Orthostatic hypotension in older adults: the role of medications

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Abstract

Orthostatic hypotension (OH) is defined as an abnormal blood pressure reduction when standing and is frequently diagnosed in older adults. Pharmacological therapy is one the main causes of orthostatic blood pressure impairment, leading to iatrogenic OH. Indeed, several medications may induce hypotensive effects and influence the blood pressure response to orthostatism. Hypotensive medications may also overlap with other determinants of OH, thus increasing the burden of symptoms and the risk of complications. Potentially hypotensive medications include both cardiovascular and psychoactive drugs, which are frequently prescribed in older patients. According to the available evidence, the antihypertensive treatment "per se" does not seem to predispose to OH, even if a higher risk is associated with polypharmacy and drug classes such as with diuretics and vasodilators. As concerns psychoactive medications, OH is a well-known adverse effect of tricyclic antidepressants, trazodone and antipsychotics. The knowledge of hemodynamic consequences of drug therapy may be helpful to improve OH treatment. A medication review is advisable in all patients presenting with OH, particularly at advanced age, aiming at optimizing medical treatment with a view to minimize the risk of iatrogenic OH.

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Introduction

Orthostatic hypotension (OH) is defined as a fall of at least 20 mmHg in systolic blood pressure and/or 10 mmHg in diastolic blood pressure within 3 minutes of standing [1]. It is highly prevalent in older adults [2,3] and is known to be associated with both short- and long-term adverse outcomes, including falls, cardiovascular events, cognitive impairment and mortality [4-6].

OH is usually classified according to the presence of a neurodegenerative etiopathogenesis, thus identifying neurogenic and non-neurogenic forms. The latter may derive from reduced plasma volume, deconditioning and exaggerated venous pooling, but also include iatrogenic or drug-related OH. Indeed, several medications may have hypotensive effects and influence the orthostatic blood pressure response. Iatrogenic OH represent the most common form of non-neurogenic OH, particularly in older patients [4]. Moreover, it may coexist with other causes of OH, thus worsening the patients' symptoms and the risk of complications.

Data from the French pharmacovigilance service suggests that iatrogenic OH represents the 1.3% of drug adverse reactions [7]. It is more common in people presenting with several risk factors for OH, such as Parkinson disease, dehydration and diabetes [7], or taking more than one predisposing medications [8]. Additionally, the risk of iatrogenic OH increases with advancing age. Indeed, older adults frequently present a high risk profile for OH, due to comorbidities, polypharmacy and deconditioning. Moreover, age-related pharmacokinetic changes usually occur, that may alter the bioavailability and distribution of medications [9].

Drug therapy may induce OH through different mechanisms. Some drug classes interfere with reflex responses that usually counteract a blood pressure fall when standing, *e.g.*, sympathetic-mediated vasoconstriction and increased heart rate response and inotropism. Additionally, some medications may increase venous pooling (*e.g.*, vasodilators) and/or induce volume depletion (*e.g.*, diuretics), thus predisposing to OH.

The association between OH and medications has been widely investigated in the literature, with heterogeneous and partly inconsistent results. However, on the basis of the available evidence, some "high risk" drug classes can be identified.

Anti-hypertensive medications are usually considered to be a predisposing factor for OH. Yet, some evidence suggests that antihypertensive treatment may not increase the risk of an orthostatic

blood pressure fall, but rather have a protective effect [10-12]. Indeed, uncontrolled hypertension has been demonstrated to favor OH, probably due to a natriuretic effect [2,12,13]. Consistently, blood pressure control with antihypertensive treatment reduced the prevalence of OH in a previous study by Masuo *et al*., regardless of the drug class used [14]. Therefore, antihypertensive treatment "per se" does not seem to increase the patient's predisposition to orthostatic blood pressure fall. However, the risk of OH is known to increase with increasing number of antihypertensive medications, particularly when higher than three [2,8,13].

Among antihypertensive medications, some drug classes show a stronger association with OH. These include diuretics and vasodilating agents such as nitrates and α-adrenergic receptor antagonists, that reduce circulating volume, venous return and peripheral vascular resistance [8,15-16]. Additionally, beta-blockers may impair the orthostatic blood pressure response, due to their negative inotropic and chronotropic effects [12,17,18]. Among beta-blockers, hypotensive effects are expected to be more relevant for mixed alpha- and beta-receptors blockers, *e.g*. carvedilol, as compared with highly selective molecules, *e.g*. bisoprolol [19]. Conversely, ACE-inhibitors and angiotensin receptor antagonists have a higher tolerability and a low risk of OH, with some data suggesting a protective effect against the orthostatic blood pressure fall [12,17,20]. Yet, in older adults with dementia an association with syncope due to OH has been reported for ACE-inhibitors, when prescribed in a combination with nitrates or diuretics [21]. Therefore, drug interactions may further increase the risk of iatrogenic OH, particularly in more vulnerable population, *e.g*. people with dementia.

