

A Case of a Dispensing Error causing Iatrogenic Orthostatic Hypotension

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Case

A 73-year-old man with a seven-year history of Parkinson's disease (PD) presented with delirium and increasing falls for three weeks. Past medical history included tinnitus, gout, depression, and surgically corrected carotid artery stenosis. He had a one-year history of orthostatic hypotension from PD for which he was on a stable dose of midodrine 5mg by mouth in the morning and noon, and 2.5 mg by mouth in the evening. His PD was well controlled on levodopa/carbidopa. His other medications were clopidogrel, paroxetine, and rosuvastatin; there was no history of steroids. Medications had not changed recently and were administered from weekly dosettes packaged by a private caregiver. He denied cognitive changes, visual hallucinations, bleeding, nausea, vomiting, or polyuria. He had delirium.

On physical examination, profound orthostatic hypotension was noted; supine, his blood pressure was 191/93 and dropped to 119/75 mmHg when standing; his heart rate rose from 56 to 74 beats per minute. Cardiac and volume status examination were otherwise normal. Neurological examination showed masked facies but no other overt signs of PD. Cranial nerves, power, reflexes, tone, cerebellar testing, and sensation were normal.

Initial bloodwork demonstrated mild hyponatremia (131 mmol/L), hyperkalemia (5.6 mmol/L), and elevated creatinine at 219 µmol/L (110 µmol/L one year prior). He had no anemia. Urine output was normal and bladder scan did not show retention. Computed tomography of the head showed mild cortical atrophy, and hip radiographs were negative for fracture. There were no signs of hyperpigmentation and 07:00 cortisol was 670 nmol/L (normal 193-690 nmol/L).

Initial management of the patient involved intravenous fluids and weaning paroxetine as a possible contributor to his

orthostatic hypotension. In the process of collecting a best possible medication history (BPMH), the pharmacist reviewed the dosette prepared by the caregiver. The pharmacist noted that the midodrine 2.5-mg tablets were stamped with a "5" instead of "2.5". The caregiver remarked that the midodrine tablets had changed from round white pills to diamond-shaped pills when last dispensed 3 weeks ago. When the pharmacist reviewed an online database, she found that the patient had been supplied with 5-mg tablets of amiloride, a potassium sparing diuretic, instead of midodrine. The patient had been taking a total of 25 mg of amiloride daily, above the maximum recommended daily dose of 20 mg.

According to the patient's pill bottle, his prescription had been for midodrine (Figure 1). We notified the community pharmacy and discovered that a dispensing error had occurred: amiloride had mistakenly been supplied instead of midodrine, having been shelved next to midodrine according to its brand name (Midamor®). This pharmacy did not use bar-code technology.

The offending agent was stopped, and his orthostatic hypotension, electrolyte abnormalities and delirium resolved within two days. The patient was discharged in stable condition. To avoid future dispensing errors, the community pharmacy separated the two look-alike medications, held staff meetings to discuss the error, and issued a reminder for pharmacy technicians and pharmacists to both check the unique drug identification number and document this step on the dispensing record.

Discussion

By consensus, the standard definition of orthostatic hypotension is a sustained reduction of systolic blood pressure of at least 20 mmHg or of diastolic blood pressure of 10 mmHg within 3



Figure 1. Image of the patient’s pill bottle, labeled midodrine 2.5 mg, and the diamond-shaped pills inside, (top inset) midodrine pills for comparison, (bottom inset) diamond-shaped Midamor® pills.

minutes of standing, with or without symptoms. In 2011, the definition was revised to include several distinct variants and related conditions (Table 1).¹

Orthostatic hypotension is a common problem in the elderly. A longitudinal observational study of 5037 healthy adults aged 50 and over in Ireland found orthostatic hypotension occurred in 4.2% of patients aged 50–59 and 18.5% of patients over the age of 80.² These results are consistent with older observational data

reporting a prevalence of symptomatic orthostatic hypotension ranging between 5 and 30%.³ Postural dizziness is not a hallmark symptom; neurologic symptoms more closely associated with orthostatic hypotension are ataxia, vertigo, dizziness and falls.

The causes of orthostatic hypotension are varied (Table 2),⁵ and an estimated 38% of chronic cases have no identifiable cause. In this case, the relatively blunted heart rate response despite a dramatic fall in blood pressure suggested an element of autonomic dysfunction from the patient’s PD. His acute renal failure with hyperkalemia and hyponatremia were more suggestive of adrenal insufficiency once urinary retention had been ruled out. Primary adrenal failure, though, was unlikely at his age and no conventional secondary etiologies were present; his morning cortisol was also well within the normal range. Volume depletion was also unlikely as he lacked polyuria and his symptoms were not fluid responsive.

The management of orthostatic hypotension involves non-pharmacologic and pharmacologic strategies, with an aim to improve symptoms and function (Table 3). Deprescribing potential offending agents, adequate hydration, and salt intake, and cautious transitions to a standing position are initial steps. If these fail, compression stockings, abdominal binders, and raising the head of the bed are the most effective non-pharmacological treatments based on systematic review.⁶ First-line pharmacotherapy includes fludrocortisone, a mineralocorticoid which promotes fluid retention and increases intravascular volume, and midodrine, a peripherally acting alpha-1 agonist causing vasoconstriction.⁷ Fludrocortisone may cause hypokalemia, fluid overload, and worsen

Table 1. Definitions of Disorders of Orthostatic Tolerance

Disorder	Definition
Orthostatic hypotension	>20 mmHg drop in SBP or >10 mmHg drop in DBP within 3 minutes of standing, with or
Variants	
Initial orthostatic hypotension	>40 mmHg drop in SBP or >20 mmHg drop in DBP within 15 seconds
Delayed orthostatic hypotension	Symptoms persisting beyond 3 minutes
Related disorders of orthostatic tolerance	
Neurally mediated syncope	Transient loss of consciousness triggered by a change in autonomic activity (e.g., cough,
Postural tachycardia syndrome	Increase of >30 beats per minute within 10 minutes of standing without orthostatic hypotension * >40 beats per minute for those aged 12–19

DBP = diastolic blood pressure; SBP = systolic blood pressure (SBP).

