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Is there a risk of orthostatic hypotension associated with antihypertensive therapy in geriatric inpatients?☆

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ABSTRACT

Objectives: To determine the risk of orthostatic hypotension (OH) due to antihypertensive therapy in a geriatric inpatient population.
Subjects and methods: This observational cohort study included 388 patients (mean age 80.7, 68.5% female) hospitalized in a geriatric clinic. OH risk was evaluated by orthostatic testing (OT), with manual measurement of blood pressure after 30 minutes supine (T0), and after 1 (T1), 3 (T3), and 5 (T5) minutes after rising in a vertical position. OH was defined by a $\geq$ 20 mmHg decrease in systolic blood pressure and/or a $\geq$ 10 mmHg decrease in diastolic blood pressure.
Results: Age $\geq$ 80 years, history of falls and prescribed medication (antihypertensive, hypotensive, or both), were not significantly associated with OH or with OT positivity at any time point. The multivariate analysis showed that OH risk in T1 was 2.34 times higher than in T3 and T5 (confidence interval [1.49–3.68], $P < 0.001$). Presenting symptoms during OT increased the risk of obtaining a positive result by 3.67 times (confidence interval [1.52–8.87], $P = 0.004$). With each increase in one mini-mental state examination (MMS) point, a 9.9% decrease of OT positivity was observed (odds ratio = 0.907, confidence interval [0,84–0,98], $P = 0.016$).
Conclusion: The prescription of antihypertensive drugs was not significantly associated with the risk of OH in this geriatric inpatient population. OH screening in patients with cognitive impairment is critical, as with each decrease in one MMS point, OH risk increased by almost 10%.

Keywords:
Orthostatic hypotension; Hypertension; Falls; Frail elderly

1. Introduction

Although the prevalence of hypertension, particularly systolic, has been long known to increase with age, the benefits of treating hypertension in older patients have remained controversial for a very long time. The publication of the Hypertension in the Very Elderly Trial (HYVET) study, in 2008, demonstrated the cardiovascular benefits of such treatment in patients over age 80 [1].

OH and an increased risk of falls are often perceived as a risk of anti-hypertensive therapy. The prevalence of OH in the HYVET study was the same in treated and control patients. However, the population studied included patients who were relatively healthy for their age, presented with few comorbidities and very few medications. The risk of OH associated with treatment may be much more important in a population of geriatric patients, due to the impact of comorbidities and/or other drug prescriptions. The objective of our study was to assess the risk of OH and falls associated with antihypertensive therapy in a hospitalized, and thus more vulnerable, older population [2].

2. Methods

2.1. Population

We prospectively included 388 patients hospitalized in the geriatrics department of Valais Hospital. The inclusion of patients started in June 2009 and lasted over 11 months. Patients with delirium, with an orthopedic or traumatologic disorder impeding rising to a standing position, admitted for palliative care, or with an unreliable past personal medical history for the previous 6 months were excluded. Orthostatic testing could not be performed in 48 patients due to their inability to maintain a prolonged standing position, although they were initially included in the study. The time of orthostatic testing was variable during the day, and the schedule of drug and meal administration was not known.

Drug prescriptions were classified as follows: antihypertensive drugs (A drugs: diuretics, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II antagonists [A2As], renin inhibitors, calcium channel blockers, beta-blockers, centrally acting antihypertensive drugs) and drugs with potential hypotensive (H) effects,

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or enhancing the risk of fall via other mechanisms (H drugs: neuroleptics, nitrate derivatives, benzodiazepines, antidepressants, antiparkinsonians, opioids). The history of falls during the previous 6 months was recorded in the observation protocol (one, two, more than two episodes, or hospitalization due to a fall).

Cognitive function was assessed by the Mini-Mental-State [3] (MMS), and functional abilities assessed by the Barthel Index [4], between day 1 and day 3 after geriatric hospitalization. All patients with delirium were excluded. Admission albumin and plasma creatinine levels were transcribed from the medical chart, glomerular filtration rate was estimated using the Modification Diet in Renal Disease (MDRD) equation [5].

2.2. Measures

In the first 24 hours, orthostatic testing (Schellong's test) (OT) was performed on 340 patients. Manual measurements of blood pressure using mercury sphygmomanometers were performed after 30 minutes in the supine position (T0), and 1 (T1), 3 (T3) and 5 (T5) minutes after rising to a vertical position. OH was defined as a decrease $\geq$ 20 mmHg in systolic blood pressure and/or a decrease $\geq$ 10 mmHg in diastolic blood pressure. The occurrence of OH symptoms such as vertigo, dizziness, visual disturbances, fatigue, general weakness, headaches, slurred speech, was recorded [6,7].

