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Drugs and Orthostatic Hypotension: Evidence from Literature

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Abstract

Orthostatic hypotension is defined as the reduction of systolic blood pressure of at least 20 mmHg or the dropping of diastolic blood pressure of at least 10 mmHg within 3 minutes of standing compared to baseline values. It can be divided into neurogenic and non neurogenic forms. Neurogenic forms are caused by a primitive damage to autonomic nervous system, while drugs are the most common cause of non neurogenic orthostatic hypotension; they may also complicate or aggravate neurogenic forms.

Many drugs can determine orthostatic hypotension, including both cardiovascular drugs and therapies used for neurological and psychiatric disorders. This effect is furthermore enhanced by multiple pharmacological treatments. It is important for the clinician to know the potential hazard of orthostatic hypotension, in order to avoid syncope, falls, hypoperfusion symptoms, excess of mortality and loss of compliance to treatment.

Keywords: Orthostatic hypotension; Adverse drug reaction; Hypertension; Anti-hypertensive treatment; Parkinson's disease

Introduction

Orthostatic hypotension is defined as the reduction of systolic blood pressure of at least 20 mmHg or the dropping of diastolic blood pressure of at least 10 mmHg within 3 minutes of standing compared to baseline values [1]. Recent studies suggest a change in reference values to 30 mmHg in diabetic patients and hypertensive subjects with clinostatic systolic blood pressure higher than 160 mmHg [1,2], as this would more accurately estimate the probability of autonomic neuropathy in those populations. Multiple system atrophy is a neurodegenerative disorder characterised by parkinsonian features, cerebellar ataxia, and autonomic failure. In a recent consensus, reference values for the diagnosis of orthostatic hypotension in multiple system atrophy have been upgraded to 30 mmHg in systolic blood pressure or 15 mmHg in diastolic blood pressure, within 3 minutes of standing [3].

Orthostatic hypotension can be divided into neurogenic and non neurogenic forms. Neurogenic forms are caused by a primitive damage to autonomic nervous system. Non neurogenic forms involve organs or systems regulating metabolic homeostasis and hemodynamics of the organism; in other instances, they may also be determined by external factors, such as the use of drugs, alcohol and other substances [4].

Drugs are the most common cause of non neurogenic orthostatic hypotension; they may also complicate or aggravate neurogenic forms.

Orthostatic hypotension is a common cause of falls and syncope, especially in elderly people [5-7]. Longitudinal studies have demonstrated an association between orthostatic hypotension and increased cardiovascular morbidities (such as coronary artery disease [8,9] and stroke [10]), and between orthostatic hypotension and mortality in the general population [8,11].

Moreover, when orthostatic hypotension is due to an adverse drug reaction, it is common in clinical practise to observe a general loss of compliance to therapies. To optimize a treatment with vasoactive drugs, by avoiding orthostatic hypotension, represents a matter of enormous importance in the management of lifelong-treated patients with neurological and cardiovascular diseases.

Antiparkinsonian Drugs

Orthostatic hypotension plays an important role in Parkinson's disease (PD): its prevalence ranges between 14% and 80% [12]. It is related to older age, severity and duration of the disease [13,14] and can be caused by autonomic dysfunction, drugs, or both causes. Few studies have evaluated the specific mechanisms of orthostatic hypotension in patients with PD. Lowering of blood pressure may be mainly due to drugs (in particular levodopa), when autonomic cardiovascular function tests are normal [15]. On the other hand, the absence of activation of compensatory chronotropic mechanisms to low blood pressure while standing may be due to autonomic failure [16].

Dopaminergic agonists (levodopa, carbidopa) frequently cause orthostatic hypotension, even at the beginning of therapy, through the activation of dopamine receptors, determining cutaneous, mesenteric and renal vasodilation, but also through other mechanisms, such as a reduced central sympathetic tone, which causes a small reduction in heart rate, and an impaired release of renin and aldosterone [17,18]. However, among antiparkinsonian drugs, selegiline seems to be more frequently involved in the onset of orthostatic hypotension, even after long-term therapy, if compared to levodopa [16,19]. Furthermore, while combined treatment with both drugs can determine severe orthostatic hypotension [20,21], levodopa alone is less often responsible for this phenomen. In fact, in additon to the peripheral vasodilatation due to dopamine agonists, the decreased reuptake of dopamine and norepinephrine in central neurvous system caused by selegiline causes a reduction in sympathetic tone [22]. Ha et al. [13] did not find a significant difference in dopaminergic agonist doses between PD patients with and without symptoms related to orthostatic hypotension, suggesting that other factors, such as age and other concomitant therapies, may be responsible for orthostatic hypotension in PD [13]. These data were further confirmed by Perez-Lloret et al.

