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Original Research Article

Statins Associated With Orthostatic Hypotension in the Aging Hypertensive Adult of Caribbean Descent and the Protective Benefits of Angiotensin Enzyme Inhibitors

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ABSTRACT

Aim: This study examined prevalence of OH among aging hypertensive patients of Caribbean decent and drug associations.
Methods: A cross-sectional study was conducted at the Community Health and Psychiatry Health Centre from February 2011 to March 2012. Patients ≥ 60 years and taking antihypertensive drugs were grouped as OH positive by reduction systolic blood pressure (SBP) of ≥ 20mmHg or diastolic blood pressure(DBP) of ≥10mmHg within three minutes of standing.
Results: One hundred subjects participated; the prevalence of OH was 20% (95% confidence interval [CI] 12.2-27.8). OH positive subjects were significantly older (77.3 ± 8.0 versus 72.4 ± 8.2 years, p=0.019) and had higher sitting SBP (160.0 ± 12.6 versus 143.5 ± 18.1 mmHg, p=0.000). Odds ratio (OR) analysis controlling for age and sitting SBP identified risk of OH as increasing significantly with number of antihypertensive drugs (OR 2.230, 95% CI 1.147-4.694, p = 0.019). OH risk increased with statin use (OR 6.886, 95% CI 1.761- 26.920, p = 0.006) and its co-administration with thiazide/thiazide-like diuretics (OR 9.143, 95% CI 2.355-35.488, p=0.001), atenolol (OR 7.152, 95% CI 1.789- 28.584, p=0.005) or vasodilatory calcium channel blockers (OR 5.987, 95% CI 1.282- 27.968, p=0.023), but not with angiotensin converting enzyme inhibitors.
Conclusions: This is the first report of statins increasing the risk of OH in the aging adult of Caribbean descent; however, co-administration of angiotensin converting enzyme inhibitors may be more protective that other common antihypertensive therapy.

Keywords: Orthostatic hypotension, aging, statins, angiotensin converting enzyme, Caribbean

INTRODUCTION

According to the American Autonomic Society and the American Academy of Neurology, orthostatic hypotension (OH) is defined as the reduction of systolic blood pressure of at least 20mmHg or a diastolic blood pressure of at least 10mmHg from a sitting position to within three minutes of standing. [1] OH may be asymptomatic or symptomatic and be as a

result of neurogenic causes such as multisystem atrophy and diabetic neuropathy; or non-neurogenic causes such as intravascular volume depletion, cardiac insufficiency, venous pooling and drugs. [1-3]

OH is more commonly encountered in older adults (≥ 60 years as defined by the United Nations Programme on Ageing [4] and implicated to be associated with antihypertensive drugs. [5,6] Most of these agents increase the risk for developing OH through vasodilatory mechanism or through sympathetic nervous system interruption. [7] Among older adults, OH risk also increases with the presence of morbidities, such as coronary heart disease, myocardial infarction, and transient ischaemic attacks. [8-11] Some studies have found a modest increase in risk of mortality among those with OH. [8,10,12,13] Thus, the presence of OH in the older population possesses great risk to their health and hence it is important for older adults to be screened for this adverse drug reaction.

No published studies of OH being examined in the aging population of Caribbean decent on antihypertensive drugs was found; this study therefore aimed to identify possible predictors of OH among aging patients at the Community Health and Psychiatry Health Centre (CHPHC) on antihypertensive drugs. The CHPHC was established to serve the persons in communities surrounding the University of the West Indies and on average reviews 1000 patients per month.

