# MIDODRINE OVERDOSE

## 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.

Taken in overdose midodrine can result in severe hypertension with reflex bradycardia.

**Given its relatively short half-life, vasodilator agents and supportive care are likely all that is required for treatment.**

**See also separate document on Midodrine (in Drugs 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.

## Preparations

Midodrine hydrochloride as:

Tablets:

- 2.5 mg
- 5.0 mg

## Toxicology

The toxicity of midodrine is essentially due to an extension of its normal therapeutic effect, i.e an alpha -1 receptor agonist.

The cause of its central effects in, overdose, are unknown.

## 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%

*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:*

- Following oral or IV dosing, midodrine undergoes enzymatic hydrolysis (deglycination) in the systemic circulation.

  Midodrine is nearly undetectable in plasma 2 hours after an oral dose. It is unclear if any hepatic metabolism occurs.

- Desglymidodrine is 45 - 75 % renally excreted.

## Risk assessment

Children and adults who have ingested ≥ **2 mg/kg** of midodrine are susceptible to toxic effects. [2]

## Clinical features

Clinical features in overdose include:

1. GIT upset
   - Nausea / vomiting.
2. CVS:

Hypertension:

- This can be severe

  Secondary hypertensive complications are possible:

  - ♥ Intracranial haemorrhage
  - ♥ ACS
  - ♥ Aortic dissection
  - ♥ Cardiogenic acute pulmonary edema.

Hypotension:

- While hypertension is much more likely, hypotension has also been observed, though this is rare.

  If hypotension occurs, it is generally profound and the result of total "cardiovascular collapse".

Bradycardia:

- This is essentially a reflex response to the systemic hypertension.

3. CNS:

   - There are case reports of reduced conscious state.

     The cause of decreased conscious state remains unclear.

     Although in therapeutic dosing midodrine does not cross the blood brain-barrier, permeability and CNS effects are unknown at excessively high blood concentrations.

     Hypertensive encephalopathy may be a causes, however this typically starts around 12 hours after a sustained blood pressure increase, while in midodrine overdose altered conscious state may occur with just a few hours.

4. Piloerection

5. Urinary urgency / retention

## Investigations

1. Blood tests:

Consider coingestion:

- Serum paracetamol
- Blood alcohol levels.

2. ECG:

- Check cardiac rhythm / QRS duration / QT interval.

3 Midodrine and desglymidodrine blood levels:

- Midodrine and desglymidodrine blood levels can be done in specialized laboratories

  The peak effect on the blood pressure appears to coincide with the peak of the metabolite desglymidodrine concentration

4. CT scan:

- Patients with an altered conscious state should have a cerebral CT scan.

## Management

1. Immediate attention to any ABC issues.

2. Charcoal:

- The benefit of gastric decontamination is uncertain.

  Consider oral activated charcoal if the patient presents within 1 hour of ingestion of 2 mg/kg or more midodrine, provided the airway can be protected.

3. Hypertension:

Use vasodilating agents

Options include:

- GTN patch/ IV infusion.
- Labetalol IV
- Phentolamine IV

Pure beta -blockers should be avoided (unopposed beta-2 effects may aggravate hypertension.

4. Bradycardia with **hypo**tension:

    - Atropine IV

5. Other **supportive care** as required.

*Disposition:*

All patients should be observed for at least 6 hours after a potentially toxic ingestion.

Experience with midodrine overdose is extremely limited, and so cases should be discussed with a **Clinical Toxicologist**.

*References*


1. L. Y. Wong, A. Wong, T. Robertson, K. Burns, M. Roberts, G. K. Isbister. Severe Hypertension and Bradycardia Secondary to Midodrine Overdose. J. Med. Toxicol. (2017) 13:88 - 90

    - DOI 10.1007/s13181-016-0574 - 4.

2. Midodrine Overdose in Toxbase Website, November 2015

3. Midodrine Overdose in Toxinz Website, March 2018.



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