In addition to cardiovascular medications, some psychoactive drugs may likewise induce hemodynamic effects and influence the blood pressure response to orthostatism. Indeed, OH is the most commonly reported cardiovascular side effect of psychoactive therapies. OH is reported in 10-50% of patients taking tricyclic antidepressants, due to the blockade of alpha-adrenergic receptors [16,20]. A similar mechanism is described for trazodone [8] and antipsychotics [22,23], the latter being more prone to induce OH as the drug's affinity for α-adrenergic receptors increases [24]. The association of OH with SSRI antidepressants [8,16,25] and benzodiazepines [26,27] has been described in previous studies, but the underlying mechanism remains unclear. Finally, antiparkinsonian drugs such as levodopa and selegiline are known to induce OH independently of the presence of autonomic dysfunction, probably due to vasodilation and reduced sympathetic outflow [28,29].

Iatrogenic OH related to psychoactive medications may be of great clinical and prognostic relevance. Indeed, psychoactive drugs may also induce sedation and psychomotor slowing and negatively impact on attention, gait and balance control, thus increasing the risk of falls. Additionally, psychoactive medications are frequently prescribed in older patients at high risk of falling, as is the case of antipsychotics in older patients with cognitive impairment. In this clinical context, their hypotensive effects may further increase the risk of adverse events. Therefore, psychoactive medications should be prescribed with caution in older patients with OH and/or at high risk of falling.

Frail older adults may be more prone to develop iatrogenic OH, particularly in the presence of sarcopenia. In a study by O'Connell *et al*., frailty was found to be associated with an abnormal BP recovery after standing [30]. Therefore, medications potentially predisposing to OH should be prescribed with caution in frail older people, in whom hypotension may lead to negative health outcomes such as falls, hospitalization, disability and mortality. Similarly, an intensive approach to antihypertensive treatment may lead to more harm than benefits in these patients. Indeed, evidence supporting an intensive blood pressure control derive from clinical trials involving predominantly healthy patients, with mild levels of frailty [31]. Conversely, frailer adults and those with orthostatic hypotension were excluded, which limits the transferability of these results to the "real world" geriatric population.

Given the relevant role of muscle mass in the blood pressure response to gravity stress [32,33], also sarcopenia may increase the risk of iatrogenic OH. Indeed, it may exacerbate the hypotensive effects of medications that mediate an increase in venous pooling and/or myorelaxation, such as vasodilators and benzodiazepines [34]. Conversely, ACE-inhibitors seem to positively impact on physical performance [35], which may at least partly explain their low-risk profile in the context of drug related OH.

Given the above, a careful medication review should be carried out in patients presenting with an orthostatic blood pressure fall, with a view to minimize the risk of iatrogenic OH. The following practical suggestions may be helpful to optimize medical therapy in these patients.

- Re-evaluate the indication of potentially hypotensive medications and consider drug withdrawal in case of inappropriate prescription
- If withdrawal is not possible, consider dosing adjustments to achieve to lowest effective dose, since hypotensive effects are usually dose-related
- Suggest a low initial dose and slow progressive up-titration according to clinical response
- Consider evening administration for medications with hypotensive and/or sedative effects, since the orthostatic blood pressure fall is usually more relevant in the morning
- For each drug class, prefer molecules showing reduced hypotensive effects, *e.g*. selective beta-blockers instead of mixed alpha- and beta-receptors blockers
- If available, prefer prolonged drug-release formulations, resulting in lower peak plasma concentrations
- Modify drug dosing as appropriate in case of renal impairment, to avoid accumulation.

In addition to medication review, additional risk factors for OH should be addressed and counselling should be provided concerning non-pharmacological treatment of OH, including appropriate hydration, physical countermeasures, use of abdominal binders and compressive stockings, and physical conditioning.

In conclusion, pharmacological therapy is a common cause of OH, particularly in older patients. Both cardiovascular and psychoactive medications may impact on the blood pressure response to orthostatism, thus inducing or exacerbating OH. Therefore, a careful medication review is advisable in people presenting with OH, with a view to minimize iatrogenic causes.

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