The clinic provides special care to aging adults through scheduled visits every three months, as well as providing outreach activities to facilitate healthy aging. The clinic is also used for teaching medical and other health related disciplines

MATERIALS AND METHODS

The study was approved by the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee and follows guidelines described by the Declaration of Helsinki. A cross-sectional study design was followed from February 2011 to March 2012 with consenting patients from the CHPHC who were at least 60 years old and on antihypertensive drugs. Patients were excluded if they were unable to stand or diagnosed with primary autonomic dysfunction such as Parkinson's disease. Each subject's sitting and standing blood pressure was measured using a standard mercury sphygmomanometer with stethoscope (American Diagnostic Corporation). After sitting blood pressure was obtained the participant was asked to stand and within three minutes of standing, the standing blood pressure measurement was obtained. These reading were done in the mornings while subjects were in a fasted state. A total of three sets of readings were recorded for each sitting and standing blood pressure measurement. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) in both sitting and standing positions were calculated. Other data collected included gender, age, weight, height, heart rate, disease state and drugs commonly prescribed for cardiovascular diseases (antihypertensive drugs, statins and anti-platelets).

Data analysis

Continuous data was expressed as mean with standard deviation (SD) and median with interquartile range (IQR) where relevant and normality was assessed. Orthostatic Hypotension (OH) was assessed by a reduction of the mean SBP of at least 20mm/Hg or mean DBP of at least 10mm/Hg from a sitting to a standing position. Subjects were grouped into those with OH (OH positive) and those without OH (OH negative). They were also grouped as having elevated blood pressure defined as a SBP of >140mmHg and/or DBP of >

90mmHg according to British Hypertension Society guidelines. [14] Comparison between groups was done using unpaired students t-test (for parametric data) or Mann-Whitney –U (for non-parametric data) where appropriate. Fisher's exact t test was used for associations with the presence of OH. Logistic regression to calculate odds ratio (OR) and 95% confidence intervals (CI) for dichotomous data was used to determine predictors of OH. Probability (p) values of less than 0.05 were considered statistically significant. The data was assessed using SPSS version 17.0 software package.

RESULTS

During the study period, a total of 100 subjects were recruited and completed the study of which 93 were females and 7 males. The age range was 60 to 91 years and was found to be normally distributed with a mean age (±SD) of 73.4 ± 8.3 years. Twenty subjects were found to have OH (20%, 95% CI 12.2%-27.8%). Subjects who were OH positive were significantly older and had a significantly higher sitting SBP (Table 1). Fifty-eight (58) subjects had elevated blood pressure at the time of assessment (17 with OH, 41 without OH); however, logistic regression analysis controlling for age and sitting SBP found that elevated blood pressure was not a predictor of the presence of OH (OR 0.630, 95% CI 0.079 - 5.047, p = 0.664).

Co-morbidities included diabetes (56/100), cardiovascular diseases (13/100, subjects with coronary heart disease, heart failure or stroke), asthma (7/100), cancer (2/100) end stage renal failure (2/100), depression (4/100), of which none were found to be associated with OH (Table 2).

Table 1. Illustrates normal distribution of age, blood pressure and heart rate among OH groups for older adults at the CHPHC

Characteristics	OH positive (n=20)	OH negative (n=80)	p
Age/years:			
Mean ± sd	77.3 ± 8.0	72.4 ± 8.2	0.019*
Median (IQR)	78.5 (11.8)	71.0 (12.5)	
BMI(kg/m²)			
Mean ± sd	27.3 ± 4.5	28.9 ± 8.3	0.482
Median (IQR)	27.7 (6.2)	28.3 (10.8)	
Sitting SBP (mm/Hg)			
Mean ± sd	160.0 ± 12.6	143.5 ± 18.1	0.000*
Median (IQR)	160.0 (20)	143.0 (30)	
Sitting DBP(mm/Hg)			
Mean ± sd	80.0 ± 10.8	77.2 ± 11.1	0.305
Median (IQR)	80.0 (10)	80 (17)	
Heart rate (beats/min)			
Mean ± sd	72.3 ± 12.4	72.4 ± 13.7	0.977
Median (IQR)	72.0 (16.5)	72.0 (18)	
Disease status (frequency)			
Elevated blood pressure	17	41	0.010*
Cardiovascular diseases	4	9	0.287
Diabetes mellitus	12	44	0.803
Cancer	0	2	1.000
Asthma	2	5	0.625
End-Stage Renal disease	0	2	1.000
Depression	2	2	0.178

* Difference between groups is statistically significant. Students t test or Mann-Whitney U for continuous variables; Fisher's exact test for proportions.

