Midodrine: use and current status in the treatment of hypotension

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Midodrine is a sympathomimetic agent used in the treatment of hypotension resulting from various aetiologies. Debate around the use of midodrine recently increased after it was threatened with a licence withdrawal in the USA. The reason cited was a failure of the manufacturing drug companies to provide previously agreed post-market studies. Conversely, midodrine has never received a licence from the UK regulatory authorities.

We provide a review of its current status and a brief description of our own experience with midodrine over the last 11 years.

Introduction

Epidemiological studies suggest that at least 40% of the population will experience at least one episode of syncope in their lifetime.[1] The list of potential therapies available to treat hypotension and reduce the likelihood of syncope is extensive (**table 1**).

Midodrine is a potent α_1 adrenergic agonist that has found widespread use in the treatment of low blood pressure and neurocardiogenic syncope. The active metabolite of midodrine, desglymidodrine, exerts vasopressor actions through activation of alpha-adrenergic receptors of the arteriolar and venous vasculature. Its effects are largely to raise both supine and, more particularly, standing blood pressure through a vasoconstrictor effect to increase peripheral vascular resistance. Although not widely used, midodrine currently ranks ninth in the Medicines and Healthcare products Regulatory Agency (MHRA) list of the top 10 unlicensed medicines imported into the UK in 2010.[3]

Role in treating hypotension

Hypotension, both postural (acute) and chronic has many aetiologies which can usually be addressed by the top five interventions shown in **table 1**. While infrequently used as first-line therapy, midodrine has established a role in patients who are unresponsive to more conservative manoeuvres (increased salt and fluid intake and physical counter-pressure techniques) and for patients who do not respond to treatment with the mineralocorticoid fludrocortisone.[4] Midodrine has a short half-life of around three hours, which should necessitate a three times daily regimen. In practice, a proportion of patients seem adequately treated when it is used twice daily.

The most serious potential adverse effect from this drug is supine hypertension. One precaution to help prevent this is to advise patients not to take their last dose of the day later than early evening. Other potential side effects include urinary urge, retention and frequency, in addition to visual disturbances and headaches. Less serious are dermatological symptoms of pruritis (particularly of the scalp), 'creeping skin' sensation, piloerection ('goosebumps'), parasthesae and chills. Aside from significant supine hypertension, additional contraindications to midodrine include severe organic heart disease, acute renal disease, urinary retention, phaeochromocytoma and thyrotoxicosis.

Current licence agreements

In the UK, midodrine occupies a unique position in the pharmacologic treatment of hypotension by remaining an unlicensed drug. Despite widespread use, no information appears in the latest *British National Formulary*, even with the suffix, as for some medicines, of being a recognised unlicensed use.[5] In prescribing such products, the General Medical Council states "one should be satisfied that an alternative licensed product would not meet the patients needs and that there is sufficient evidence base or experience to demonstrate its safety and efficacy." The prescribing physician bears the responsibility for the use of an unlicensed medicine and for overseeing the patient's care, including monitoring and any follow-up treatment. The patient's notes should indicate the medicine prescribed and, when it does not follow common practice, the reasons for using this product.

In effect, this is not dissimilar to the use of 'licensed' medicines when used 'off-label', as for example the use of selective serotonin-reuptake

Table 1. Common, less common and controversial therapies to combat hypotension

Common therapies
Avoidance of precipitants (dehydration, prolonged standing, hot environment)
Avoidance of drugs exacerbating low blood pressure
Increase in dietary sodium and fluids
Increase in physical activity
Physical/postural counter manoeuvres (hand grip, leg crossing and muscle tensing)
Mineralocorticoids (fludrocortisone being the most common)
Selective serotonin-reuptake inhibitors (fluoxetine, sertraline, paroxetine)
Compression garments (support stockings or waist height leotard)
Vasoconstrictor agents (midodrine)
Less common and more controversial therapies*
Other vasoconstrictor agents (ephedrine, norfenefrine and etilefrine)
Alpha-receptor blockers (theophylline)
Anticholinergic agents (scopolamine or disopyramide)
Negative cardiac inotropes (beta$_1$-adrenergic blockers or disopyramide)
Alpha$_2$-adrenergic agonists (clonidine)
Central nervous system stimulants (methylphenidate, phentermine)
Cardiac pacemakers
Antidiuretic vasopressin analogues (desmopressin)
Erythropoietin (increases red blood cell count, augmenting cerebral oxygenation)
Somatostatin analogues (octreotide) in post-prandial hypotension
Non-steroidal anti-inflammatories (indomethacin and ibuprofen)
Ergotamine analogues (dihydroergotamine)
Stimulants including caffeine (coffee x 2 cups/day)
Alcohol

