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REVIEW ARTICLE

Medications and Orthostatic Hypotension. Are They Complimentary or Contradictory?

B.R. Kartheek

Faculty of Medicine, Masterskill University College of Health Sciences, Pasir Gudang Campus, Jalan Lembah, Bandar Seri Alam- 81750 Masai, Johor, Malaysia

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ABSTRACT

Orthostatic hypotension - a sudden fall in blood pressure when a person stands up - is a common problem in elderly adults as well as in people with multiple system atrophy, Parkinson's disease, diabetes, and a mixture of other disorders. Orthostatic hypotension is caused by loss of function in the autonomic nervous system, which controls the tightening and relaxing of blood vessels needed to maintain normal blood pressure. People with orthostatic hypotension usually experience dizziness, blurred vision, light headedness or fainting when they stand.

Midodrine is the standard treatment for postural hypotension, which helps to alleviate symptoms. However, standard doses of midodrine also raise blood pressure on lying down. The treatment for postural hypotension mainly depends on the underlying cause. Mild orthostatic hypotension can be controlled by sitting or lying down immediately after feeling lightheaded upon standing. When low blood pressure is caused by medications, changing the dose of the medication or stopping it entirely controls the situation. The aim of this review is to provide comprehensive information on action of various drugs on orthostatic hypotension especially in elderly people, various associated conditions and future research opportunities. All the relevant information on orthostatic hypotension was collected through MEDLINE/PUBMED.

Key words: Orthostatic hypotension, Midodrine, Blood pressure, Medication, drugs, treatment, elderly.

INTRODUCTION

Drug Interactions and Orthostatic Hypotension

Orthostatic hypotension (OH) and space motion sickness are commonly encountered by astronauts during re-entry in to earth's atmosphere. Promethazine combined with midodrine, increased the incidence of orthostatic hypotension (OH) by inhibition of sympathetic responses through enhancement of the inhibitive effects of GABA. Response of the renin angiotensin system during orthostatic challenge test was also inhibited [1]. Orthostatic hypotensive effect of the antipsychotic drugs in rats was mediated through alpha1A-adrenoceptors [2]. Reports from the literature describe orthostatic hypotension as the most common adverse autonomic side effect of antipsychotic drugs [3]. Octreotide (Long acting release) suppressed tachycardia and improved standing time in patients with orthostatic intolerance [4]. In a prospective cohort study done in geriatric outpatient clinic, outcome of tilt-table tests OH improved after withdrawal of fall-risk-increasing drugs [5]. In a study done on conscious dogs, the combination of midodrine and dihydroergotamine lead to abolition of the pressor effect induced by midodrine. This antagonistic effect on blood pressure could explain worsening of OH clinically in humans [6]. In patients with neurogenic orthostatic hypotension, L-threo-3,4-dihydroxyphenylserine, a synthetic catecholamino acid increased blood pressure and ameliorated orthostatic intolerance [7]. In an epidemiological retrospective cohort study in 46 medical practices in Germany, Korodin Herz-Kreislauf-Tropfen, a herbal drug containing D-camphor and a liquid extract of fresh hawthorn berries was proven as effective and safe in the treatment of OH for all age groups and independent of initial blood pressures [8]. In a placebo-controlled, two-stage, two-way, crossover study on patients with benign prostatic hyperplasia who received vardenafil 10 mg (or placebo), followed by vardenafil 20 mg (or

***Corresponding Author:** Dr.B.R. Kartheek**, Email:** drkartheek@yahoo.com, **Phone No:** 07-386 0541/0542 ext: 193

placebo), simultaneously with tamsulosin, clinically significant hypotension was not reported [9].

In patients with OH associated with neurocardiogenic syncope, clinical trials have demonstrated that beta-blockers, especially beta(1)-selective agents without intrinsic sympathomimetic activity such as midodrine, atenolol, and paroxetine decrease the recurrence of syncope [10]. Double-blinded, independent, randomized, placebo-controlled studies using sublingual/oral administration of D-camphor, an extract from fresh crataegus berries, and a combination (CCC) of these compounds showed that CCC, exerts a significant effect that counteracts an orthostatic fall in blood pressure [11]. For treating OH, fludrocortisone and midodrine are the drugs of first choice. Norepinephrine therapy was effective in mobilizing otherwise immobile patients [12]. Homozygosity for 3435T alleles of multi-drug resistance gene ABCB1 was a risk factor for occurrence of nortriptyline-induced postural hypotension [13]. High sodium intake was an effective treatment for OH in combination with vasoactive drugs [14]. L--threo-3,4-dihydroxyphenylserine taken before hemodialysis prevented development of OH in patients undergoing hemodialysis. It also alleviated interdialytic symptoms related to orthostatic hypotension [15]. In a study on patients with autonomic failure, Clonidine and dihydroergotamine caused increase in supine arterial pressure and forearm vascular resistance. Forearm venous tone was increased by dihydroergotamine but was unaffected by clonidine. A single, calculated dose of clonidine was far less effective than a single dose of dihydroergotamine in maintaining arterial pressure during graded orthostatic stress [16]. Management of OH in patients with Parkinson's disease must always start with patient education and nonpharmacological treatment. Drug therapy must be reserved for symptomatic patients who do not get benefit from nonpharmacological management. Alpha1-adrenergic agonists - midodrine or plasma volume expanders - fludrocortisone were the commonly used drugs [17]. Ruscus aculeatus, a phytotherapeutic agent containing ruscogenins and flavonoids ameliorated the symptoms of OH and improved the quality of life [18]. Fludrocortisone, indomethacin, midodrine, and atrial tachypacing were recommended, for patients in whom nonpharmacologic measures to control OH proved ineffective [19].

