S, *et al.* Possible protein binding displacement interaction between glibenclamide and metolazone. *Eur J Clin Pharmacol* 1990; **38**: 93-5.

**Ciclosporin.** An increase in serum-creatinine concentration in a renal transplant patient was attributed to a toxic drug interaction between metolazone and ciclosporin.<sup>1</sup> Serum-creatinine concentrations returned to pretreatment values when metolazone was stopped.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and ciclosporin. *BMJ* 1987; **294**: 578.

**Pharmacokinetics**

Metolazone is slowly and incompletely absorbed from the gastrointestinal tract. An average of about 65% of a dose has been reported to be absorbed after oral doses in healthy subjects, and an average of about 40% in patients with cardiac disease. In some countries a formulation with enhanced bioavailability is available. About 95% of the drug is bound in the circulation: about 50 to 70% to the red blood cells and between 15 and 33% to plasma proteins. The half-life has been reported to be 8 to 10 hours in whole blood, and 4 to 5 hours in plasma, but the diuretic effect persists for up to 24 hours or more. About 70 to 80% of the amount of metolazone absorbed is excreted in the urine, of which 80 to 95% is excreted unchanged. The remainder is excreted in the bile and some enterohepatic circulation has been reported. Metolazone crosses the placenta and is distributed into breast milk.

◇ References.

1. Tilstone WJ, *et al.* Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther* 1974; **16**: 322-9.

**Uses and Administration**

Metolazone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Unlike thiazides in general, metolazone is reported to be effective in patients with a glomerular filtration rate of less than 20 mL/minute. Diuresis starts in about 1 hour, reaches a peak in about 2 hours, and lasts for 12 to 24 hours depending on the dose.

A preparation with enhanced bioavailability, which is effective in lower doses than conventional formulations, is available in some countries. Doses given in *Martindale* refer to the conventional tablet formulation unless otherwise stated.

In the treatment of **oedema** the usual dose is 5 to 10 mg daily; in some cases doses of 20 mg or more may be required. No more than 80 mg should be given in any 24-hour period. In refractory cases, metolazone has been used with furosemide or other loop diuretics, but the electrolyte balance should be monitored closely.

In the treatment of **hypertension** the usual dose is 2.5 to 5 mg daily either alone, or with other antihypertensives. An initial dose of 1.25 mg has also been used. The dosage may be adjusted after 3 to 4 weeks according to response. A maintenance dose of 5 mg on alternate days may be used.

Formulations with enhanced bioavailability are given in doses of 0.5 to 1 mg daily in the treatment of hypertension. They are not bioequivalent to the conventional tablet formulation and should not be used interchangeably.

**Preparations**

**USP 31:** Metolazone Oral Suspension; Metolazone Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Canad.:** Zaroxolyn; **Chile:** Pavedal; **Ger.:** Zaroxolyn†; **Gr.:** Metenix; Zaroxolyn†; **Hong Kong:** Zaroxolyn; **India:** Metoz; **Israel:** Zaroxolyn; **Ital.:** Zaroxolyn; **Port.:** Diulo; **S.Afr.:** Zaroxolyn†; **Switz.:** Zaroxolyn†; **UK:** Metenix; **USA:** Mykrox; Zaroxolyn.