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[14]: in their recent study, older age, poly-therapy, amantadine and diuretics were independent factors related to orthostatic hypotension in PD, while dopaminergic agonists were not. These data demonstrate that orthostatic hypotension due to antiparkinsonian therapy is particularly important in elderly patients with comorbidities, treated with multiple drug classes [13,14,23]. On the other hand, entacapone seems to have a protective effect against orthostatic hypotension in PD [14], because of its mechanism of action: this drug, in fact, inhibits the metabolism of cathecolamines in peripheral blood [24].

Sedative -Hypnotics

In hypovolemia, congestive heart failure and other diseases that reduce cardiovascular function, pharmacological doses of sedative-hypnotic drugs could determine further depression of cardiovascular activity, mainly for their effects on vasomotor centers of the brainstem. These drugs can reduce myocardial contractility and vascular tone through both central and peripheral actions [24]. However, a systematic review concerning the use of barbiturates and iatrogenic orthostatic hypotension is lacking. Benzodiazepines may cause hypotension by means of decreased left ventricular contractility and cardiac output: in particular, temazepam can induce more profound hypotension than zolpidem or placebo [25]. Strogatz et al. [26] found different evidence: they described a reduced prevalence of orthostatic hypotension in elderly patients treated with sedative-hypnotic drugs, compared to people who were not treated with these principles (OR 0.27, 95% CI 0.08 to 0.94).

Anesthetics

Anesthetics alter the heart rate acting directly on depolarization of the sinus node and interfering in a more complex way on the balance of autonomic nervous system. Through reduction of cardiac contractility and arteriolar vasodilation and their concurrent hypotensive effect, they decrease consumption of oxygen by the myocardium [24].

Cardiovascular effects of local anesthetics are partly the result of direct actions on cardiac and smooth muscle and partly derived from indirect actions on autonomic nervous system. In particular, hypotensive effects of lidocaine are due to a synergic and dose-dependent mechanism during general anesthesia, despite concomitant administration of amines or inotropic drugs such as ephedrine and adrenaline [27,28]. When administered in awake or mildly sedated patients, lidocaine does not cause significant systemic hypotension [24].

Data sheets of anesthetics report orthostatic hypotension as an adverse drug reaction in all the different subtypes, with dose-dependent or concentration-dependent mechanisms.

Such effects can be carried out through different pathways. Flurani cause a decrease in systemic vascular resistance. For several of them, blood pressure reduction is balanced by increase in heart rate (isoflurane and desflurane). Halothane, however, has a significant negative chronotropic and inotropic effect, associated with a slight systemic vasodilation [24]. Propofol may cause hypotension through vasodilatation and moderate depression of myocardial contractility by inhibiting type L-calcium channels in the myocardium [29]. It also attenuates baroreceptor reflex and it is directly vagotonic [24].

However, there are no specific data on the hypotensive effects of these drugs [30]. Risk factors for the development of intraoperative hypotension are: advanced age, history of hypertension and use of volatile anesthetics rather than intravenous ones [31]. In literature there are no sufficient data to choose a class of anesthetic over the other in patients who are at high risk for intra-operative hypotension. In these patients, especially during a spinal block, concurrent intravenous administration of ketamine is indicated in order to obtain hemodynamic stability, due to its indirect sympathomimetic effect [32-34].