***Note:** Several of the therapies shown have no clinical evidence to support their continued use. In addition, many are inappropriate for some aetiologies of syncope. A full review of the management of syncope can be found in the current 2009 European guidelines.[2]

inhibitors (SSRIs) for vasovagal syncope. Many health trusts have assembled approved lists for either 'unlicensed medicines' or 'unlicensed use of licensed medicines', based on published evidence. The latter is common in paediatric prescribing, with evidence extrapolated from randomised-controlled trials in adults or 'established' clinical practice.

In the USA, midodrine was approved by the US Food and Drug Administration (FDA) agency in 1996, under the FDA's accelerated approval regulations for drugs that treat life-threatening diseases. Seventy-nine of the 90 drugs approved through this process were for the treatment of cancer, human immunodeficiency/AIDS or the inhalation of anthrax.[6] Approval for midodrine was granted on the basis that clinical trials be conducted to demonstrate improvement in the surrogate end point of blood pressure. The required post-market studies were to verify the clinical benefit of the drug; for example, in terms of improving a patient's ability to perform day-to-day activities and safety.[7] In August of 2010, the FDA threatened to withdraw the licence for midodrine, on the basis that post-approval studies to confirm the clinical benefit of the drug had not been performed.[8] This represented a landmark step, being the FDA's first attempt to remove a marketed medication on these grounds.[7]

Following intense pressure from patients and doctors, the FDA relented on their proposed action on the 6th September 2010, to allow time for the necessary data to be collected and certain 'legal issues' to be sorted out.[9]

Indications for the use of midodrine

Because midodrine can cause marked elevation in supine blood pressure (both systolic and diastolic), it is recommended that its use be restricted to patients whose lives are considerably impaired despite all standard clinical therapies. Vasovagal syncope is the most common abnormal response to upright posture and usually responds to education, increased dietary salt and fluids. Drug therapy becomes necessary when syncope is associated with physical injury, occupational hazard and a lack of warning. In vasovagal syncope, no convincing data exist to support the use of one drug over another as first-line therapy.[1] Placebo-controlled studies provide limited evidence for the use of midodrine and SSRIs. Beta blockers are not now recommended to treat reflex-induced syncope.[2] Permanent cardiac pacing is rarely needed and randomised trials do not support its use.[10]

Midodrine has been prescribed for various aetiologies of symptomatic hypotension. These comprise neurocardiogenic syncope,[4,11] including vasovagal syncope,[12,13] orthostatic hypotension in the elderly,[14,15] autonomic nervous system dysfunction, haemodialysis-induced hypotension,[16] spinal cord injury,[17,18] infiltrative protein deposition disorders (e.g. amyloidosis),[19] neurodegenerative diseases (e.g. Parkinson's disease), through to a potential use in post-space-flight orthostatic hypotension.[20] Perhaps more controversially, midodrine has recently been used successfully in advanced heart failure to raise the blood pressure sufficiently to prescribe disease-modifying therapies.[21]

Clinical trials and reviews of midodrine

In neurocardiogenic syncope, a baroreceptor-mediated reflex response results in hypotension and bradycardia, which can occur with orthostatic stress. Randomised-controlled trials in patients with severe symptomatic neurocardiogenic syncope have shown that midodrine is substantially more effective at relieving symptoms than more conservative approaches with increased fluids, salt and counselling.[22,23] In a double-blind, placebo-controlled, tilt study on 12 patients with neurally mediated syncope, patients received a nonpressor 5 mg dose of midodrine or placebo. A positive tilt-test result occurred in 67% of patients in the placebo arm and 17% of patients taking midodrine.[24]

