Midodrine for Orthostatic Hypotension

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1.0 Summary for Patients

- Midodrine is a tablet used for treating low blood pressure (hypotension). People who suffer with low blood pressure can feel dizzy, and fall or faint when they stand up.

- A number of things can help including standing up slowly and crossing the legs while standing. People may be asked to try to change their eating habits, increase their fluid intake or to wear special stockings before being given medicines for low blood pressure.

- Several medicines can treat low blood pressure. One, called fludrocortisone, is often used first. If this doesn’t help, midodrine may be tried instead of, or together with, fludrocortisone.

- Studies in patients with low blood pressure show that midodrine can stop blood pressure falling too much when a person stands up, and may reduce dizziness and other symptoms.

- Some people with low blood pressure cannot carry out normal daily tasks properly such as dressing, washing and cooking. Studies have not yet shown that midodrine makes these any easier.

- Midodrine does not work in everyone, but any benefits are seen after only a few days.

- Midodrine can cause goose bumps, itching and tingling. A serious side effect that can occur in some people is a large increase in blood pressure when lying down.

1.1 Summary for Healthcare Professionals

- Studies of midodrine for the treatment of orthostatic hypotension (OH) are not particularly robust, but the evidence base for other drugs currently used to treat OH is no better, and probably worse than that for midodrine.

- The efficacy of midodrine has been assessed mainly on the surrogate outcome of raising systolic blood pressure on standing compared to placebo. There is little evidence that midodrine improves patients’ abilities to carry out activities of daily living, which is the principal aim of treatment. The two largest studies, which between them enrolled 268 patients (but had high drop-out rates), suggest that midodrine may reduce symptoms associated with OH, such as light-headedness, and make patients ‘feel better’.

- None of the reviewed studies extended beyond four week’s treatment and comparative data are lacking.

- Supine hypertension is the most serious potential adverse reaction.

- Midodrine (10mg three times a day) costs between £780 and £3,200 per year per patient depending on brand (inclusive of VAT). No published health economic data have been identified.
The figure below highlights the balance of benefits, risks, evidence, regulatory status and costs for this intervention:

The data in the diagram above is taken from assessment against the standard options below:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td><strong>Health benefits expected</strong></td>
<td>Minor symptom control, or potential but unproven patient benefit</td>
<td>Symptom control, improved health-related quality of life (HRQoL)</td>
<td>Major HRQoL gain e.g. months of life gained</td>
<td>Transforming HRQoL e.g. years of life gained</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Early death or substantial morbidity</td>
<td>Severe side effects affecting HRQoL</td>
<td>Moderate side effects</td>
<td>Minor side effects</td>
</tr>
<tr>
<td><strong>Strength of evidence</strong></td>
<td>Speculative approach</td>
<td>Single case or small case series, uncontrolled studies</td>
<td>Small controlled studies</td>
<td>At least one large RCT</td>
</tr>
<tr>
<td><strong>Regulatory status</strong></td>
<td>No UK licensed product. No licence globally</td>
<td>No UK licensed product. Licensed products exist in US/Europe but not necessarily for this intervention</td>
<td>UK licensed product. Intervention off-label in UK, and in US/Europe</td>
<td>UK licensed product. Intervention off-label in UK but licensed in USA/Europe</td>
</tr>
<tr>
<td><strong>Affordability</strong></td>
<td>Very significant costs above current best care option</td>
<td>Increased costs above current best care option</td>
<td>Modest increased costs or cost neutral</td>
<td>Cost saving compared with current best option</td>
</tr>
</tbody>
</table>
2.0 Intervention

Orthostatic or postural hypotension is defined as a reduction in systolic blood pressure (BP) of at least 20mmHg and/or a reduction in diastolic BP of at least 10mmHg within three minutes of standing or upright tilt table testing to 60-75° [1]. It can occur acutely as a result of blood loss or volume depletion or be a consequence of autonomic system disorders (e.g. Parkinson’s disease, diabetic autonomic neuropathy). Medication, inadequate fluid intake and decreased autonomic nervous system function are frequently implicated in the elderly.

