Review Article

PREVALENCE OF ORTHOSTATIC HYPOTENSION AND RELATIONSHIP WITH DRUG USE AMONGST OLDER PATIENTS

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ABSTRACT

Introduction: Orthostatic hypotension (OH) is said to be highly prevalent in older people. Drugs are often involved as causative factor. Nevertheless, few data are available about the prevalence of OH and its relationship with drugs in olders.

Objectives: To review data about (i) the prevalence and characteristics of OH in older patients; and (ii) the relationship between OH and drugs.

Methods: Review of publications from Ovid (PubMed) from 1980 to May 2011 using the following key words: "orthostatic hypotension" combined with "elderly" or equivalent for the analysis of prevalence (first search) and "orthostatic hypotension" combined with "drugs" or equivalent to assess the relationship between OH and drugs (second search).

Results: Fifty-one publications (of which 14 with original data) were retrieved from the prevalence search, 31 for the second search (8 with original data: 7 retrospective studies and 1 prospective cohort study) and 12 reviews or experts opinions. Prevalence of OH varies according to the characteristics of the subjects, the settings of the studies, and the procedures of blood pressure measurement. In acute geriatrics units, two studies reported a prevalence of over 30% and one study mentioned that 68% of the patients presented with at least one episode during the day. OH was associated with several geriatric problems: gait disorders, balance disorders, falls, cerebral hypoperfusion, transient ischemic attacks, cognitive impairment, acute myocardial infarct and systolic hypertension. OH can also be asymptomatic or with atypical presentation: falls, gait disorders and confusion. Psychotropic agents (antipsychotics, sedatives, antidepressants), and cardiovascular drugs (antihypertensive agents, vasodilators, diuretics) were associated with OH.

Discussion: If the hypothesis of causality between drug treatment and OH is confirmed, the identification of the involved drugs could be of value for the prevention of OH and its complications. In this context, the *Working Group Pharmacology Pharmacotherapy and Pharmaceutical Care* of the *Belgian Society of Gerontology and Geriatrics* proposes to conduct a multicentre study to assess the prevalence of OH in Belgian acute geriatrics units and its relationship with drugs.

Key words: orthostatic hypotension, drugs, elderly, acute geriatric ward

INTRODUCTION

Older patients often experience drug-related problems leading to hospital admission, with reported rates ranging from 4% to 30% (1). The majority of these problems concerns

adverse drug reactions and several studies have estimated that at least 50% of drug-related problems in older subjects were avoidable (2-7).

Orthostatic hypotension (OH) is defined as a fall of at least 20 mm Hg in systolic blood pressure or of at least 10 mm Hg in diastolic blood pressure within 3 minutes after standing (8). It is common in older adults, increasing with advancing age, degenerative diseases and polypharmacy. The real prevalence of OH in geriatric units and its possible association with problems leading to hospital admission remain unknown. Moreover, the existing evidence concerning the relationship between OH and drug use in older in-patients is limited.

Identifying potentially responsible drugs could improve the awareness of geriatricians and help them preventing OH.

OBJECTIVES

The objective of this work is to review data about (i) the prevalence and characteristics of OH in older patients; and (ii) the relationship between OH and drugs.

METHODS (search strategy)

Two different searches were performed using Ovid (PubMed) from 1980 to May 2011.

The first search aimed to identify papers on the prevalence of OH in older people. Keywords relative to OH (orthostatic hypotension, postural hypotension, hypotension postural, hypotension orthostatic) were combined with keywords relative to older people (elderly, senior citizen, older adult, old age, elderly over 65, aged person, geriatric, aged, senescence). The main researcher selected papers based on title and abstract first, and then based on full text. Only original studies were considered for the analysis of prevalence.

The second search aimed to identify papers on the relationship between OH and drugs. Keywords relative to OH (orthostatic hypotension) were combined with keywords relative to drugs (drugs.

RESULTS

Prevalence

We found 2963 publications using the term "Orthostatic hypotension" or related ones and 24614 publications using the term "elderly" or related ones. Fifty one papers were found when both searches were combined, among which 14 publications reported original data. Table 1 summarises the characteristics and main findings of these 14 studies.

The prevalence of OH varies according to the definition of OH used, patients' characteristics (diabetes, arterial hypertension, etc.) and the time of measurement, but also because orthostatic blood pressure responses may not be reproducible even in patients with documented symptomatic OH, particularly if autonomic function is normal and measurements are taken in the afternoon. Repeated systolic blood pressure measurements in the morning may be necessary to make a diagnosis (9, 10) In the Coronary Health Study (11) the prevalence of asymptomatic OH was 16.2%.