2.3. Statistical analyses

To analyze OT results, which are categorical variables (positive vs negative) measured thrice for each patient (T1, T3, and T5), a generalized mixed effects model was used [8]. Gender, age, marital status, Barthel Index and MMS scores, albumin and creatinine levels, number of medications per day, hospitalization due to falls, number of falls in the previous 6 months, type of medication taken (A drugs or H drugs) and patients' provenance (home, surgical department, medical department) were included in the analyses. All analyses were performed with the Stata software [9].

We also analyzed having at least one positive ST result during the first 5 minutes (T1, T3, and T5 combined) vs having only negative ST. In order to test whether there was a difference between ST patterns and information related to patients, we used a χ^2-test to analyze categorical variables and a *t*-test to analyze continuous variables. When variables weren't normally distributed, Mann-Whitney non-parametric tests were performed.

3. Results

3.1. Patients

Two hundred and thirty-three women and 107 men were included in the study (Table 1). Their mean age was 80 $\pm$ 8.2 years (mean + SD). The mean MMS score was 25 $\pm$ 5.0 points, and the Barthel Index was 70 $\pm$ 19.0 points. Exactly 53.5% of patients lived alone and 26.5% of patients were admitted directly from their home. In the 6 months before the study, 42.9% of patients (146/340) suffered at least one fall. Among these patients, 57.5% (84/146) fell once, 15.7% fell twice, and 26.7% fell more than twice. Falls were the main reason for admission in 59.5% (87/146) patients.

3.2. Medication

The mean number of prescribed drugs was 7.4 $\pm$ 3.2 per patient. Exactly 90.3% of the patients were taking either A or H drugs, whereas 33 patients (9.7%) did not take either medication. The prevalence of A drug therapy was 67.9% in the whole study population, and 74.0% in patients $\geq$ 80 years old. It should be noted that 234 patients (68.8%) were receiving an active substance with a potential H effect in their daily medication ration. Taking A drug therapy didn't promote the occurrence of falls (44.6% in fallers versus 55.4% in non fallers), with the same observation for patients $\geq$ 80 years old (49.7% in fallers versus 50.3% in non fallers). Exactly 30.3% of the patients were taking only one class of A drug therapy, 27.3 two, 8.8% three and 1.5% four classes of A drugs).

3.3. Orthostatic testing

Overall 144 patients (42.3%) had OH, defined as a drop in SBP or DBP at any of the three time points (T1, T3, T5). Forty patients fulfilled OH criteria at all three time points, whereas 10 patients

Table 1
Clinical characteristics of patients and Schellong's test.

Characteristics	All patients n = 340	OH n = 144 (42.4%)	No OH n = 196 (57.7%)	*P*-value
Age	80.7 $\pm$ 8.2	81.3 $\pm$ 7.7	80.3 $\pm$ 8.59	0.303
Age $\geq$ 80 years (%)	204 (60)	90 (62.5)	114 (58.2)	0.420
Female gender (%)	233 (68.5)	92 (63.9)	141 (71.9)	0.114
Living alone (%)	182 (53.5)	70 (48.6)	112 (57.1)	0.119
Provenance: home (%)	90 (26.5)	44 (30.6)	46 (23.5)	0.143
Barthel Index	70.9 $\pm$ 19.0	69.3 $\pm$ 20.0	72.1 $\pm$ 18.3	0.303
MMS	25.0 $\pm$ 5.0	24.0 $\pm$ 5.5	25.6 $\pm$ 4.4	0.018
Albumin level (g/l)	37.4 $\pm$ 4.4	37.0 $\pm$ 5.0	37.6 $\pm$ 4.0	0.506
Creatinine clearance (ml/min)	69.8 $\pm$ 32.6	66.8 $\pm$ 28.8	72 $\pm$ 35.1	0.291
Drugs prescribed (number/day)	7.4 $\pm$ 3.3	7.4 $\pm$ 3.4	7.4 $\pm$ 3.2	0.992
A drugs (%)	231 (67.9)	99 (68.8)	132 (67.4)	0.784
H drugs (%)	234 (68.8)	98 (68.1)	136 (69.4)	0.793
A+H drugs (%)	158 (46.5)	66 (45.8)	92 (46.9)	0.840
Fall within the previous six months (%)	146 (42.9)	67 (46.5)	79 (40.3)	0.225

Continuous variables are shown as mean $\pm$ SD, and categorical variables as n (%). *P*-values were calculated using χ^2-test for categorical variables and *t*-test or Mann-Whitney non-parametric test depending on the distribution for continuous variables.