The prevalence of orthostatic hypotension (OH) increases with age. The reported prevalence is 5 to 30% in patients 65 years and older [1]. In elderly patients, OH can significantly affect morbidity, cause disability as a result of falls and fractures, and increase the risk of overall mortality [1,2].

The normal response to standing is a drop in systolic BP of 5-10mmHg and an increase in diastolic BP of 5-10mmHg as around 500-1000mL of blood shifts from the central to the peripheral vascular system. In healthy individuals this results in an increase in heart rate and vascular resistance [1]. In people with autonomic dysfunction, the compensatory reflexes are lost resulting in a fall in both systolic and diastolic BP on standing with associated symptoms of dizziness, light-headedness, weakness, blurred vision, syncope (fainting), shoulder pain and shortness of breath [1,2]. If the person sits or lies down, symptoms subside as BP normalises.

The goal of treatment is to improve the patient’s ability to carry out daily functions, improve their quality of life and prevent injury, rather than to achieve a target BP. Guidelines published by the European Federation of Neurological Societies on managing symptomatic OH recommend non-pharmacological treatments first, including avoiding aggravating factors (e.g. large meals), using physical counter manoeuvres (e.g. leg crossing) and compression stockings, and increasing salt and water intake [2]. The guidelines recommend fludrocortisone as initial drug treatment and midodrine as second line, either as monotherapy or in combination with fludrocortisone. They acknowledge the recommendation to use fludrocortisone is not based on strong evidence (level C) and suggest the evidence base for midodrine is more robust (level A). Other guidelines do not indicate a particular order of use [3,4,5].

Alternative drugs that have been used for treating OH include domperidone, ephedrine and pyridostigmine. SIGN guidance on the management of Parkinson’s disease states that there is not enough evidence to recommend any drug for the treatment of OH due to small numbers of studies, small sample sizes and short study duration [3].

There are no products licensed in the UK for treating OH. Fludrocortisone, domperidone and pyridostigmine are used off-label; midodrine is not licensed in the UK for any indication. Droxidopa is a potential new treatment for OH that is currently in phase III studies. It is unlikely to be licensed before 2012 [6].

Midodrine is a pro-drug; its active metabolite desglymidodrine is a peripherally acting α-1 adrenoceptor agonist that increases BP by causing vasoconstriction. The elimination half-life of the metabolite is two to three hours and the duration of action of midodrine is approximately four hours [2].
3.0 Review of Data Available

There are few studies investigating the value of midodrine to treat OH that are of suitable quality for a formal assessment. Four published controlled trials meet the inclusion criteria for this review (see section 6.2 for reasons for excluding studies). These studies are the principal means of assessing benefits and risks, and are discussed below.

3.1 Benefits

Parallel group studies
The two largest studies are randomised, double-blind, parallel group trials designed to compare the effects of midodrine and placebo on BP and symptoms of OH in the out-patient setting [7,8]. Patients were enrolled if they were aged 18 years or over with OH due to autonomic failure causing a drop in systolic BP from supine to standing of 15mmHg or more and/or symptoms of dizziness, light-headedness, unsteadiness and syncope. They were excluded if they had pre-existing supine hypertension of ≥180/110mmHg or significant systemic illness, including renal, hepatic and cardiac disease. Patients already prescribed a sympathomimetic agent, a vasoactive drug or an α-agonist were either excluded or the drugs were stopped. The use of fludrocortisone, a high salt diet and compression garments were allowed during the studies. Primary outcomes in both studies were one hour post-dose systolic BP measured one minute after standing, and symptoms of OH.