Antidepressants and Antipsychotics

Treatment of depression in elderly patients with cardiovascular diseases often determines orthostatic hypotension: this issue has been studied for many years. Craig [35] described 50 cases of orthostatic hypotension in elderly patients: in 40 of them the cause was iatrogenic. Diuretics were identified as the leading cause of orthostatic hypotension in these patients. After these, 26% of cases were due to the assumption of benzodiazepines, 24% to antidepressants (amitriptyline, in particular) and 22% to antiparkinsonian drugs (among 11 patients treated for PD, 6 were taking L-dopa, 2 selegiline, 2 anticholinergic drugs and 1 bromocriptine). Antidepressants and antipsychotics may induce orthostatic hypotension through the inhibition of sodium, potassium and calcium channels in the synapses. Recently it has been described that symptomatic orthostatic hypotension may not only be due to "classic" antidepressants (such as tricyclics, monoamine oxidase inhibitors and neuroleptics) but also to selective serotonin reuptake inhibitors and new antipsychotics [36-38]. Mechanisms through which tricyclic antidepressants may induce hypotension are well known: the blockade of postsynaptic α1 receptors and, in the first phase of therapy, also the blockade of pre-synaptic α2 receptors [24,39]. Among the selective serotonin reuptake inhibitors, fluoxetine and citalopram appear to induce orthostatic hypotension through inhibition of calcium channels leading to vasodilatation [36,40]. Fluoxetine also acts on vasomotor centers in the central nervous system, leading to an increased risk of hypotension, orthostatic hypotension and syncope, especially in elderly people [41].

Antipsychotics, including chlorpromazine, clozapine and risperidone, frequently cause orthostatic hypotension, acting on α1 postsynaptic receptors. Atypical neuroleptics seem to be frequently responsible for orthostatic hypotension, but data are limited [24,42]. In a recent study by Shi et al. [43], in which eight subjects underwent measurement of blood pressure in supine and standing position during different drug treatments (without drugs; midodrine only; promethazine only; midodrine and promethazine), orthostatic hypotension had an increased incidence during treatment with promethazine ($p < 0.01$), even in combination with midodrine ($p < 0.05$). This effect is probably due to inhibition of responses in the sympathetic and renin-angiotensin systems.

Opioid Analgesics

Regarding treatment with opioid analgesics, blood pressure is generally unchanged, except in cases in which the cardiovascular system is under stress. In this instance, hypotension is mediated by peripheral arterial and venous dilatation due to various factors, such as histamine release and depression of vasomotor center. For example, morphine may cause orthostatic hypotension through peripheral vasodilatation, decreased peripheral resistance and reduced vasomotor reflexes [24]. Particular attention should therefore be placed towards patients with hypovolemia, who are more sensitive to lowering of blood pressure.

Antihypertensive and Cardiovascular Drugs

Cardiovascular drugs are often related to orthostatic hypotension.

Antihypertensive drugs may be classified into seven classes: calcium channel blockers (dihydropyridine and non-dihydropyridine), diuretics, renin-angiotensin-aldosterone system inhibitors (angiotensin convertase enzyme (ACE) inhibitors, angiotensin II receptor blockers, direct renin inhibitors), α-blockers, β-blockers, centrally acting drugs, and direct vasodilators [24].

On average, 11.9 to 73% of patients with orthostatic hypotension are taking medications [44,45]. Besides the type and mechanism of action of each drug, the total number of vasoactive drugs is crucial. In a study by Poon and Braun [46] in elderly subjects, prevalence of orthostatic hypotension was 35% in *naive* individuals and 65% in those taking at least three vasoactive drugs ($p = 0.002$). The study of Kamaruzzaman et al. [47], carried out on a cohort of elderly women, confirms this trend. In this study, predictors of orthostatic hypotension are poorly controlled hypertension (prevalence 38% vs. 21% in hypertensive patients well controlled by therapy, $p < 0.001$), and the use of at least three vasoactive drugs (OR 1.99, 95% CI 1.30 to 3.05, $p = 0.003$). Another study [48] shows that in elderly hypertensive patients undergoing pharmacological wash-out, prevalence of orthostatic hypotension is reduced from 23% to 0% during 12 months ($p < 0.05$), while there are no differences in people who did not undergo therapeutic changes.

In literature there are also countertrend data. In two studies, the first carried out on elderly residents in long-term care [23] and the second focused on comparing hypertensive and normotensive individuals [49], a strong correlation between orthostatic hypotension and supine high blood pressure was detected, while there was no correlation with the antihypertensive treatment (no statistical significance [23]; RR 0.41, 95% CI 0.18 to 0.93, $p = 0.034$ [49]).

