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Is Droxidopa Safe and Effective in Reducing Symptoms of Neurogenic Orthostatic Hypotension?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not droxidopa is safe and effective in reducing the symptoms of neurogenic orthostatic hypotension.

Study Design: Systemic review of three English-language primary studies, conducted in 2014 or later.

Data Sources: Three double-blind, randomized trials comparing the safety and efficacy of droxidopa to placebo in patients with diagnosed neurogenic orthostatic hypotension, found via PubMed in peer-reviewed journals.

Outcomes Measured: Improvement of symptoms was measured utilizing patient responses to the Orthostatic Hypotension Questionnaire (OHQ), which consists of a six item Orthostatic Hypotension Symptom Assessment (OSHA) and the four item Orthostatic Hypotension Daily Activity Scale (OHDAS), each measured on a 1-10 scale. Also utilized was the patient-rated Clinical Global Impression (CGI) severity and improvement 7-point scales. Safety was measured through incidence of adverse effects during the randomized trial.

Results: Biaggioni, et al, exhibited 46% of droxidopa recipients describing themselves as much or very much improved according to CGI ratings, compared to 27.5% of those receiving placebo, although with a p-score of 0.384. Hauser, et al, exhibited mean improvement in OSHA item 1 at week 1 as 2.3 for droxidopa, compared to 1.3 in the control group, with a p-value of 0.018. Kaufmann, et al, exhibited improvement of greater than 3 units in composite OHQ score in 27.2% of droxidopa recipients compared to 11.4% of placebo recipients, with a p score of 0.016. Numbers needed to harm were presented for each studied, obtained through measurement of adverse effects of experiment vs control during randomized trial, and consisted of -13 in Biaggioni, et al, 38 in Hauser, et al, and 28 in Kaufmann, et al.

Conclusions: These results indicate that droxidopa showed statistical improvement in symptoms in two studies and numerical improvement in another, in addition to being relatively well tolerated. However, the difference in end points measured in each studies and inconsistencies in study design prevent any strong conclusion, and further study is required.

Key Words: droxidopa, neurogenic orthostatic hypotension

Introduction

Neurogenic orthostatic hypotension (nOH) is a reduction in sustained blood pressure as a result of inadequate norepinephrine response to postural changes. This paper evaluates three randomized, double-blind, placebo-controlled trials comparing the efficacy of droxidopa in treatment of neurogenic orthostatic hypotension compared to placebo.

Neurogenic orthostatic hypotension is a common complication for patients with Parkinson's disease, with its prevalence ranging from 16 to 58%.[1] It is also seen in 30 to 50% of patients with dementia with Lewy bodies.[1] NOH is also considered a hallmark sign of Multiple System Atrophy (MSA), affecting about 80% of patients with that diagnosis.[2] The presence of orthostatic hypotension has also been shown to increase the 4 year age-adjusted mortality rate compared to patients without the diagnosis.[3]

Neurogenic orthostatic hypotension can also present significant costs to the health care system, largely due to its effect of increasing the risk of falls in patients who are affected. The use of droxidopa resulted in estimated cost savings of $14,574 over 12 months, and was also cost-effective against the standard of care.[5] Proper treatment of neurogenic orthostatic hypotension could also help to prevent the burden on the health care system by reducing health care visits for the condition. Although the specific numbers are unavailable for neurogenic orthostatic hypotension, the prevalence of general orthostatic hypotension in the elderly is estimated to be between 5 and 30%.[3]

Orthostatic hypotension is typically defined as a blood pressure drop of 20 mm Hg in systolic blood pressure or a drop of 10 mm Hg in diastolic blood pressure within 3 minutes of standing.[1] When this drop is attributed to a deficit within the autonomic nervous system reflexes,

where the body does not release enough norepinephrine to counteract postural changes, it is termed neurogenic orthostatic hypotension (nOH).[5] This deficit can result in a variety of symptoms, such as dizziness and syncope, that can contribute significantly to the morbidity and mortality of patients afflicted by it.[1] However, the true prevalence and morbidity associated with neurogenic orthostatic hypotension is unknown, due to its potential to exist asymptomatically for long periods of time and the multifactorial conditions of many falls.

There are currently limited options available for treatment of nOH. Non-pharmacologic treatment, composed mostly of a stepwise progression when changing position to standing and increased physical conditioning, is often recommended.[1] The only other FDA-approved medication for nOH is midodrine, an oral prodrug that is converted into desglymidrodrine, a selective α_1-adrenoceptor agonist.[6] Although midodrine is generally well-tolerated, its use can be limited by adverse effects and there are some questions regarding its efficacy in treating this condition.[6] As such, droxidopa is a potential option as a more efficacious and cost-effective treatment for neurogenic orthostatic hypotension.

Objective

The objective of this selective EBM review is to determine whether or not droxidopa is safe and effective in reducing the symptoms of neurogenic orthostatic hypotension.