The first study included 171 patients (overall mean age not reported but was likely to have been about 60 years) [7]. It comprised a one week single-blind placebo run-in period, followed by a three week double-blind period in which patients were randomised to receive 10mg midodrine or placebo three times daily and ended in a two week single-blind wash-out phase. BP was measured at weekly intervals, one-hour post-dose. Standing BP was significantly improved in the midodrine group compared to the placebo group at the first evaluation in the double-blind period (P<0.001). Patients on midodrine had a mean increase in systolic BP of 21.8mmHg (a 23% increase) and in diastolic BP of 12.3mmHg (20%). The corresponding figures for the placebo group were 4.6mmHg (5%) and 2.2mmHg (3%), respectively. The one-hour post-dose increase in BP with midodrine was maintained throughout the treatment period and was independent of existing treatment (fludrocortisone, compression garments) and OH severity (systolic BP fall on standing of <30mmHg vs. ≥30mmHg).

The additional primary outcome for this study was light-headedness, scored on an eleven-point scale (where zero is always light-headed and 10 is never). Light-headedness scores improved for both midodrine and placebo treated groups during the double-blind phase from a baseline of around 3.4 for both groups. Although consistently higher in the midodrine group (highest score 5.3 vs. 4.7 for placebo, estimated from a graph), the scores for this group were only statistically significantly different from placebo at week two of the double-blind phase (P=0.02).

A secondary outcome was a composite of light-headedness, ability to remain standing and ability to perform activities of daily living. This was measured on a six-point scale, where zero was no improvement and 5 was excellent improvement. At the end of the double-blind period, midodrine was associated with greater improvement compared to placebo for both patient (2.7 vs. 2.2; P=0.03) and investigator scores (2.8 vs. 2.0; P<0.001).

The second parallel group study included 97 patients (mean age 61 years, range 22 to 86 years) [8]. It comprised a one week, single-blind placebo run-in period followed by four week’s treatment with placebo or midodrine 2.5mg, 5mg or 10mg three times daily. Patients randomised to higher doses of midodrine were titrated slowly over one to two weeks. An increase in standing systolic BP one-hour post-dose was seen with all midodrine doses, but only the 10mg midodrine dose produced a statistically significant mean increase of 22mmHg (a 28% increase) compared to 3mmHg with placebo (4% increase; P<0.001). Compared to placebo, midodrine was associated with a mean percentage improvement in all symptoms assessed by patient-completed questionnaire. This
reached statistical significance for the ability to stand for more than 15 minutes (2.5mg only), for light-headedness and weakness (5mg only) and for syncope, energy level and depression (10mg only). The clinical significance of these changes is uncertain. A secondary outcome, measured using a global impression score, found more than 70% of patients taking midodrine 2.5mg or 10mg ‘felt better’ compared with 50% on 5mg and 40% on placebo (taken from a graph).

**Cross-over studies**

A small, randomised, placebo-controlled, cross-over, in-patient study compared midodrine to oral ephedrine in eight patients [9]. The trial had similar inclusion and exclusion criteria to the parallel group studies above, except that the diagnosis of OH was confirmed by Valsalva and cold pressor tests. All patients had previously shown no response to other treatments for OH. The study comprised a two day single-blind placebo run-in period followed by a double-blind titration period over three to five days. Study medication was midodrine 2.5mg to 10mg three times daily or ephedrine 6mg to 24mg three times daily, given until a supine systolic BP of 140 to 180mmHg and a standing systolic BP of at least 80mmHg was reached. This was then followed by a maintenance period of three to five days, followed by a four day placebo wash-out. The patients’ treatment was then crossed-over. The mean maintenance doses were 8.4mg three times daily for midodrine and 22.3mg three times daily for ephedrine.

The primary outcome was mean standing BP measured hourly throughout the day during the three to five day maintenance period. There was a mean increase from baseline in standing systolic BP of 17mmHg for patients on midodrine compared to 1mmHg for those on ephedrine and –2mmHg for those on placebo (P<0.001 for both comparisons vs. midodrine). The percentage of standing systolic BP readings ≥80mmHg was significantly higher with midodrine than placebo (81.8% vs. 54.8%, respectively), but not for ephedrine (59.1%) vs. placebo. In the midodrine group, the number of instances in which patients could not stand unsupported to have their BP measured was halved (from 10.7% to 5.3%; P<0.01 vs. placebo); there was no significant difference between ephedrine and placebo.