The prevalence of OH increased to 18.2% when the definition also included those in whom the procedure was aborted due to dizziness upon standing. Only a few epidemiological studies have examined the cross-sectional (11, 12) or longitudinal (13) associations of OH with various parameters. The prevalence is assumed to increase with age. But because of the heterogeneity of the studied populations, this association was not confirmed. Rather than age itself, geriatric characteristics such as polypathology, dehydration and/or polypharmacy could be associated with OH.

Although OH can be present in healthy elders (14), it occurs in more than half of frail, older nursing home residents.

The prevalence of OH is higher during summer than winter. Thus, more attention should be paid to the diagnosis of OH in summer (15).

The prevalence of OH was less investigated in hospital geriatric practice although it is considered to be common (16-18). Prevalences of respectively 32% and 34% (16, 17) were reported and Weiss et al. showed that 68% of inpatients experienced OH at least once during the day (18).

Clinical relevance and atypical presentation

OH is assumed to be an important cause of generalized cerebral hypo-perfusion leading to dizziness, syncope, and falls, (19-21) and may be a cause of focal cerebral hypoperfusion as manifested by transient ischemic attacks or neuropsychological disorders (22-26).

At middle age OH is predictive of ischemic stroke, even after adjustment for numerous stroke risk factors; it is an easy-to-obtain measurement that might help to identify middle-aged persons at risk for stroke (27, 28).

OH may also be associated with pathological changes, such as the degree of atherosclerosis, inducing cardiovascular and cerebro-vascular disease. Physiological alterations in older adults, which may exacerbate orthostatic blood pressure (BP) changes, include a loss of baro-receptor responsiveness, which is primarily responsible for maintaining BP upon standing (19, 29-31) .These physiological alterations are implicated as causative factors in orthostatic BP changes, and they may be exacerbated by meals, (30, 31) certain medications (32), particularly antihypertensive and antidepressant agents, (19) or various disease states (13, 19).

A drop in diastolic blood pressure immediately after standing up identifies older subjects at a high risk of subsequent myocardial infarction (33).

OH seems to be associated significantly with gait disorders (odds ratio, 1.23; 95% confidence interval, 1.02-1.46), frequent falls (odds ratio, 1.52; confidence interval, 1.04-2.22), history of myocardial infarction (odds ratio, 1.24; confidence interval, 1.02-1.30) and transient ischemic attacks (odds ratio, 1.68; confidence interval, 1.12-2.51) (11). In addition, OH seems associated with isolated systolic hypertension (odds ratio, 1.35; confidence interval, 1.09-1.68), major electrocardiographic abnormalities (odds ratio, 1.21; confidence interval, 1.03-1.42), and the presence of carotid artery stenosis based on Doppler-ultrasonography (odds ratio, 1.67; confidence interval, 1.23-2.26). OH is negatively associated with body weight. It is associated with cardiovascular disease, particularly those manifestations measured objectively, such as carotid stenosis. It is also associated with general neurological symptoms, but this link may not be causative (11).

Table 1: Prevalence of orthostatic hypotension among older people

Authors, year	Setting	Country	Design	N	Age (yr)	Outcomes	Results
Ooi et al. 1997	frail residents in 45 nursing homes	US	Cross-sectional study	911	>60	Prevalence of OH	– 50% OH – more OH when high BP
Kao et al. 2001	Geriatric assessment centre	US	Cross-sectional study	262	78(7)	Risk factors for dizziness	– OH S: 52% when dizziness +, 35% when dizziness – ($p=0.03$); 1.9 (1.0-3.6)OR
Chan et al. 2001	Acute medical units at one hospital	Australia	Cross-sectional study	219	82(NA)	ADE causing emergency medical admissions in the elderly	– 53% of ADE admission preventable commonest manifestations: falls and OH (24.1%)
Weiss et al. 2002	One acute geriatric ward	Israel	Cross-sectional study	489	82(7)	Prevalence of OH	68% OH at least once during a day OH D more prevalent than OH S (57%vs43%)
Yu et al. 2003	Community-dwelling	Korea	Cross-sectional study	74	>60	Prevalence and risk factors for OH	17% OH risk factor: high basal sBP
Roberts et al. 2003	Haemodialysis unit	UK	Cross-sectional study	33	78(5)	OH, symptoms and falls	– 35% OH pre-dialysis – 70% OH post-dialysis
Luukinen et al 2004	Home-dwelling population	Finland	Prospective cohort study	792	76(5)	Risk of myocardial infarction associated with OH, 3.58 yrs follow up	– OH D: 8% – OH S: 27% – Diastolic OH associated with high risk of MI
Boddaert et al. 2004	Acute and intermediate-care geriatric ward at one hospital (patients admitted for falls)	France	Cross-sectional study	57	>80	Association arterial stiffness and OH	– 32% OH – arterial wall stiffness greater in presence of OH ($p<0.02$)
Rose et al. 2006	Community	US	Prospective cohort study	13,152	54 at inclusion	13-year mortality	– At baseline 5% OH – OH significantly predicts mortality in middle-aged adults.
Weiss et al. 2006	One acue geriatric ward	Israel	Prospective cohort study	471	82(7)	Prevalence 4-year mortality	– 34% at baseline – No impact on mortality ($p=0.67$)
Fisher et al. 2006	8 aged-care hostels	Australia	Prospective cohort study	179	83(NA)	BP parameters and mortality	– 23% of OH – No association with falls
Hiitola et al. 2009	home-dwelling elderly persons	Finland	cross-sectional analysis of a population-based cohort	653	NA	OH prevalence	– 34% OH
Boele van Hensbroek et al. 2009	Emergency department at one hospital	The Netherlands	Nested case-control study	200	73(NA)	OH among risk factors for falls	– 31% OH by fallers – 22% OH by controls ($p=0.27$)
Shaffer et al. 2010	Internal medicine resident primary care continuity clinics	US	Needs assessment chart review for single-site pre-/ post intervention study	166	NA	Screening for geriatric problems Including OH	– 19% OH