These data suggest that optimal treatment of hypertension may improve blood pressure regulation and may reduce orthostatic intolerance, which is often seen in patients on politherapy with vasoactive drugs and diuretics. Masuo et al. [50] compared the prevalence of orthostatic hypotension in a population of normotensive and hypertensive elderly people before and after the beginning of an antihypertensive treatment. Orthostatic hypotension was decreased in hypertensive subjects after treatment (prevalence of orthostatic hypotension pre-treatment: 20% in hypertensive subjects, 4% in normotensive, $p = 0.159$; post-treatment: 1% in hypertensive subjects, 4% in normotensive, $p = 0.406$). These data suggest that optimal long-term antihypertensive treatment may result in reducing the burden of orthostatic hypotension.

Among antihypertensive therapy, each drug class is related to a different prevalence of orthostatic hypotension, sometimes correlated to the specific mechanisms of action.

Table 1 resumes cardiovascular drugs potentially implicated in hypotensive events and orthostatic hypotension.

Nitrates

Nitrates may determine orthostatic hypotension through the induction of vasodilatation, predominantly on the venous district, due to the release of nitric oxide. Nitric oxide activates the enzyme guanilatociclase and determines an increase in cGMP. Although orthostatic hypotension is listed as an adverse drug reaction in the data sheet of these drugs and severe hypotension is reported as a controindication, in population studies no data of significant correlation are available [51,52]. This may be due to the absence of a significant number of people treated with these drugs in the analyzed population. Although in combination with other vasoactive drugs nitrates may be significantly associated with orthostatic hypotension or syncopal events related to excessive blood pressure fall in orthostatism ($p < 0.001$) [5], Kamaruzzaman et al. [47] identify a weak protective effect against orthostatic hypotension using nitrates (RR 0.70, 95% CI 0.51 to 0.96, $p = 0.05$), probably consequent to the development of tolerance during protracted treatment.

Calcium Channel Blockers

Calcium channel blockers act on L-type calcium channels, reducing the entrance of calcium into smooth muscle cells of blood vessel walls: in this way, they determine vasodilatation, mainly on arteries. Luukinen et al. [53] and Vara Gonzalez et al. [54] showed that treatment with calcium channel blockers is an independent risk factor for orthostatic hypotension, especially with non-dihydropyridine calcium channel blockers (RR 3.23, 95% CI 1.05 to 9.87). There are no studies that correlate dihydropyridine calcium channel blockers (in particular amlodipine [55] and nicardipine [56,57]) to orthostatic hypotension. This is likely due to their major effect towards vascular smooth muscle cells: during treatment with this class, compensatory increase in heart rate as a result of adrenergic stimulation on sinoatrial node is still possible. On the other hand, the prevalent effect of non-dihydropyridine calcium channel blockers is dromotropic negative and inotropic negative. These drugs may determine, in fact, orthostatic hypotension is because of the lack of compensatory chronotropic response on standing [54]. In main population studies which analyzed the overall class of calcium channel blockers (without distinctions between dihydropyridines and non-dihydropyridines), orthostatic hypotension shows a 2-to-5-times increase in prevalence during treatment with these drugs, especially in elderly population [8,53,58], while there is no association between the use of calcium channel blockers and orthostatic hypotension in diabetes [52,59].

ACE Inhibitors and Angiotensin II Receptor Antagonists

The drugs acting directly on the renin-angiotensin-aldosterone system (ACE inhibitors, angiotensin II receptor blockers, and direct renin inhibitors) may cause significant hemodynamic changes on standing through multiple mechanisms. By blocking the neurohumoral axis, they determine a reduction of vasoconstrictor and sodium-retentive effects mediated by angiotensin II, with a consequent reduction of total peripheral resistance and noradrenergic peripheral transmission, decreased release of catecholamines by the adrenal medulla and modifications of hemodynamics, such as decreased renal reabsorption of sodium and water, caused by the fall in renal sympathetic tone and reduced plasma levels of aldosterone [24]. The role of ACE inhibitors in the development of orthostatic hypotension is controversial. Large population studies did not find any correlation between orthostatic hypotension and intake of ACE inhibitors even in the subgroup consisting of diabetic and hypertensive patients [9,11,47,48,52,59,60]. According to Fedorowski et al. [49], this drug class seems to be related to a decreased prevalence of orthostatic hypotension in patients with hypertension under pharmacological treatment. This may be partially explained by the protective action ACE-inhibitors exert on the kidney and by their final effect on blood pressure decrease. Considering the individual active principles, some studies show a correlation between the use of captopril and the onset of severe hypotensive events [61-63], first-dose orthostatic hypotension (estimated prevalence: 0,7-13,7% in