A further double-blind cross-over study was conducted in seven in-patients with ‘severe’ OH (drop in mean BP on standing ranging from 12 to 60mmHg, plus abnormal results on tilt and Valsalva tests) [10]. After a seven day baseline period with no therapy, patients received midodrine (initially 10mg/day increasing up to 40mg/day, based on weight) for up to two weeks and were then randomised to either 100 microgram fludrocortisone daily plus placebo or fludrocortisone plus midodrine for the next week. After a two day wash-out period, treatments were crossed-over for the final week. A statistically significant increase in mean daytime standing arterial BP was noted in three patients on midodrine alone and in one patient on fludrocortisone alone. The combination of midodrine and fludrocortisone was more effective than midodrine alone in only one patient. An analysis suggested that compared to responders, midodrine non-responders had significantly greater impairment of autonomic reflexes.

**Summary**

Two studies, involving a total of 268 patients, have shown midodrine (10mg three times a day) for three to four weeks to be significantly more effective than placebo in increasing standing systolic BP by up to 22mmHg and standing diastolic BP by up to 15mmHg, as measured by the surrogate endpoint of one-minute standing BP one-hour post-dose [7,8]. This effect seems to be dose-dependent [8].

Midodrine may improve symptoms associated with OH, such as light-headedness, although this was only achieved in week two of the study of 171 patients [7]. There are few comparative data with other agents used to treat OH. Results from two small cross-over studies suggest that midodrine may be more effective than ephedrine and fludrocortisone in increasing standing BP [9,10].
3.2 Strength of Evidence

Appropriate endpoints to measure clinical response in OH have not been established. Most studies, including three of those discussed above, have used one-minute standing BP values measured one hour post-dose as a primary outcome measure. This is a surrogate endpoint.

Symptom assessment is a more relevant patient-oriented outcome but there are no validated scales in OH. The studies reviewed have used different methods for assessing the effect on symptoms. Ongoing phase III studies with droxidopa are using the Orthostatic Hypotension Questionnaire (OHQ) composite score as a primary outcome, but this has not been used in studies of agents currently used in clinical practice. The score incorporates defined measures of ability to carry out activities of daily living and is more likely to correspond to clinical benefit than outcomes used in older studies [6].

The first of the studies discussed above is the most robust: it included the greatest number of patients (n=171) and the power calculation for sample size was based on light-headedness as an outcome [7]. It was randomised (method not described) and double-blind, although patients may have been able to identify if they were on active treatment because of the recognisable side effects of midodrine. It had more stringent inclusion criteria than the second study reviewed as all patients were required to have a reduction in systolic BP from supine to standing of ≥15mmHg (but note that this criterion does not meet the current definition of OH of a reduction of ≥20mmHg). Midodrine also improved light-headedness but this was documented as a 0.6 point increase on an 11 point visual analogue scale and clinical significance is uncertain. A principal drawback of the study was the number of subjects who dropped out; only 59 of the 82 patients randomised to midodrine completed the study (72%) compared to 80 of 89 (90%) randomised to placebo.

The second study was also randomised (method not described) and double-blind, but the sample size was not supported by a power calculation [8]. 87 patients (of 97 enrolled) completed the study and, of these, only 75 had BP readings that were evaluable. Data on symptoms were collected using a patient completed questionnaire. The questionnaire was amended during the study as patients had difficulty in completing it and questionnaires from only 63 patients were analysed. Multiple comparisons were made vs. placebo without any statistical adjustment.

The two cross-over studies described were too small to draw any firm conclusions from their results [9,10].

