

MEDICATION REVIEW OF ELDERLY PATIENTS PRESENTING WITH ORTHOSTATIC HYPOTENSION

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INTRODUCTION

Orthostatic hypotension (OH) is defined as more than a 20mmHg decline in systolic, and/or a 10mmHg decline in diastolic blood pressure from baseline within three minutes of standing. This drop in blood pressure is often associated with symptoms of cerebral hypoperfusion. The symptoms can range in severity from mild to disabling. OH occurs in 10-20% of people aged over 65 years, with the prevalence increasing with age.^{1,2} A lower rate is seen in elderly individuals living in the community and higher rates in those living in an institution or in the acute care setting (see Table 1).

Drug therapy is often felt to be the cause of OH in the elderly. The relationship between OH and medication is complex. There are a number of variable factors. Symptoms may be intermittent, being manifest at certain times such as in the morning. They may present in the presence of other factors such as cerebrovascular disease, prolonged bed rest, dehydration or intercurrent illness. A careful history, with attention to both prescribed and non-prescribed medications, is essential in the evaluation of an elderly patient who presents with symptomatic OH.

The following is a review of the medications that contribute to iatrogenic OH.

CARDIOVASCULAR MEDICATION

Anti-hypertensive medication

One of the main causes of OH is thought to be anti-hypertensive medication. Although they can theoretically, as a group, worsen OH, the majority of cross-sectional studies have found no association (see Table 2). Elderly patients with hypertension, who have a high prevalence of OH in the untreated state,³ related to age-related physiological changes in baroreceptor function and vascular tone, are at particular risk of adverse reactions to these drugs. Homeostasis is impaired and elderly patients may have reduced dose requirements due to altered renal or hepatic function. Table 3 illustrates the physiological changes in the older person and emphasises the need for regular medication review and dose adjustment.

Diuretics

Fluid depletion by diuretics can cause OH. This can be further exacerbated by elderly people restricting their fluid intake because of a fear of incontinence and poor mobility.

Apart from hypovolaemia, diuretics do not appear to significantly contribute to OH. An epidemiological study found no significant difference in the prevalence of OH in a diuretic group compared to controls in a population of 3,101 subjects aged 50-99 years.⁴ Further work on the response to thiazide therapy supports this.⁵ The OH effects of loop and thiazide diuretics have been compared in 70 frail elderly patients.⁶ It was 60% in those receiving a thiazide diuretic, 20% in those on a loop diuretic and 37% in those on no diuretic. This study also reported a higher incidence of hypokalaemia in patients receiving thiazide therapy, which has been reported to be associated with OH⁷ and those receiving loop diuretics were receiving a high dose of potassium supplementation. Another confounding factor is hyponatraemia, which can also occur with diuretic therapy and is also associated with OH.⁸

β -blockers

β -blockers reduce cardiac contractility and renin secretion leading to reduced angiotensin II levels. These effects lead to a reduction in blood pressure. In contrast to the effects of other drugs, β -blockers tend to work less well in an elderly population because of an altered β -receptor responsiveness with age.

β -blockers with an intrinsic sympathomimetic activity may have a positive effect on OH. Cleophas et al⁹ reported that in 1,971 patients treated with nebivolol for six months, the original decrease in pulse pressure upon standing for one minute was reversed. On the other hand, β -blockers that also have an α -adrenoceptor antagonism, such as carvedilol, may be associated with an increase in risk of OH in up to 40%.¹⁰

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARAs)

The renin-angiotensin system (RAS) can be inhibited

at multiple levels. ACE inhibitors inhibit the enzymatic conversion of angiotensin I to angiotensin II. They produce their anti-hypertensive effect by decreasing the angiotensin II and increasing the kinin levels, both leading to vasodilation. ARAs are competitive antagonists to the angiotensin receptor type 1 and block the RAS more distally. Apart from the risk of first dose hypotension, OH is relatively uncommon with ACE inhibitors. A post-marketing study of 4,676 patients suggested a rate of 0.25% of those receiving lisinopril developed OH.¹¹ A comparative study of enalapril and nifedipine, showed none of the ACE inhibitor group developed OH, whereas 15% of those on nifedipine did.¹² ACE inhibitors may improve baroreceptor sensitivity and hence the low rate of OH observed.

In the CONSESUS II Trial, however, the incidence of first-dose hypotension in the enalapril treated group was 10.5% compared with 2.5% of those treated with placebo¹³ and mortality was increased in patients showing this effect. Elderly people and patients with inferior myocardial infarction were at increased risk of developing hypotension.