In elderly hypertensives on medications, no association was found between the prevalence of OH and the number of drugs used [20]. TA-606 [(3-pentyloxy)carbonyloxymethyl-5-acetyl-2-n-propyl-3-[2'(1H -tetrazole-5-yl)biphenyl-4-yl]methyl-4,5,6,7-tetrahydro imidazo[4,5-c]pyridine-4-carboxylate hydrochloride], AT1-receptor antagonist had a potent hypotensive effect in conscious 2K,1C-renal hypertensive dogs [21]. In a study done on elderly subjects with hypotension, reduction in the number and frequency of drug doses and better knowledge about drugs improved compliance [22]. The combination of midodrine (an alpha adrenergic agonist), and octreotide (an SRIH analogue) was more potent than either drug alone [23]. No association was found between use of antihypertensive therapy and OH on prolonged standing in an elderly in-patient population [24].

In a model of neurogenic orthostatic hypotension obtained by sinoaortic denervation in chloralose-anaesthetized dogs, yohimbine, at an alpha 2-adrenoceptor selective dose (0.05 mg/kg), caused an increase in sympathetic tone and delayed the fall in blood pressure due to head-up tilting [25]. Isosorbide impaired the systemic vascular response to orthostatic stress in elderly patients with stable coronary artery disease. Nicardipine decreased vascular responsiveness to sympathetic activation [26]. In a model of neurogenic orthostatic hypotension, obtained by chronic sinoaortic denervation in chloralose-anaesthetized dog's octreotide, was not able to correct the fall in blood pressure (BP) during head-up tilt test [27]. Sino-aortic denervation in dogs elicited a reproducible postural fall in BP with impaired adaptation of sympathetic nervous system activity [28]. A review done by Senard and Montastru elucidated the limits of the clinical pharmacology of drugs used for the treatment of orthostatic hypotension [29]. In a study on brain infarct patients with OH, propranolol therapy prevented the excessive adrenaline release produced by standing and normalized their nor-adrenaline response to posture. Metoclopramide administration prevented the post-orthostatic adrenaline discharge but had no significant influence on nor- adrenaline response to posture. Both drugs exerted a favorable influence on postural hypotension [30]. For drugs in which hypotension is a known but unwanted adverse effect like nitrates, anti-

Parkinsonian drugs, antidepressants, antipsychotics, responses were greater in the elderly and OH occured quite often [31]. Antagonistic dopaminergic drug, metoclopramide, 30 mg/day was used for treating a 38 year-old woman, with OH secondary to autonomic dysfunction accompanied by sympathetic hyperactivity and excess of dopamine [32]. A combination of dextroamphetamine, atropine and fludrocortisone, exhibited a beneficial effect on orthostatic hypotension induced by 7-day 6 degrees head-down bed rest, a model used to simulate the weightlessness of space flight [33].

Even though no uniform effective treatment regimen exists, OH can be effectively managed with a combination of nondrug and drug therapies. The drug of choice for all types of OH was fludrocortisone acetate [34]. Cardiac pacing was highly successful in preventing severe symptoms of OH encountered in clinical practice [35]. Ambulatory monitoring of blood pressure was a simple and reproducible method to assess the effects of drugs used in the management of OH on BP parameters. Yohimbine was not effective correcting OH of Parkinson's disease [36]. Diuretics were responsible for hypovolemia and hypokalaemia leading to OH. Mechanisms involved were interference of drugs with vegetative blood pressure regulation [37].

Frequency selective inhibition in the peripheral sympathetic nervous system was responsible for postural hypotension with usage of guanethidine, clonidine DA2 and 5-HT1A receptor agonists in rats [38]. Drugs used for the treatment of psychiatric illnesses like phenothiazines, tricyclic antidepressants and monoamine oxidase inhibitors and cardiovascular drugs like dopamine agonists, antianginals and antiarrhythmics were all associated with a significant incidence of orthostatic hypotension[39]. Caffeine administered before eating food, with abstinence for the rest of the day was very effective in treating patients with postural hypotension [40].