PHARMACOLOGICAL CLASS	HYPOTENSION OH (DATA SHEET)	REFERENCE	POPULATION	N	ASSOCIATION WITH OH	ADJUSTMENT FOR
NITRATES	Hypotension/OH (contraindicated in presence of severe hypotension)	Vara Gonzalez 2001	Elderly (≥65 years) hypertensive	295	RR 3.9; 95% CI 1.6-9.8	Not specified
		Mussi 2009	Access to Emergency Department due to syncope (>65 years)	259	RR 5.20; 95% CI 1.99-13.61; p<0.001	Age, sex, comorbidities, posology
		Kamaruzzaman 2009	Women (60-80 years)	3775	RR 0.70; 95% CI 0.51-0.96; p=0.05	Age, drugs
CALCIUM CHANNELS BLOCKERS	Hypotension	Luukinen 1999	Elderly (>70 years)	833	RR 2.31, 95% CI 1.14-4.68	Not specified
		Rose 2000	General population (mean age 54 years)	2433	Hypertensive: not associated with OH; Normotensive: associated with OH; p<0.0001	Age, sex, ethnic groups
		Rose 2006	General population (mean age 54 years)	13152	Hypertensive: associated with OH; p=0.05	Not specified
		Fedorowski 2010	General population (mean age 66 years)	101	RR 5.29; 95% CI 1.03-27.14; p=0.046	Age, sex, BMI
ACE-INHIBITORS	Hypotension/OH	Kamaruzzaman 2009	Women (60-80 years)	3775	RR 1.27; 95% CI 1.00-1.61; p=0.04	Age; not significant if corrected for comorbidities and lifestyle
		Fedorowski 2009	469 hypertensive during treatment vs 453 normotensives (mean age 62 years)	922	Protective effect RR 0.41; 95% CI 0.18-0.93; p=0.03	Not specified
DIURETICS	Hypotension/OH	Luukinen 1999	Elderly (>70 years)	833	RR 2.29; 95% CI 1.15-4.59	Not specified
		Mussi 2009	Access to Emergency Department due to syncope (>65 years)	259	RR 3.73; 95% CI 1.23-11.28; p=0.02	Age, sex, comorbidities, posology
		Hirai 2009	Type 1 diabetes (mean age 45 years)	440	RR 1.84; 95% CI 1.01-3.38; p<0.05	Age, sex, BMI
LOOP DIURETICS	Hypotension/OH	Fedorowski 2010	Syncope due to OH (mean age 66 years)	101	RR 10.22; 95% CI 1.22-89.08; p=0.032	Age, sex, BMI
THIAZIDE DIURETICS	Hypotension/OH	Kamaruzzaman 2009	Women (60-80 years)	3775	RR 1.25; 95% CI 1.02-1.53; p< 0.05	Age
β- BLOCKERS	Hypotension/OH	Vara Gonzalez 2001	Elderly (≥65 years) hypertensive	295	RR 4.25; 95% CI 1.15-15.48	Not specified
		Kamaruzzaman 2009	Women (60-80 years)	3775	RR 1.58; 95% CI 1.19-2.09; p<0.01	Age, drugs, comorbidities, lifestyle
α-BLOCKERS	Hypotension/OH	Kamaruzzaman 2009	Women (60-80 years)	3775	RR 1.81; 95% CI 1.08-3.03; p<0.05	Age

Table 1: Cardiovascular drugs potentially implicated in hypotensive events and orthostatic hypotension. OH: orthostatic hypotension; RR: relative risk; CI 95%: 95% confidence interval; N: number of subjects.

general population and 2-33% in patients with heart failure) [64,65] and the presence of related symptoms [66]. The short half-life and rapid action of this drug are likely to be strongly linked to these events. On the other hand, ramipril and perindopril appear to be associated with a lower prevalence of orthostatic hypotension and hypotensive events [9,61,62,67,68].

Angiotensin II receptor antagonists are not significantly connected to orthostatic hypotension, either in the elderly, or in patients with hypertension, particularly when compared to other drugs (calcium channel blockers and ACE inhibitors) [69-72].

