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†.

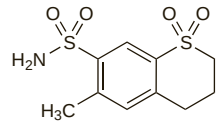
Multi-ingredient: ***Arg.:*** Normatensil†; ***Austria:*** Aldoretic; ***Braz.:*** Hydromet; ***Canad.:*** Apo-Methazide; PMS-Dopazide; Supres†; ***Gr.:*** Hydromet†; ***Ital.:*** Medozide; Saludopin; ***Port.:*** Aldoretic†; ***USA:*** Aldoclor; Aldoril†.

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

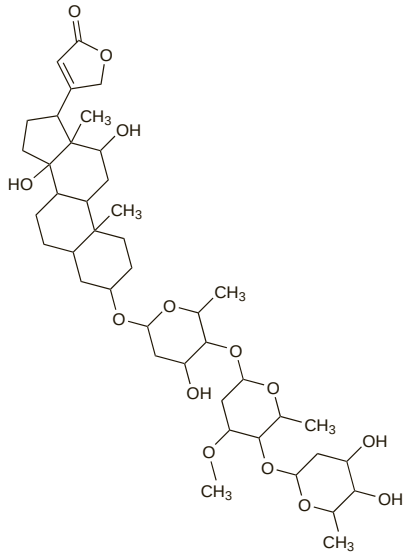
Meticrane is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used in the treatment of hypertension.

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

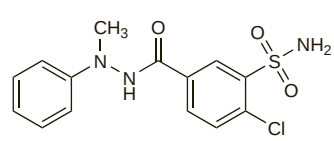
Proprietary Preparations (details are given in Part 3)

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.