All the reviewed studies were of short duration. There are no long-term controlled studies of midodrine in OH and comparative data are lacking. The evidence base for midodrine in treating OH is not robust. However, it appears to be better than that for other agents currently used for this indication [2]. Further research in this area is required.

3.3 Risks

In both parallel-group studies, the frequency of adverse effects was higher in patients taking midodrine than taking placebo. In the larger study, the most frequently reported adverse effects were piloerection (goose bumps - 13% midodrine vs. 0% placebo), scalp pruritus (10% vs. 2%), paraesthesia (9% vs. 3%), scalp paraesthesia (9% vs. 1%), urinary retention (6% vs. 0%) and supine hypertension (6% vs. 0%) [7]. In the second study, the main adverse effects were pruritus (14% midodrine vs. 2% placebo), supine hypertension (8% vs. 1%) and urinary urgency (4% vs. 0%) [8]. Urinary effects are a particular concern in elderly patients and can adversely affect quality of life.

The overall incidence of adverse effects was not given in the larger study, but the difference between groups was described as statistically significant (P=0.001) [7]. Fifteen patients (18%) in this study withdrew because of adverse drug reactions (ADR)s to midodrine (seven due to urinary
urgency or retention, five to supine hypertension and three to piloerection reactions). A number of patients who experienced ADRs with midodrine during the study asked to continue treatment. In these patients, side effects were managed by dose adjustment after the trial had ended. In the second study, the incidence of ADRs was 27% in the midodrine group and 22% in the placebo group; 7% vs. 3% of patients, respectively, withdrew because of adverse effects [8].

Long-term tolerability data have been reported from a prospective registry of 135 elderly subjects (mean age 84 years) referred to a geriatric unit for assessment of syncope or unexplained falls and who were subsequently treated with midodrine. Patients were followed up for a median of 2.7 years. Around one-third of patients had OH. Thirty-four subjects discontinued therapy early (although 37 actually had no benefit from the drug). Incidences of ADRs were assessed at each clinic visit and although 19 patients reported drug-related events, only six discontinued treatment because of them (hypertension n=3, and one report each of lower urinary tract obstructive symptoms, palpitations and nausea). The majority of subjects were taking lower then the usual recommended dose of 10mg three times a day (49% were taking 2.5mg and 30% 5mg, three times a day) [11].

There are few direct data comparing the tolerability of midodrine and other agents used in the treatment of OH; a French prospective, observational study gives an indirect comparison. In the study, 127 consecutive out-patients (mean age 67.6 years) taking drug treatment for OH were asked about possible ADRs at a scheduled clinic visit [12]. Forty-two patients were on midodrine alone, nine on fludrocortisone alone and 28 on a combination of the two. Other drugs used included heptaminol and dihydroergotamine. Eighty-eight patients reported a total of 141 ADRs with no statistical difference in the incidence between therapies. Thirty-four patients on midodrine alone reported 56 ADRs of which nine were classed as serious; 21 patients on the combination of midodrine with fludrocortisone reported 37 ADRs of which 12 were serious. Three of the eight reports of ADRs associated with fludrocortisone monotherapy were serious.

Supine hypertension is the most frequently reported serious ADR with midodrine. US prescribing information advises patients to only take doses during daytime hours with the last dose taken at least four hours before bedtime [13]. Supine and standing BP should be monitored regularly. Supine hypertension is more likely to occur in patients with a high pre-treatment systolic BP. As a consequence midodrine is contraindicated in patients with persistent and excessive supine hypertension. Other contraindications include severe heart disease, urinary retention, phaeochromocytoma and thyrotoxicosis.

In the studies discussed above, patients with renal disease were excluded. In clinical practice, many patients with orthostatic hypotension will have concomitant renal impairment. US prescribing information recommends using midodrine cautiously in such patients and, if used, a low starting dose (2.5mg) should be given.

Midodrine should also be used cautiously with drugs that cause vasoconstriction (e.g. decongestants such as pseudoephedrine or phenylpropanolamine which are included in many over-the-counter preparations) and with digoxin [13].