ARAs also show a low overall rate of OH. A four-week study using valsartan showed 14% developing OH compared to 8% in the placebo group.¹⁴

Calcium channel blockers

Calcium channel blockers reduce peripheral vascular resistance, dilating coronary and peripheral arteries. Some, for example verapamil, have negative chronotropic effects which can prevent the normal physiological response to a fall in blood pressure. The incidence of hypotension with verapamil varies from 1% to 7.5% of patients.¹⁵

Nifedipine has been found to increase nocturnal natriuresis, which can further worsen orthostatic blood pressure decline.¹⁶

The hypotensive effects of calcium channel blockers can be increased when used in combination with other agents, for example β -blockers, diuretics or nitrates.

Nitrates

Nitrates are direct vasodilators. They can produce orthostatic pre-syncope and syncope if their vasorelaxant effects outstrip vasoconstrictor response to postural change. The incidence of this increases with age.

In one study, nitrates were the most common drug precipitant of syncopal presentations to an emergency department.¹⁷ Some people are particularly sensitive to the effects of nitrates. They are used to provoke a vasovagal reaction during head up-tilt to assist in the diagnosis of unexplained syncope.

α -adrenoceptor antagonists

α -adrenoceptor antagonists produce their anti-hypertensive effect by blocking post-synaptic α 1-adrenoceptors, leading to a reduction in arteriolar resistance and venous capacitance. Initially they can produce OH and possibly syncope but this effect subsides with prolonged treatment. Clinical studies have shown that OH is more common with prazosin than with hydralazine.¹⁸ Older patients lack compensatory reflex tachycardia, resulting in an increased hypotensive response to these drugs.

More recent preparations of α -adrenoceptor antagonists have a slower onset of action and hence lower risk of OH. A meta-analysis of doxazosin in hypertensive and diabetic patients showed no difference between users and nonusers in OH and syncope.¹⁹

Table I. Prevalence of OH by population in key studies.

Study (year)	Mean age [years] (range)	Sample size	Prevalence rate (%)
POPULATION SAMPLE			
NHANES-II (1991)	NP (25-74)	8,574	6.6
SHEP (1992)	NP (\geq 60)	4,736	12
CHS (1992)	NP (\geq 65)	5,201	16.2
HHP (1998)	NP (71-93)	3,522	6.9
Luukinen et al (1999)	76 (\geq 70)	969	30
ARIC (2003)	NP (45-65)	13,152	5
ACUTE CARE PATIENTS			
Weiss et al (2002)	81.6 (62-99)	502	67.9
NURSING HOME OR REHABILITATION RESIDENTS			
Ooi et al (1997)	NP (\geq 60)	911	51.5
Kong and Chuo (2003)	58.4 (\geq 40)	71	52.1

Key. ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study; HHP = Honolulu Heart Program; NHANES = National Health and Nutrition Examination Survey; NP = not provided; SHEP = Systolic Hypertension in the Elderly Program.

Table 2. Studies investigating the association between anti-hypertensive therapy and OH by sample size and type.

Study	No. of patients	Population	Study type	Association	Medications
COMMUNITY POPULATION					
Strogatz et al	659	Mixed	CS	None	DIU, OTH
Raiha et al	480	Mixed	LON	None	BAA, DIU, OTH
Fotherby et al	86	HTN	LON	Yes	Various
Burke et al	843	Mixed	CS	None	Various
SHEP	4,736	HTN	CS	None	Various
Syst-Eur	2,716	HTN	CS	Yes	Various
CHS	5,201	Mixed	CS	Yes	Various
NURSING HOME OR REHABILITATION RESIDENTS					
Ooi et al	911	Mixed	CS	None	Various
ACUTE CARE PATIENTS					
Panayiotou et al	40	Stroke	CS	None	ACEI, CCA, OTH
Fotherby and Iqbal	74	HTN	CS	None	Various

Key. Study participants were receiving different classes of anti-hypertensives. ACEI = ACE inhibitor; BAA = α -adrenoceptor antagonist; CCA = calcium channel antagonist; CHS = Cardiovascular Heart Study; CS = cross sectional; DIU = diuretic; HTN = hypertensive; LON = longitudinal; OTH = other; SHEP = Systolic Hypertension in the Elderly Program; Syst-Eur = Systolic Hypertension in Europe.

