Metirosine *(BAN, rINN)*

L-588357-0; Metirosiini; Metirosin; Metirosina; Métirosine; Metirosinum; Metyrosine *(USAN)*; MK-781. (–)-α-Methyl-L-tyrosine; 4-Hydroxy-α-methylphenylalanine.

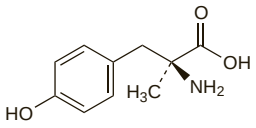
Метирозин

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

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

ATC — C02KB01.

ATC Vet — QC02KB01.



NOTE. The term α-methyltyrosine (α-MPT; α-MT; α-methyl-*p*-tyrosine) is used below since although metirosine, the (–)-isomer, is the active form the manufacturers state that some racemate (racemetirosine; (±)-α-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 α-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 α-methyltyrosine in a patient with Huntington's chorea.[1]

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 α-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.

α-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 α-methyltyrosine is withdrawn.

When α-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 α-methyltyrosine may be potentiated by alcohol and other CNS depressants. Use with phenothiazines or haloperidol may exacerbate extrapyramidal effects.

Pharmacokinetics

α-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 α-methyldopa, α-methyldopamine, α-methylnoradrenaline, and α-methyltyramine.

Uses and Administration

α-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, α-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.

α-Methyltyrosine is not effective in controlling essential hypertension.

α-Methyltyrosine has also been tried in patients with schizophrenia.

Preparations

USP 31: Metyrosine 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-*o*-tolylquinazoline-6-sulphonamide.

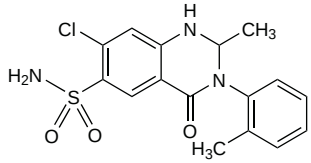
Метолазон

$C_{16}H_{16}ClN_3O_3S$ = 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.[1] 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.[1]

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.[1] 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; **i:** 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.[1] 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.[1] Serum-creatinine concentrations returned to pretreatment values when metolazone was stopped.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *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.:*** Zaroxolyne†; ***UK:*** Metenix; ***USA:*** Mykrox; Zaroxolyn.