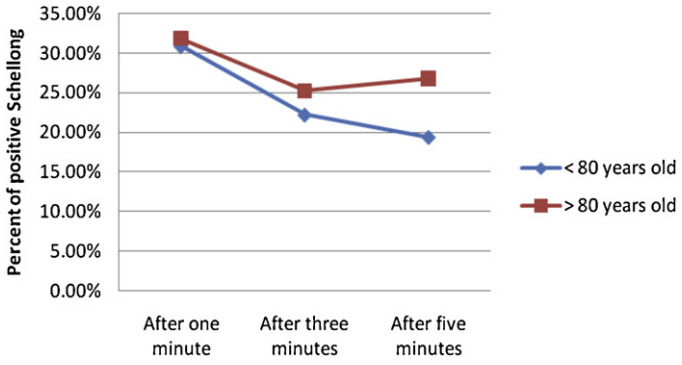

Fig. 1. Positive Schellong according to age.

had a positive ST only at T5 (T1 and T3 negative). By categorizing STs according to measurement time, there were more positive OTs at T1 (31.4%) than T3 (24%) or T5 (23.7%).

Patients' characteristics according to OH status are shown in Table 1. We observed no differences in age and in the rate of A, H or A + H drug prescriptions in patients with or without OH. Further, there was no significant difference between the number of positive OTs and the prescription of A, H or A + H drugs. The small sample sizes may explain the latter finding (only 33 patients received neither H nor A drugs).

The association of several A drugs didn't increase the risk of presenting OH. With one class of A drug, the prevalence of OH is 45.6% (versus 54.4%, P = NS), with two 36.7% (versus 63.4%, P = NS), with three 46.7% (versus 53.3%, P = NS). Among the five patients with four classes A drugs, four had OH but the sample is too small and the difference not significant.

The prevalence of OH at admission was similar in patients with or without a history of falls (32.2% versus 30.9% in T1, 27.6% versus 21.3% in T3, P = NS). The prevalence of OH in T1 was 30.9% (22.2% in T2) in patients < 80 and 31.9% (25.2% in T3) in patients ≥ 80 (differences not significant). Further, there was no significant interaction between results at the different time points and age, even if it seemed that the difference between age groups was more pronounced at the latest time point (Fig. 1). In the multivariate statistical analysis (Table 2), the MMS was inversely associated with the prevalence of OH (odds ratio = 0.907, P = 0.016). Moreover, presenting symptoms during the OT increased the risk of obtaining a positive result by 3.67 times (odds ratio = 3.674, P = 0.004). It is important to understand that symptoms associated with performing the test are not a necessary condition for test interpretation, first because 12.2% of patients with negative OT presented symptoms, and second because 85% of patients with a positive OT in T1, 81% in T3, and 79% in T5 presented a positive OT without associated symptoms. The risk of having a positive ST in T1 compared to T3 and T5 was 2.34 times higher (odds ratio = 2.338, $P < 0.001$).

4. Discussion

OH affects 6% of elderly individuals living at home, and 50 to 68% of patients living in an institution, mainly because of the simultaneous presence of several comorbidities, and the medication with several antihypertensive drugs [2,10].

Table 2
Results of the positive Schellong test multivariate analysis.

	Odds ratio	Confidence interval	P-value
After 1 minute	2.34	[1.49–3.68]	< 0.001
Symptoms	3.67	[1.52–8.87]	0.004
MMS	0.91	[0.84–0.98]	0.016

In our group of 340 individuals, taking into account all blood pressure measurements performed for each patient, 42.4% presented a positive OT result (T1 and/or T3 and/or T5), a figure that increased to 44.1% in patients over age 80. Even if the population considered was hospitalized, OH prevalence seemed relatively high, considering that these patients were living at home and more than half of them were living alone.

None of the variables defined in the clinical characteristics of our patients was a statistically significant factor associated with OH, except for a decrease in the MMS score, related to the risk of presenting a positive OT result (Tables 1 and 2). Our results showed that each one point of increase in the MMS was associated with a 9.9% decrease in OH risk (odds ratio = 0.907, $P < 0.016$). Thus, we suggest to check blood pressure with OT in demented patients, even if the test could be more difficult because of the lack of compliance (behavioural symptoms, movements, agitation...).

Although theoretically, using antihypertensive drugs could worsen OH, most published observational studies and clinical trials have failed to consistently demonstrate this association [11]. Our results concur with these findings, indicating that taking an antihypertensive drug, an hypotensive drug, or a combination of both, didn't increase the risk of OH in our overall sample or in patients over 80 years old. We don't find, as Kamaruzzaman et al. [12], a statically significant relation between OH and the use of three or more antihypertensives. Our population examined is probably too robust (Barthel Index: 70.9 ± 19.0) because of our exclusion's criteria, and we don't know the coexisting illnesses of patients (such as diabetes, cardiovascular disease, frailty, or neurological conditions) that might affect the responses to the OT.