Any benefits of midodrine are seen within a few days of treatment. Given that the majority of data to support the use of midodrine in OH are from short-term studies, it seems sensible to continue midodrine only in those patients who report significant symptomatic improvement within the first one or two weeks.

3.4 Regulatory Status

Midodrine is not available as a licensed preparation in the UK but is marketed elsewhere including Germany, France and Eire, where it is licensed for the treatment of hypotension or OH [14]. It can be imported into the UK on a named patient basis.
Midodrine is also available in the US where it was licensed for treating OH in 1996 under the accelerated approval process. This allows earlier approval of drugs for serious or life-threatening conditions on the basis of surrogate endpoints. Such approval requires that the manufacturer conduct post-marketing studies proving benefit in clinical outcomes [15]. In August 2010, noting that the expected clinical benefit had not been verified by data submitted to the regulator, the Food and Drug Administration (FDA) proposed withdrawing approval for midodrine [16]. However, professional organisations, health care professionals and patients appealed against this. The FDA is now working with manufacturers, physicians and patient organisations to identify any relevant existing supporting data, and in the planning and design of two clinical studies that, if successful in establishing midodrine’s effectiveness in relieving symptoms of OH, would be acceptable for regulatory purposes [17]. Figures from the FDA suggest that around 100,000 patients filled prescriptions for midodrine in the US in 2009 [16].

3.5 Affordability

Depending on brand, midodrine, at a dose of 10mg three times a day, using 5mg strength tablets, may cost between £780 and £3,200 per year per patient (inclusive of VAT) [18]. There are no associated costs apart from BP monitoring requirements. No published health economic data were identified during this review. Fludrocortisone, at a dose of 100 to 200 micrograms daily, costs between £18.50 and £37 per year per patient [19].
4.0 References

18. Personal communication. IDIS World Medicines. 9/12/10.
5.0 Quality Assurance

5.1 Author
Christine Proudlove, North West Medicines Information Centre.

5.2 Checker
Joanne McEntee, North West Medicines Information Centre.

5.3 Expert Comment
6.0 Appendix

6.1 Search strategy

The following strategy was used to find the evidence contained in this report:

- Embase (1980 to November 2010): midodrine (exp) and orthostatic hypotension (exp) and controlled clinical trial; Limit to human.
- Embase (1980 to November 2010): midodrine (exp) MJ and randomised controlled trial; limit to human and English.
- Medline (1950 to November 210): midodrine (exp) and orthostatic hypotension (exp); limit to human and clinical trial.
- Cochrane Central: midodrine and hypotension.
- Citations review for all papers retrieved via Embase and Medline.

6.2 Data selection

Reasons for excluding papers

Studies identified through Medline
n=24

Studies identified through Embase
n=15

Studies identified through other sources
n=23

Studies after duplicates removed
n=37

Studies screened
n=37

Studies excluded n=33 because:
- wrong population (e.g. healthy volunteers, children) [n=15]
- midodrine not principal intervention studied (n=2)
- experimental or pharmacokinetic study (n=7)
- single-dose study (n=4)
- non-English language (n=3)
- only available as an abstract (n=2)

Studies included
n=4
6.3 Acknowledgements
Dr John Staniland, Consultant in the Care of the Elderly Medicine, Salford Royal Hospital.
Nycomed Products Limited, Dublin, Eire

6.4 Declarations of Interest
None declared from all those participating in the creation of this review.

6.5 Disclaimer
This review relates solely to the medicine and clinical intervention described within the text and reflects UK practice. Should you have any doubts about whether it is relevant to a specific patient, or are unsure whether you understand it, seek appropriate professional assistance.

The contents were believed to be an accurate reflection of the medical literature at the time of preparation. However, you should always consult the literature and take account of new developments.

The authors are not responsible for the content of external websites and any links are made available solely to indicate their potential usefulness. You must use your judgement to determine the accuracy and relevance of the information they contain.