Diuretics

In large population studies, diuretic therapy does not appear to be related to orthostatic hypotension [9,11,51,52,73,74]. In PD patients, diuretics are related to orthostatic hypotension, as previously described [13]. The hypotensive effect may be different within diuretics subclasses. The wide majority of the studies in literature distinguish thiazide diuretics from non-thiazide diuretics. Among the latter category, only one study [49] revealed a strong association between orthostatic hypotension and potassium-sparing antialdosteronic diuretics (specifically, spironolactone) (RR 3.29, 95% CI 1.50 to 7.21,

p = 0.003), although this type of adverse drug reaction is not indicated in the data sheet of the drug. The hypotensive mechanism is mediated by the blockage of aldosterone on the final part of the distal tubule and collecting ducts, thereby reducing the reabsorption of sodium and free water.

Loop diuretics are frequently used in the treatment of heart failure. They act through inhibition of the symport Na^+-K^+-$2Cl^-$ in the thick ascending limb of loop of Henle, leading to inhibition of reabsorption of sodium and water. The acute effect of these drugs determines an increase in the capacitance of venous district and a reduced filling pressure of the left ventricle, resulting in decreased cardiac output. Fedorowski et al. [75] detected a significant association between the intake of furosemide and orthostatic hypotension in elderly patients (RR 10.22, p=0.032), as previously shown by Poon and braun [46].

Thiazide diuretics determine the inhibition of the Na^+-Cl^- symport in the distal convoluted tubule: through this mechanism, they reduce sodium and water reabsorption determining plasma volume depletion, thus possibly inducing orthostatic hypotension. Kamaruzzaman et al. [47] identified a significant correlation between this class of diuretics and orthostatic hypotension (RR 1.25, 95% CI 1.02 to 1.53). Poon and braun [46] noticed that in an elderly population 65% of patients with orthostatic hypotension was undergoing treatment with hydrochlorothiazide. Moreover, an increased prevalence of orthostatic hypotension has been detected in patients with heart failure treated with thiazide diuretics, if compared with patients treated with non thiazide diuretics [76].

β-Blockers

Drugs that act directly on the peripheral sympathetic nervous system may be classified into three categories: α-blockers, β-blockers, and drugs with mixed action.

β -blockers carry out their action, reducing the activity of renin-angiotensin-aldosterone system (blockade of β1 receptors located on the membrane of renal juxtaglomerular cells and consequent inhibition of renin release and production of angiotensin II and aldosterone) and decreasing the release of norepinephrine in response to β-adrenergic action on presynaptic receptors. They also have negative inotropic and chronotropic effects. They can be divided into three main categories, according to their prevalent action on different types of β-adrenergic receptors: non selective β-blockers, selective β1-blockers, α-β non-selective β-blockers. β-blockers do not seem to determine significant orthostatic hypotension [11,51,52,59,77,78]. In older individuals with an initial, age-related, autonomic and baroreceptorial dysfunction, the use of these drugs may affect the compensatory response to orthostatism (increase of heart rate and peripheral vasoconstriction) [79], as noticed by Kamaruzzaman et al. [47] and Vara Gonzalez et al. [54]. There are no studies comparing the prevalence of orthostatic hypotension in patients treated with different types of β-blockers.

α-Blockers

α1-antagonists inhibit the vasoconstrictor effect mediated by catecholamines through selective blockade of α1-adrenergic receptors, in the absence of changes in cardiac output, plasma renin levels, and baroreflex function. At high doses they determine further vasodilators effects, mainly on arteries, through the inhibition of the phosphodiesterase enzyme in smooth muscle cells of arterial walls. The development of orthostatic hypotension in patients treated with α1-antagonists may be fostered by the combination of plasma volume depletion and the absence of vasoconstriction mediated by α1-adrenergic receptors at standing [80]. Some studies [46,47] point out the increased risk of developing orthostatic hypotension with these drugs: it can be twice as high during intake of α1-antagonists. Prazosin is the fast-acting α1-antagonist with the greatest affinity for α1 receptor. It is, therefore, more closely related to orthostatic hypotension and syncopal events than other active ingredients, including terazosin and doxazosin. The latter are less powerful than prazosin but highly specific for α1 receptors and are thus associated with orthostatic hypotension (7-9%, mostly resulting in elderly) [81-83], while alfuzosin and tamsulosin are less associated with this adverse drug reaction (1,3-3.4%, usually asymptomatic) [84-86].