Table 3. Pharmacokinetic changes influencing drug effects in the elderly

Physiological parameter	Age related change	Significance
ABSORPTION	Decreased salivary flow. Increased gastric pH. Delayed gastric emptying. Decreased absorptive surface. Reduced splanchnic flow. Decreased gastrointestinal motility.	Mildly decreased absorption.
DISTRIBUTION	Decreased lean body mass. Increased body fat:lean body mass ratio. Decreased total body water. Decreased serum albumin.	Increased distribution and half-life of lipid soluble drugs. Increased alpha-1 acid glycoprotein. Higher concentration of water-soluble drugs. Decreased free fraction of basic drugs.
METABOLISM	Decreased hepatic metabolism. Decreased hepatic mass. Decreased hepatic blood flow.	Decreased Phase I biotransformation (oxidation/reduction, hydrolysis) leading to decreased first pass metabolism and/or elimination of lipid soluble drugs.

PSYCHIATRIC MEDICATION

Phenothiazines

The prevalence of OH in a systematic study of 200 consecutive schizophrenic inpatients receiving chronic neuroleptic medications was 77% at one minute and 17% at three minutes after standing compared to no OH in controls.²⁰ No patient was symptomatic, however. The prevalence was unaffected by age or sex and was poorly correlated with drug dose. Of the three drugs used in this study, thoridazine was associated with significantly higher blood pressure drop at three minutes than haloperidol or chlorpromazine. These drugs had a much greater hypotensive effect when used in combination.

OH in the setting of phenothiazines is felt to be related to anti- α -adrenergic effects in the autonomic nervous system.

Antidepressants

Tricyclic antidepressants (TCAs) can have cardiotoxic effects at therapeutic doses but are particularly dangerous in overdose. They can slow intra-ventricular conduction and PR and QRS intervals can increase. They can cause OH by inhibiting sympathetic neural outflow reducing sympathetically mediated vasoconstriction, negative inotropic effects of α 1 adrenergic receptor blockade and impaired cardiac contractility, and increased effects on α 2 adrenergic receptors, reducing peripheral resistance. Patients

with impaired left ventricular function are at particular risk.²¹ The risk of hip fracture is increased three-fold in depressed patients prescribed TCAs.²² TCAs are best avoided in elderly patients not only because of their effects on blood pressure but also the well documented effects on cognition.

Serotonin selective reuptake inhibitors

OH occurs rarely in this group but there are some case reports of bradycardia and syncope.

Monoamine oxidase inhibitors (MAOIs)

MAOIs can cause OH, particularly in hypertensive patients. Six per cent of a group of depressed patients treated with an MAOI developed OH compared to 8% in a group treated with imipramine.²³

Trazodone

Trazodone, a triazolopyridine derivative, can cause OH and syncope, particularly on initiation of treatment in elderly patients.^{24,25} Initiation at low dose with regular monitoring is recommended.

CEREBROACTIVE DRUGS

Dopamine agonists and levodopa

The prevalence of autonomic dysfunction in Parkinson's disease is unclear, varying in studies from 23% to 80%. The medication prescribed to treat the disease can also contribute to OH. There is evidence to support that levodopa,²⁶ or levodopa in combination with selegiline,²⁷ exacerbates the tendency towards OH. Recent studies, however, demonstrate that disease duration, severity and patient age are more important factors in the development of OH than levodopa.^{28,29}

Benzodiazepines

All benzodiazepines have the potential to precipitate hypotension. The effect of oral temazepam was studied in 12 elderly subjects in a double-blind, randomised, placebo controlled study. Each patient received placebo, 15mg temazepam and 30mg temazepam. Temazepam caused a significant fall in blood pressure after the larger dose.³⁰

Opiates

All the opiate analgesics have the potential to cause hypotension, an effect which is dose related.

Conclusion

There is a high prevalence of orthostatic hypotension in the elderly. Many patients with the condition are asymptomatic. The addition of some medication can potentially turn a benign asymptomatic condition into a symptomatic one with dizziness, presyncope, syncope or falls. The resultant major deleterious

outcomes can include loss of confidence, loss of independence, decreased mobility, hip fracture and even death. It is, therefore, essential that lying and standing blood pressures be performed prior to prescribing these medications. Commencing on the lowest dose is recommended with slow incremental increases thereafter. Furthermore, it would be advisable to make patients aware of the possible side effect of OH and how to manage the symptoms.

Caution needs to be taken when prescribing in the elderly. By only prescribing the minimum amount to manage their conditions with regular review and rationalisation of their medication, we should help limit the problem of symptomatic OH in these patients.



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