Table 2. The association between drug class and OH presence among older patients≥ 60 years.				
Drug (*frequency; dose range /mg)*	OH positive (n=20)	OH negative (n=80)	Fisher test p	OR, 95% CI, p, adjusted for age and sitting SBP
Tz/TzL diuretics *Bendroflumethiazide (8; 5.0) Hydrochlorothiazide (36;12.5-50) Indapamide(8; 1.5-5.0)*	14	38	0.084	2.262, 0.710-7.214, 0.168
ACEi *Enalapril (45; 2.5-30.0) Lisinopril(16; 2.5-40.0) Captopril (2; 25.0-50.0)*	13	50	1.000	-
Losartan *(17; 10.0-100.0)*	6	11	0.101	-
Atenolol *(16; 25.0-100.0)*	6	10	0.084	4.360,0.414-45.719, 0.219
CCBv *Nifedipine (28; 10.0-30.0) Amlodipine (2; 5.0-10.0)*	5	25	0.786	-
Other antihypertensive *Reserpine (4; 0.15) Terazosin(2; 5.0)*	1	5	1.000	-
Statins *Simvastatin (35; 10.0-80.0) Atorvastatin(7; 20.0-80.0) Pravastatin (2; 10.0-15.0) Rosuvostatin (1; 10.0)*	13	32	0.077	6.886, 1.761- 26.920, 0.006*
Antiplatelets *Aspirin only (51; 81.0) Clopidogrel only (1;75.0) Both agents (5)*	13	44	0.460	-
Combination with statin				
Tz/TzL diuretics	10	12	0.002*	9.143, 2.355-35.488, 0.001*
Atenolol	6	5	0.008*	7.152, 1.789-28.584, 0.005*
CCBv	5	6	0.040*	5.987, 1.282-27.968,0.023*
ACEi	8	18	0.153	-
*Difference between groups is statistically significant. Tz/TzL: Thiazide/Thiazide like diuretics; CCBv: vasodilatory calcium channel blocker, ACEi: angiotensin converting enzyme inhibitor				

Only twelve subjects were taking one antihypertensive drug; most subjects were taking more than two antihypertensive drugs: twenty-five subjects were taking 2 agents, 28 subjects taking 3, 23 subjects taking 4 agents, nine subjects taking 5 and 3 subjects taking 6. The risk of OH increased with the overall number of antihypertensive drugs being taken after adjustment for age and sitting SBP (OR 2.230, 95% CI 1.147-4.694, p = 0.019). Except for borderline significance with Thiazide/Thiazide like (Tz/TzL) diuretics and atenolol, no single antihypertensive drug class was associated with the presence of OH. After controlling for age and sitting SBP, logistic regression failed to show these as being predictors of OH. Use of statins was also found to have borderline association with the presence of OH; further assessment with logistic regression analysis found use of statins to significantly increase the risk of OH after controlling for age and sitting SBP (OR 6.886,95% CI 1.761- 26.920, p = 0.006) .

Further assessment of subjects on statin therapy (45 out of 100) identified only a significantly lower sitting DBP compared to subjects not on statin therapy (75.3 ± 10.4 versus 79.7 ±11.3; p=0.044); there was no difference in age, BMI, sitting SBP, standing SBP, standing DBP or heart rate between these groups.

Co-administration of statins with Tz/TzL diuretics, or atenolol, or vasodilatory calcium channel blockers (CCBv) as associated with OH. Logistic regression of these combinations, controlling for age and sitting SBP identified

statins co-administered with Tz/TzL diuretics resulted in 9.143 times greater risk of OH. Statin with atenolol resulted in 7.152 greater risks and with CCBv, 5.987 greater risk of OH (Table 2). The combination of statins with ACEi was not associated with the presence of OH.

