MIDODRINE

Introduction

Midodrine is a peripherally acting **alpha-1 agonist** agent.

It is a **prodrug** which forms an active metabolite, **desglymidodrine**.

It is used as a second line treatment for symptomatic orthostatic hypotension where other standard treatments have proven inadequate.

It is not marketed in Australia but is available through the Special Access Scheme.

See also separate document on Midodrine Overdose (in Toxicology folder).

History

Midodrine was approved in the United States by the Food and Drug Administration in 1996 for the treatment of dysautonomia and orthostatic hypotension.

Chemistry

Following oral or intravenous administration, midodrine is hydrolyzed to a pharmacologically active metabolite, desglymidodrine which appears to be primarily responsible for therapeutic activity.

Desglymidodrine is structurally similar to **methoxamine** and produces alpha-adrenergic receptor stimulation of both arterial and venous systems

In vitro studies have demonstrated this metabolite to be approximately 15 times as potent as midodrine itself in producing vasoconstriction.

Physiology

Actions of the alpha-1 receptor mainly involve smooth muscle contraction.

It causes vasoconstriction in many blood vessels

Preparations

Midodrine hydrochloride as:

Tablets:

- 2.5 mg
- 5.0 mg

Mechanism of Action

Midodrine is a prodrug which forms an active metabolite, desglymidodrine.

Desglymidodrine is a **peripherally** acting **alpha-1 receptor agonist**.

It exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure.

Midodrine appears to enhance peripheral vascular tone and reduce venous pooling.

Desglymidodrine does **not** stimulate cardiac beta-adrenergic receptors

Pharmacodynamics

Midodrine is a **relatively long acting** alpha-1 agonist agent.

In comparison with other sympathomimetic agents, midodrine appears to be as effective *without* producing the increases in heart rate (in most patients) that is seen with this class of drugs.

Following a 10 mg dose, standing systolic blood pressure rises by approximately 15 - 30 mmHg at 1 hour and can persist for up to 3 hours.

Pharmacokinetics

Absorption:

- Midodrine is a prodrug which forms an active metabolite, **desglymidodrine**.

  Midodrine itself only minimally contributes to pharmacologic effects.

  Absorption from the GIT tract is rapid following ingestion.

- Oral bioavailability is around 93%

- Peak plasma concentrations reached after 30 minutes.

  For its active metabolite, desglymidodrine, peak plasma concentrations are reached after approximately 1 hour.

Distribution

- Volume of Distribution is 4 - 4.6 L/kg
- In animal studies, midodrine does *not* cross the blood-brain barrier; however, there are no human studies.
- Neither midodrine nor desglymidodrine are bound to plasma proteins to any significant extent.
- It is unknown if midodrine can cross the human placenta
- It is unknown if midodrine is excreted in human breast milk.

Metabolism and excretion:

- Midodrine undergoes enzymatic hydrolysis (deglycination) in the systemic circulation.

  It is unclear if any hepatic metabolism occurs.
- The elimination half-life of midodrine is **30 minutes.**

  The elimination half-life of desglymidodrine is 3 hours.

  Midodrine is nearly undetectable in plasma 2 hours after an oral dose.
- Desglymidodrine is 45 - 75 % renally excreted.

Indications

Midodrine is used mainly as a second line treatment for symptomatic orthostatic hypotension where other standard treatments have proven inadequate

It is used for:

1. Patients with neurocardiogenic syncope
2. Patients with refractory recurrent vasovagal syncope
3. It may be of benefit in some patients with POTS.
4. Orthostatic hypotension due to autonomic dysfunction in general
5. Dialysis-associated hypotension

Contra-indications/precautions

These include:

1. Known hypersensitivity
2. Renal disease:
    - Dosing adjustments may be indicated in patients with renal insufficiency.
3. Urinary retention
4. Persistent and excessive supine hypertension
5. Pheochromocytoma
6. Severe organic heart disease
7. Thyrotoxicosis

Safety and efficacy in paediatric patients have not been established.

Pregnancy

There is no information on midodrine in pregnancy.

It should be given only if the potential benefit justifies the potential risk to the fetus.

Breast feeding

Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding.

Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

Adverse Effects

These include:

1. Supine hypertension:
    - Marked elevation of **supine** blood pressure may occur.

      Because midodrine can cause marked elevation of supine blood pressure, it should only be used in patients whose lives are considerably impaired despite standard clinical care.

2. Arrhythmias:

   Bradycardia:

   - Slowing of the heart rate may occur primarily due to **vagal reflex**; use caution when administering with drugs that directly or indirectly lower heart rate (digitalis, beta blockers).

   Tachyarrhythmias:

   - May occur due to direct cardiac effects.

3. Orthostatic hypotensive patients with diabetes.

4. Hepatic insufficiency

5. Ophthalmic:

   - Patients with history of vision disorders and receiving fludrocortisone are at risk of elevated intraocular pressure.

6. Renal:

   - Use caution in patients with renal impairment; assess renal function prior to treatment initiation.

7. Urinary retention.

Dosing

Usual adult dosing is:

- Midodrine orally, 2.5 - 10 mg three times daily

  Give at approximately 4 hour intervals during daytime hours when the patient is upright.

  It may be given in 3 hour intervals if necessary to control symptoms, but not more frequently than this.

Do not give after evening meal or less than 4 hours before bedtime

Maximum dosing:

Single doses up to 20 mg have been given, but severe hypertension is more likely.

Total daily doses greater than 30 mg have been tolerated by some patients, but the safety and usefulness of doses this high are unclear

The **maximum** recommended daily dose is **40 mg**.

References

1. Midodrine in Micromedex Website, Accessed September 2017.

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