Legend: ADE: adverse drugs events; BP: blood pressure; sBP: systolic blood pressure; NA: not available; OH: orthostatic hypotension; OH D: diastolic orthostatic hypotension; OH S: systolic orthostatic hypotension.

Data from Passant et al. support the clinical impression that OH and low blood pressure are common factors which could play a role in dementia(34), which is supported by the presence of cognitive impairment in such non-demented patients with OH and the finding in patients with dementia that a drop in systolic blood pressure during a tilt test is concomitant with lowered regional cerebral blood flow (35). These findings suggest that OH needs to be considered, and actively sought for, in dementia as many patients may lack the typical symptoms of OH, despite a marked fall in blood pressure (36) However, the relationship between OH and cognitive decline remains controversial. (37, 38).

One-third of patients with severe OH are completely asymptomatic during the head-up tilt table test. In addition, one-quarter of these patients express atypical complaints, suggesting that the diagnosis of OH can easily be overlooked in a subset of patients (39).

In fifty older adults with OH Craig (40) identified three main modes of presentation: (1) falls or mobility problems; (2) mental confusion or dementia; or (3) predominantly cardiac symptoms. Medication was responsible for OH in 66% of patients and striking examples of polypharmacy were encountered. However, 34% of cases were not iatrogenic. This study stressed the fact that a high level of alertness is needed to diagnose OH in older subjects as the condition can often be overlooked. Measurement of blood pressure both in lying and in standing position should therefore be a routine part of the clinical examination in patients with geriatric syndromes such as gait problems or falls, mental confusion or dementia (40).

A recent study shows that older adults with uncontrolled hypertension and systolic OH at 1 minute are at greater risk for falling within 1 year (20).

In a large epidemiological study carried out in ambulatory older male patients, OH was relatively uncommon (less than 7%). However the data suggested that it may be a marker for physical frailty, since it was a significant independent predictor of 4-year all-cause mortality (41).

Relationship with drug use

If we hypothesize that a relationship exists between OH and drugs, in view of the associations observed between OH and a series of geriatric problems (gait disorders, falls, cognitive disorders, cerebral hypo-perfusion, dizziness, myocardial infarctions, etc.), identification of those drugs should help geriatricians to lower the risk of OH and its consequences.

We found 31 publications combining the key words "orthostatic hypotension" and "drugs" or equivalent terms. We kept four retrospective cohort studies (32, 42-44), two cross-sectional studies (3, 45), one prospective controlled interventional study (46), and reviews or expert opinions (47-59). We excluded derived papers that did not add original data. As mentioned above, OH is highly variable over the day. It is most prevalent in the morning when subjects first arise and when supine blood pressure (BP) is highest (60, 61). In this latter study the relationship of OH with elevated BP, but not antihypertensive medication use, suggests that the treatment of hypertension may improve postural BP regulation.

Although both postprandial hypotension (PH) and OH are commonly observed in nursing home residents, their reproducibility, relationship to each other, and association with chronic use of cardiovascular medications are poorly understood. Jansen et al. (44) assessed both in 22 nursing home residents. Reproducible patterns were identified: PH was more common than OH, their co-occurrence was infrequent and both seemed to be unaffected by chronic use of hypotensive medications.