DISCUSSION

Aging patients are at a greater risk of experiencing adverse drug reactions and thus assessment of the risk factors, provides an opportunity for improved management. In this study it was first determined that the risk of OH increased with the increasing number of drugs used for management of cardiovascular diseases, these finding are consistent with what has already been established. Also already established and was a finding is this paper was the higher risk of OH with increase age. [2,9,15] It was also determined that OH positive subjects had significantly higher sitting SBP and this is likely as a result of physiological changes to compensate for the changes in blood pressure control that occur with aging.

The presence of cardiovascular diseases was found to be associated with increased risk of developing OH, which is consistent with the findings of Kamaruzzaman. [5]

There was no evidence of increased risk of OH with any single antihypertensive drug; however patients on statins were at a higher risk of experiencing OH. Both simvastatin and atorvastatin promote decrease in blood pressure [16,17] and statins are being suggested as beneficial to all hypertensive patients with cardiovascular diseases, irrespective of cholesterol levels. [14,18] This study however identified the use of statins as increasing the risk of OH and thus this potential to promote OH occurrence in the aging hypertensive patient is of concern and requires further investigation.

Review of two major drug information websites (http://www.drugs.com and www.epocrates.com), as well as scientific databases did not identify any report of OH as an adverse drug reaction of statins and thus this is the first documentation of statins being associated with an increased risk of OH. In a cross-over double blind placebo control study by McGowan et al involving 14 non-hypertensive subjects, simvastatin was found to decrease muscle sympathetic nerve activity and also increase endothelium-independent vasodilation, while patients were in the supine position. These effects were attributed to non-cholesterol, centrally mediated neurogenic effect; [19] it is therefore possible that such effects may impair the physiological adjustments required to maintain blood pressure with positional change and thus precipitate OH. McGowan also suggested lower diastolic blood pressure was associated with simvastatin therapy; in this study, subjects on statins were found to have lower sitting diastolic blood pressure, thus supporting previous findings that statins lower diastolic blood pressure.

According to the collaborative British Hypertension Society and National Institute for Health Care Excellence guidelines, standard combinations for aging patients of Caribbean decent involves starting with a vasodilatory calcium channel blockers or thiazide/thiazide-like diuretics. [20,21] The guidelines of the Caribbean Health Research Council (http://chrc-caribbean.org/Portals/0/Downloads/Publications/Clinical%20Guidelines/Hypertension.pdf) recommends thiazide diuretics as first choice, irrespective of age because of proven efficacy black populations and cost. Combination is generally required for better control; but, this increases the potential for drug–drug interactions. Statins combined with Thiazide/Thiazide like diuretics,

atenolol or vasodilatory calcium channel blockers were found to significantly increase the risk of OH in this study. Thus, while these combinations might provide greater blood pressure control, attention should be given to the increased risk for developing OH. Interestingly, the combination of statins with angiotensin converting enzyme inhibitors was not associated with OH, suggesting that this combination may be offering protection from this adverse drug reaction.

Some potential limitations of this study include the small sample size, lack of assessment of adherence to drug therapy and the underrepresentation of males at CHPCH. In terms of the combination drug data, the study assessment was limited to only assessing the risk of OH on the combination of two drugs and did not assess differences in doses. This study only evaluated the associations using diagnostic assessment of OH; assessment of symptomatic OH would have facilitated a greater understanding of clinical significance of the risks identified in this study.

CONCLUSION

In conclusion, this is the first study to examine the potential of common antihypertensive drugs to cause OH in an aging Caribbean population. While no one class of antihypertensive was identified as increasing the risk of OH, statins are being reported for the first time to be associated with greater risk of OH among the aging adult on antihypertensive drugs. Additionally, with combinations being the more common protocol for management of hypertension, consideration should be given to choosing combinations least likely to promote OH and the associated morbidities. Future studies are required to evaluate symptomatic presentations and mechanism associated with statin induced OH; the positive benefits that may be derived from combining statin with angiotensin converting enzyme inhibitors also requires exploration.

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