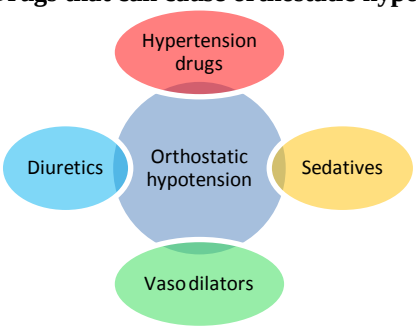
No single drug was universally successful in relieving the symptoms of OH [41]. In a patient with severe orthostatic hypotension, tilt table conditioning had a beneficial effect than adjunct drug therapy [42]. Patients on thiazide diuretics had a higher incidence of postural hypotension than patients on loop diuretics [43]. A relatively lower risk of postural hypotension was found after carvedilol treatment than with the other drugs like prazosin, labetalol and guanethidine [44]. In a double-blind, placebo controlled study in patients with psychotropic drugs induced orthostatic hypotension, 10 mg per day dihydroergotamine prevented immediate drop in blood pressure after standing up [45].

In a patient with Shy-Drager syndrome, oral DL-threo-3,4-dihydroxyphenylserine caused a reduction in the fall in mean arterial blood pressure on head-up tilting and had no syncope on standing. the same beneficial effect on OH was observed when peripheral decarboxylase inhibitor was combined with DL-threo-3,4-dihydroxyphenylserine [46]. Treatment with beta-blocking agents such as propranolol as an adjunct to sympathomimetics in a juvenile-onset insulin-dependent diabetes mellitus patient with severe OH showed improvement in the blood pressure response to sympathomimetic drugs [47]. Treatment with phenelzine sulfate and salt tablets for hypotension was successful in a woman with agoraphobia and panic attacks who could not tolerate other medications like imipramine and propranolol [48]. Drug-induced OH was useful in antihypertensive therapy in patients with moderate to severe hypertension [49]. Bupropion produced no significant alterations in systolic blood pressure or orthostasis as compared to placebo in patients who had clinically significant OH caused by treatment with tricyclic antidepressants [50]. In a study in done in Wellington, the causative factors for OH were found to be drugs such as diuretics and antihypertensive agents apart from cerebrovascular accidents and peripheral neuropathies [51]. Study done on conscious normotensive rats showed Alpha blockers – prazosin induced only moderate dose-dependent postural hypotensive (PH) effects while producing profound hypotensive effects. Direct vasodilators – minoxidil, calcium antagonists - nifedipine and a converting enzyme inhibitor- captopril, were free of PH effects despite moderate hypotensive effects. Clonidine exhibited greater PH than hypotensive effects. Propranolol and hydrochlorothiazide exhibited neither PH effects nor lower blood pressure [52]. Metoclopramide, alone or combined with the nonsteroidal agent flurbiprofen was effective in the treatment of postural hypotension associated with diabetes mellitus [53]. Significant association between symptomatic orthostatic hypotension and cardiac medication in depressed patients treated with imipramine hydrochloride [54]. Blood pressure increased significantly in healthy individuals with relatively low blood pressure who received 20 mg etilefrine, 2 mg Dihydergot or the combination-

Dihydergot plus for one week [55]. Guanethidine, the ganglionic blocker mecamylamine, and a high dose of reserpine resulted in significant PH after 4 days of oral administration in chloralose-urethane-pentobarbital anesthetized rats [56]. Hydralazine induced dose-dependent hypotension, but no change in blood pressure response from control tilts in conscious normotensive rats [57]. Inhibitors of peripheral sympathetic vasoconstrictor mechanism (phentolamine, prazosin, guanethidine) produced marked OH at antihypertensive doses in conscious normotensive dogs [58].

Postural hypotension or tachycardia was not found before vasodilator therapy or during therapy with nitrates or hydralazine in patients with chronic congestive heart failure [59]. The alpha-adrenergic blockers- phentolamine and prazosin and the adrenergic neuron blocker-guanethidine inhibited compensatory responses to upright tilt at antihypertensive doses in conscious spontaneously hypertensive rats [60]. nitroglycerine caused increase in heart rate and decrease in systolic blood pressure in the diabetic subjects with autonomic neuropathy [61].

Fig 1: Drugs that can cause orthostatic hypotension



Patients with idiopathic OH, showed a marked pressor response to topical ocular application of 2.5% phenylephrine ophthalmic solution [62]. An association of L-Dopa and mono-amine-oxydase inhibitor increased blood pressure sufficiently so as to block the diturbances of postural adaptation, without inducing hypertensive jerks in a case of grave OH (Shy-Drager's syndrome) with major postural disturbances [63]. Recurrent episodes of OH were observed in elderly hypertensive patients treated with alpha-methyldopa, beta-blockers and clonidine alone or associated with diuretics and/or reserpine and/or hydralazine [64]. Nitrangin and ergocomb decreased orthostatic fall in blood pressure in patients with pacemakers [65]. Patients with neurogenic orthostatic hypotension were successfully treated with a combination of tyramine and tranylcypromine, a monoamine oxidase inhibitor [66]. Guanethidine, debrisoquine and bethanidine produced hypotensive symtoms related to exertion in patients with mild hypertension [67]. Normalization of circulatory regulation occurred with Dihydergot treatment in subjects with orthostatic syndrome [68].

CONCLUSION

From the data cited above, it can be concluded that medications that affect the autonomic nervous system as well as medications used for high blood pressure control can cause OH even if taken as prescribed. OH is a side effect of many psychiatric medications, including tricyclic antidepressants.

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