Table 2. Common Causes of Orthostatic Hypotension

Acute Causes of Orthostatic Hypotension	
Hypovolemia (e.g., dehydration, bleeding, vomiting, diarrhea)	
Cardiac (e.g., arrhythmia, myocardial infarction, valvular incompetence)	
Endocrine (e.g., adrenal insufficiency, hypoaldosteronism)	
Medication side effects	
Antihypertensives (alpha blockers, RAAS blockers, beta blockers, and diuretics)	
Antipsychotics (first generation antipsychotics, clozapine, risperidone, quetiapine)	
Antidepressants (tricyclic antidepressants, SNRIs, MAOIs and SSRIs)	
Anticholinergics (antispasmodics)	
Marijuana	
Chronic Causes of Orthostatic Hypotension	
Primary autonomic dysfunction	
Parkinson's disease and other similar conditions (e.g., Lewy body dementia, multi-system atrophy)	
Pure autonomic failure (Bradbury-Eggleston syndrome)	
Secondary autonomic failure	
Diabetes mellitus	
Syphilis	
B ₁₂ deficiency	
Amyloidosis	
Paraneoplastic neuropathy	
Alcoholic neuropathy	
Medication side effect (see above list)	

MAOI = monoamine oxidase inhibitors; RAAS = renin-angiotensin-aldosterone system; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

congestive heart failure. Midodrine has side effects of pruritis, paresthesias, piloerection and urinary retention. Both may cause supine hypertension. Second-line agents include pyridostigmine and octreotide. There is very limited evidence of the efficacy for any of these treatments as most trials of interventions are small

($n < 50$), with no trial exceeding 200 participants, and symptoms are not always included as an outcome of interest.⁶ More recently, droxidopa, a norepinephrine precursor, has been approved for use in orthostatic hypotension associated with PD and other Parkinson-plus syndromes, but is not yet available in Canada.

Our patient's chronic orthostatic hypotension was appropriately managed with midodrine, but he suffered an adverse drug event when he was dispensed amiloride instead. Adverse drug events are estimated to be the cause of 6.5% of hospital admissions.⁸ Amiloride treats hypertension by blocking the epithelial sodium channel in the renal collecting duct. Orthostatic hypotension is a recognized side effect. For new admissions to hospital, screening for adverse drug events involves conducting a BPMH. Interviewing patients and caregivers to ascertain actual use of medications, including recent changes, rather than relying solely on medication lists is critical. As in this case, pharmacists have an established role in conducting medication reconciliation/ BPMH,⁹ yet it is still not usual practice to inspect and confirm the identity of the actual pills in a dosette. Attention to detail by our pharmacist, coupled with a keenly observant caregiver, allowed us to make a diagnosis that would otherwise have been missed.

The community pharmacy completed root-cause analysis internally and implemented changes to prevent similar errors from occurring in the future. The dispensing process typically involves multiple checks to ensure faithful delivery of the right drug at the right dose to the right patient with the right instructions. Dispensing errors are rarely the cause of adverse drug events; error rates vary by setting, error definition and methodology and roughly fall between 0.02 to 5% of dispensed items¹⁰. One outlier study, which used covert patients prescribed warfarin, carbamazepine or theophylline (all medications with baseline high rates of dispensing error) reported an error rate of 24%, but only 4% were clinically significant. A lack of automation (e.g., bar-coding), poor lighting, interruptions, and heavy workloads likely increase the incidence of dispensing errors,¹⁰ as do look-alike drug names. Interestingly, midodrine and Midamor® do not appear on lists of look-alike drugs released by the FDA and Institute of Safe Medication Practices despite having similar dosages. This case illustrates how a dispensing error can be an occult cause of an adverse drug event and emphasizes the value of working in interdisciplinary teams as medicine becomes increasingly complex. Fortunately, this error was caught and the patient did not suffer any lasting sequelae. The feedback to the community pharmacy was well received and led to meaningful process change, highlight the importance of a culture of openly acknowledging, investigating and mitigating/preventing error as we strive for continuous quality improvement in patient safety in the health care system.

Table 3. Non-pharmacologic and Pharmacologic Strategies For Treating Orthostatic Hypotension

Non-pharmacologic Strategies
Deprescribe offending medications
Increase fluid and salt intake
Caution with changing position from supine to standing
Compression stockings (40–60 mmHg to ankles, 30–40 mmHg to hips)
Abdominal binders (20–30 mmHg)
Raising head of bed (by at least 6 inches)
Pharmacologic strategies
Fludrocortisone 0.1–0.3 mg PO daily
Midodrine 2.5–10 mg PO PRN or up to 3 times daily (during hours when awake and upright)
Pyridostigmine 30–60 mg PO PRN
Octreotide 12.5–25 mcg SC PRN
Droxidopa 100 mg PO TID, up to 1800 mg max daily dose

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