A recent meta-analysis of alpha-adrenoceptor agonist use for the treatment of vasovagal syncope, identified six randomised-controlled trials and supported the use of midodrine; citing it as a particularly efficacious compound.[25] In contrast, the European guidelines on the management of syncope (2009 version) conclude that chronic treatment with alpha agonists alone may be of little use in reflex syncope and long-term treatment cannot be advised for occasional symptoms.[2] For orthostatic hypotension midodrine should

be administered as adjunctive therapy with a level of evidence deemed at level IIa (defined as a weight of evidence/opinion in favour of usefulness/efficacy).[2]

Additional considerations

In the USA, midodrine remains the only drug approved for the treatment of orthostatic hypotension.[26] In the UK, its position as second-line therapy after fludrocortisone, could indirectly be a consequence of cost. A 5 mg three times daily dosage of midodrine is around four-fold more expensive than therapy with the 'volume expander' fludrocortisone at a dose of 100 μg daily (£16 *vs.* £2.96 per month).[5] The fact that midodrine is not licensed and has a small market (around 100,000 patients in the USA) probably accounts for the paucity of published data on its use. In some specific circumstances, notably pregnancy, the total experience amounts to only two reported cases.[27] Now 14 years after midodrine's initial approval, the original manufacturer (Shire Pharmaceuticals) reports only a half million dollars annually from sales. Such low level of reimbursement begs the question as to "who could, or indeed should (when not financially viable for the company to do so) bear the costs of performing the 'required' clinical studies?"

Audit of midodrine use in a west London district general hospital

In an audit of midodrine use, at our institution, we identified 28 patients from pharmacy records who received this drug over the last 11 years. Those under 50 years of age were predominantly female (71%), those over 50 predominantly male (67%). Thirty-two per cent of patients had a diagnosis of vasovagal syncope, 14% postural hypotension and 54% had underlying autonomic dysfunction. All patients received midodrine at a dose of between 5.0 and 47.5 mg per day (mean 17.7 mg). In addition, 20 patients received fludrocortisone and five received SSRIs. Midodrine was generally well tolerated and no patients experienced adverse events that might be ascribed to the drug. Of note, a significant proportion of these patients (37%) also suffered concomitantly from either anxiety (stress at work or during college exams) (n=3), depression (n=4) or vascular dementia (n=3). In eight patients, supine blood pressures were ≤80 mmHg. Of these, seven were elderly (mean age of 71 years) and suffered from postural hypotension, one patient was aged 37 and suffered from vasovagal syncope.

We accept that the number of patients in this audit was small, representing around one patient per 100,000/year at our hospital. These observations suggest midodrine provides benefit in elderly patients with orthostatic hypotension from a variety of causes. We illustrate this with one case study from this audit.

Case report

A 72-year-old woman presented with profound hypotension. Out-patient sitting systolic blood pressures were recorded as low as 50 mmHg in association with pre-syncopal symptomology. The patient had two hospital admissions with symptoms and was found to have an IgG-kappa monoclonal gammopathy with clinically associated peripheral neuropathy.[28] Mild benefit to blood pressure was achieved with fludrocortisone at 100 μg daily but the blood pressure was still inadequate to complete daily activities. Midodrine was started at 5 mg twice daily and gradually titrated to a daily dosage of 15 mg three times daily. Periodic adjustment of this prescription, in addition to fludrocortisone, achieved a blood pressure of 135/72 mmHg. The patient continued on midodrine for a further 92 months. Regular follow-up indicated a reasonable quality of life before eventually succumbing to overt myeloma at the age of 80 years.

Conclusion

In a 'real-world' clinical scenario, the number of patients, in whom symptoms progress to the extent that requires the use of midodrine, are small. This may reflect the caution that surrounds the use of unlicensed medicines. Midodrine appears to be well tolerated with wide application for hypotensive episodes resulting from several different aetiologies.[4,11-24] In occasional cases, as illustrated above, it can provide life-saving treatment for profound hypotension.

Given these features and its undoubted efficacy we would propose that midodrine might find an expanded role in treating hypotension

Conflict of interest

None declared.

Key messages

- Midodrine is a potent adrenergic agonist with pressor effects
- Midodrine remains an unlicensed medicine in the UK
- Midodrine has wide application in the treatment of hypotension from a variety of causes
- The available data are probably still insufficient to prove the efficacy of midodrine in vasovagal syncope (a very common cause of syncope)

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