On the other hand, Cohen et al. (45) found that symptoms of PH, reported by 2.6% of subjects, increased with the number of drugs used and with diabetes whereas symptomatic OH, recorded in 13% of subjects, related significantly to age and use of tranquillizers, antidepressants and ACE inhibitors.

Roach et al. (62) conducted a retrospective study aimed at examining whether patients experienced OH when antihypertensive medication(s) was simultaneously resumed following total joint replacement surgery. Thirty-five percent experienced a hypotensive event within the identified time frame. Among patients who had documented evidence of a hypotensive episode prior to the resumption of their antihypertensive medication, 42% of those experienced hypotension after postoperative medication administration versus 28% in patients without prior hypotensive episodes ($p = 0.50$).

In their observational study Poon et al. assessed patients aged 75 years and older attending a geriatrics day clinic (32). About 55% had OH, among whom 33% were symptomatic, and 87% had a history of falls. The prevalence of OH in patients receiving no, one, two, and three or more potentially causative medications was 35%, 58%, 60% and 65% respectively. The use of hydrochlorothiazide was associated with the highest prevalence (65%), followed by that of lisinopril (60%), trazodone (58%), furosemide (56%) and terazosin (54%). In this study, the prevalence of OH was very high in older patients and significantly related to the number of concurrent causative medications used.

To assess the frequency, severity and preventability of adverse drug events (ADE) causing emergency medical admissions in older adults, Chan et al. analyzed a cross-sectional survey of 219 patients aged 75 years and over who experienced consecutive unplanned admissions to acute medical units (3). Of all ADE admissions 53.4% were considered definitely preventable. The commonest causative drugs were cardiovascular compounds (48.4%), and the commonest manifestations were falls and OH (24.1%), heart failure (16.9%) and delirium (14.5%).

The prevalence of OH and its association with medications use in community-dwelling older women were assessed in a *cross-sectional analysis* using data from the British Women's Heart and Health (45). The prevalence of OH was 28%, which increased with age and uncontrolled hypertension. Regardless of treatment status or diagnosed hypertension, raised blood pressure was strongly associated with OH, which was strongly associated with the number of antihypertensive drugs taken. The association between OH and drugs was slightly attenuated after correction for age and co-morbidities. Women with multiple co-morbidities had markedly higher odds ratio of OH independent of age, number and type of medications taken. In that study, uncontrolled hypertension, use of three or more antihypertensive drugs and multiple co-morbidities were predictors of OH

Drug-induced OH should be suspected in any patient taking two or more drugs with hypotensive potential (40, 47, 51). A significant association has been demonstrated between

falls in older subjects and the use of hypnotic and antidepressant drugs (63-67). In psychogeriatric patients systolic OH, disease classification, and type and number of drugs taken contributed independently to dizziness and falls (63). In the study of Craig, medication was implicated in OH in 40 out of 50 patients and was thought to be primarily responsible for OH in 33 (66%) (40). The most common associated medications were diuretics (56%), benzodiazepines (26%), antidepressants (24%), and anti-Parkinson therapy (22%). In the study of Meyers et al. the frequency of postural hypotension was 4.6% in subjects treated with diuretics and 3.4% in those who were not (68).

In a *prospective cohort study*, van der Velde et al. (69), using outcomes of tilt-table tests found that withdrawal of fall-risk-increasing drugs can cause substantial improvement in cardiovascular homeostasis, suggesting that alteration of cardiovascular homeostasis may be an important mechanism by which these drugs induce falls.

CONCLUSIONS

This review shows that OH is common amongst older persons. Nevertheless thie review does not provide definite evidence for a link between the different possible causes (among which drugs) and mechanisms and OH. Despite its high prevalence and its possible association with many geriatric conditions (falls, gait disorders, cognitive impairment, etc.), OH and its causes remain unrecognized in clinical practice.

If the hypothesis of causality between drug treatment and OH is sometimes confirmed, the identification of the clinical importance of those involved drugs could be of value for the prevention of OH and its complications. In this context, the *Working Group Pharmacology Pharmacotherapy and Pharmaceutical Care* of the *Belgian Society of Gerontology and Geriatrics* is currently conducting a multicentre study to assess the prevalence of OH in acute geriatrics units and its relationship to the administered drugs. This study will determine the clinical relevance of OH with regard to geriatric syndromes and iatrogenicity amongst geriatric in-patients. According to the results, guidelines will be proposed in order to encourage screening for OH and flagging the drugs found to induce OH. Health care professionals should be educated to reduce the amount of potentially causative medications in older adults and, if they cannot be avoided, to assess the patients carefully to recognize typical and atypical signs and symptoms of OH.

CONFLICT OF INTEREST: None.

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