Central α2-agonists act on the α2 presynaptic receptors in the brainstem: they determine inhibition of sympathetic tone and reduction of vasopressor efferent impulses from the centers of the brainstem, determining orthostatic hypotension mediated by vasodilatation [87]. There are no studies in literature which evaluate the prevalence of orthostatic hypotension in hypertensive subjects treated with this class of drugs. However, in patients suffering from autonomic failure, the peripheral α2-agonist effect predominates, determining vasoconstriction: in these subjects, α2-agonists, such as clonidine, may increase blood pressure [88].

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors (sildenafil, tadalafil) seem to be associated to exacerbation of orthostatic hypotension, especially in patients with autonomic failure (PD and multiple system atrophy) [89] and during administration of other vasoactive drugs. In particular, the concomitant administration of nitrates is contraindicated [90]. Moreover, an increased prevalence of orthostatic hypotension during treatment with sildenafil or tadalafil in combination with alpha-antagonists (for example doxazosin) has been highlighted [91]. Phosphodiesterase-5 inhibitors regolate the intracellular levels of cAMP and cGMP and, indirectly, the intracellular levels of calcium, leading to relaxation of vascular smooth muscle cells, and, therefore, arterial and venous vasodilatation.

Conclusion

Orthostatic hypotension is associated with higher morbidity and mortality. Patients with PD, diabetes, hypertension (especially if poorly controlled by therapy), and the elderly in general are often treated with multiple drugs and are at high risk for orthostatic hypotension as a consequence both of an adverse drug reaction and of the underlying autonomic dysfunction.

Antihypertensive drugs may determine orthostatic hypotension through multiple mechanisms. Although most of these drugs can theoretically lead to orthostatic hypotension according to the mechanism of action and the data sheet of the drug, in clinical practice this phenomenon does not occur constantly. This discrepancy is probably due to the establishment of compensatory mechanisms in response to the drop of blood pressure in orthostatism, to the pharmacokinetic and pharmacodynamic inter-individual variability, and to the influence of external factors or comorbidities which act on autonomic nervous system and renal function. Drug classes at greater risk for development or exacerbation of orthostatic hypotension may be identified in nitrates, α-antagonists and non-dihydropyridine calcium channel blockers, while ACE-inhibitors, angiotensin II receptor antagonists, dihydropyridine calcium channel blockers and β-blockers carry a lower risk of orthostatic hypotension. In the treatment of hypertension of patients at risk of orthostatic hypotension, such as the

elderly, and subjects with diabetes and PD, it is advisable to use the latter drugs, associated to a lower risk of orthostatic hypotension.

There are no experimental data regarding the prevalence of orthostatic hypotension in elderly patients treated with centrally-acting antihypertensive drugs, so the role of these drugs in the development of orthostatic hypotension is controversial.

In the treatment of benign prostatic hypertrophy in subjects who also suffer from hypertension, a lower prevalence of hypotensive events during protracted treatment with alfuzosin and tamsulosin if compared to other -antagonists has been highlighted. Again, in the treatment of benign prostatic hypertrophy of patients at risk of orthostatic hypotension, such as the elderly, and subjects with diabetes and PD, it is advisable to use alfuzosin or tamsulosin, associated to a lower risk of orthostatic hypotension.

Furthermore, the optimization of a pharmacological treatment of hypertension seems to be related to a reduced prevalence of orthostatic hypotension.

Pertaning to drugs commonly used in neurological and psychiatric disorders, it is appropriate to evaluate blood pressure in clinostatism an orthostatism at baseline and after starting specific therapy, in particular in Parkinson's disease. Equally, it is useful to report preoperative autonomic failure or its associated comorbidities such as diabetes mellitus [92], in order to utilize anesthetics that cause less hemodynamic instability and a lower intra-operative blood pressure drop. Moreover, special caution is advised during the administration of psychoactive drugs in elderly people because they are more susceptible to their adverse effects, both cardiovascular and neuro-psychiatric.

Simultaneous presence of two or more drugs in combination therapy often leads to a synergistic or additive effect, which contributes to a more significant reduction of blood pressure levels when compared to the action of a single drug. Considering the correlation between the number of vasoactive drugs and the blood pressure drop in orthostatism, after the detection of drug-induced orthostatic hypotension, a reduction in the number and type of hypotensive drugs is auspicable, in order to reduce morbidity, mortality and symptoms related to orthostatic hypotension, as well as a selection of therapies associated to a lower risk of orthostatic hypotension.

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