However, with increasing age, taking antihypertensive drugs could promote the occurrence of OH. Poon and Braun [13], in a retrospective study including 342 patients (96% men), with a mean age of 82, showed that there was a statically significant association between OH prevalence and the number of antihypertensive or hypotensive drugs, although we didn't confirm these results in our study.

Additionally, Hiitola et al. [14] showed a positive correlation between OH prevalence and the number of drugs prescribed in the follow-up of a cohort of 653 patients aged 75 or older, living at home, and presenting a prevalence of OH of 34%. Since polymedication affected both the patients of this Finnish study and the patients of our study, it is difficult to pinpoint which single drug could be responsible for an eventual OH, because of the synergetic effects of the different drugs and their respective interactions. In subjects consuming several drugs, it becomes difficult to estimate if OH is due to medication or to the numerous comorbidities, or even to their association. It should also be noted that there are very few studies on the incidence of OH with different kinds of antihypertensive drugs [14,15].

Fall history within the previous 6 months was not a statistically significant prognostic factor for a positive OT in our subjects, considering all ages. However, among the 146 patients with fall history, 69.2% are age over 80 years old and the 3/4 were under antihypertensive therapy. According to the recent analysis by Tinetti [16] and the latest guidelines from the American and British Geriatrics Societies [17], OH is one of the main factors that predispose to falls in the elderly, and should result in a reduction or discontinuation of certain responsible medications. According to Woolcott [18], the classes of drugs involved are principally antihypertensive, neuroleptics, antidepressants, and benzodiazepines. These different medication classes, often prescribed in the elderly, do not show significant differences in OT positivity in our study. Finally, in our study, the falls history, the prescription of

H drugs or for one or more classes of A drugs, don't increase the risk of OH, contrary to the studies cited above [12–18].

The results of our study seem to be in concordance with those of Gangavati et al. [19], showing that antihypertensive therapy in the elderly does not increase the risk of falls, even in the presence of OH. The risk of a fall at 1 year, according to this study, is increased (by 2.5×) only in patients with non-controlled hypertension (defined by blood pressure equal to or greater than 140/90), and with a positive OT after 1 minute. Moreover, in the HYVET study, treatment for hypertension based on the prescription of a diuretic and an angiotensin-converting enzyme inhibitor was not associated with an increase, but rather a decrease (31%) in the number of fractures in medicated individuals [20].

According to our results, an OH in T1 is 2.34 times more likely to occur than in T3 and T5. Measurements at 3 and 5 minutes are nevertheless advisable, because 10 patients in our study presented a positive OT only in T3, and 10 other patients only in T5.

OT positivity is not constantly subjected to a concomitant occurrence of symptoms. However, their occurrence increased the risk by 3.67× of presenting a positive OT in our study. This is interesting because it should comfort our nurse teams to listen attentively to the complaints of the elderly in their daily living activities. Indeed, the complaints suggestive of OH symptoms (vertigo, fatigue, weakness, etc.) should systematically lead to performing an OT in order to diagnose an eventual OH.

The results of our study comprise a number of limitations. Inclusion criteria related to performing the OT probably favored the selection of a group of patients who were more robust, excluding those who were weaker and admitted for palliative care, after orthopaedic surgery, with walking or balance difficulties, or with cognitive impairment, thus preventing a reliable history check. Moreover, the analysis of the medication type didn't take into account the duration of antihypertensive treatment, nor if some classes were prescribed for other conditions than hypertension (such as heart failure). In addition, the time of the test was variable during the day, and the schedule of drug and meal administration was not known (role in postprandial hypotension?). Finally, given the fluctuations of OH during the day, the realization of only one test per individual during the overall stay might not allow for the detection of a portion of patients suffering from OH.

5. Conclusions

OH prevalence concerns 44% of our hospitalized subjects over age 80. OT is more frequently positive at one minute compared to 3 and 5 minutes. In the presence of orthostatic symptoms, OT is also more frequently positive. Identifying patients suffering from cognitive impairment is critical, because with each one point of decrease in the MMS, OH risk increases by almost 10%.Although the prescription of an antihypertensive drug did not significantly increase OH risk in our study, we recommend a systematic OH screening at each visit before initiating antihypertensive therapy or after modifying the dosage, because of the increased risk in cardiovascular diseases (coronary heart disease, stroke, syncope), in falls and in overall OH-associated mortality in the elderly [2,11,14,21–23].

Sponsor's role

None.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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