Methods

Specific criteria were used during the selection of studies for use in this review. The population was composed of men and women over the age of 18 with the diagnosis of neurogenic orthostatic hypotension. In all three studies, the intervention utilized was droxidopa (L-threo-3,4-dihydroxyphenylserine) which was dose optimized for each patient. Each consisted

of a treatment group receiving droxidopa, which was compared to a control group receiving placebo. Two studies measured outcomes according to improvement in the symptoms of neurogenic orthostatic hypotension as determined by the patient-rated Orthostatic Hypotension Questionnaire (OHQ). The third was also measured according to improvement in the symptoms of nOH, but determined by the self-rated Clinical Global Impression (CGI) severity and improvement scales. All studies included are randomized, double-blind, placebo controlled trials.

Research was conducted utilizing the key words of "droxidopa" and "neurogenic orthostatic hypotension". All articles were published in English with peer-reviewed journals, and were selected according to their relevance to the objective of the paper and their use of patient-oriented outcomes (POEMS). Inclusion criteria consisted of studies utilizing patients over the age of 18 and conducted utilizing a randomized, placebo-controlled format. Exclusion criteria included patients under the age of 18 and studies which exclusively measured disease-oriented evidence (DOEs) such as blood pressure readings. The statistics used and reported include p-values, numbers needed to treat (NNT), numbers needed to harm (NNH), relative benefit increase (RBI), relative risk increase (RRI), absolute benefit increase (ABI), and absolute risk increase (ARI).

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Biaggioni[6] (2015)	RCT	101	24-88	Patients over 18 years old with a clinical diagnosis of symptomatic OH, and met responder criteria	Pre-existing sustained severe hypertension, atrial fibrillation or significant cardiac arrhythmia, current use of tricyclic antidepressants or other norepinephrine reuptake inhibitors, current use of antihypertensive medication or use of vasoconstrictive agents within 2 days before baseline	14	Dose optimized droxidopa, initiated at 100 mg capsules 3x daily and adjusted upwards at 100 mg 3x daily increments until optimal dose
Hauser[7] (2015)	RCT	174	41-91	Patients over 18 years old with a clinical diagnosis of Parkinson's disease and signs and symptoms of nOH	Use of vasoconstricting agents or long-acting antihypertensive medications; sustained, severe hypertension, a Mini-Mental State Examination score under 23, significant uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or a history of myocardial infarction	45	8 weeks of maintenance at optimized dosage of droxidopa (100-600mg TID)
Kaufmann[8] (2014)	RCT	168	18-87	Patients over 18 years old with a clinical diagnosis of nOH and met responder criteria	Use of vasoconstrictor agents within 2 days before baseline, use of long-acting antihypertensives or norepinephrine reuptake inhibitors, sustained, severe supine hypertension, and significant systemic, hepatic, cardiac or renal disease	9	Droxidopa initiated at 100mg TID and titrated in 100mg increments until optimized

Outcomes Measured

In each of the three RCTs utilized, the outcomes were measured according to improvement of the symptoms of neurogenic orthostatic hypotension. In one study, the primary outcomes assessed were symptoms according to the Clinical Global Impression (CGI) severity and improvement scales, which were self-rated by patients. CGI severity is a 7 point scale scored from 1 (no symptoms) to 7 (severe symptoms) and improvement is a 7 point scale scored from 1 (very much improved) to 7 (very much worse).

In the other two studies, the primary outcomes assessed were symptoms according to the Orthostatic Hypotension Questionnaire (OHQ), which consists of a six item Orthostatic Hypotension Symptom Assessment (OSHA) and the four item Orthostatic Hypotension Daily Activity Scale (OHDAS), with each self-rated by patients on a 1-10 scale. The items of OSHA were dizziness/lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, and head and neck discomfort. The items of OHDAS were interference with standing for a short time, standing for a long time, walking for a short time, and walking for a long time.

Results

Three randomized placebo-controlled trials evaluated the effect of droxidopa on the symptoms of neurogenic orthostatic hypotension. All studies were conducted on patients aged 18 years or older, in addition to other inclusion criteria as outlined in Table 1. All patients under age 18 were excluded, in addition to the variety of exclusion criteria provided in Table 1, which helped to isolate adverse effects to the trial drug in question instead of comorbid conditions.

The study conducted by Biaggioni, et al was conducted on 101 randomized patients, which excluded 43 patients who discontinued due to adverse effects and 24 who did not meet

responder criteria at the maximum dosage of droxidopa.[6] In this withdrawal study, patients were continued on their optimized droxidopa, at 100-600mg TID, for 1 week before being randomized, and either continued on droxidopa or withdrawn to placebo for 14 days.[6] Symptoms were then evaluated utilizing the OHQ and CGI patient scale, with the primary end point item 1 of the OSHA and the remainder of the data functioning as secondary end points.

From randomization to end of study, item 1 increased by 1.3 units on average for the droxidopa treatment group, compared to 1.9 units on average for the placebo group, with a p-value of 0.509.[6] All other units of the OSHA questionnaire and the composite score similarly failed to reach statistical significance, although all but item 2 favored droxidopa numerically. When evaluating through CGI scores, 46% of patients on droxidopa rated themselves as much or very much improved, compared to 27.5% of the placebo group.[6] This led to a relative benefit increase of 67%, an absolute benefit increase of 18.5%, and a numbers needed to treat of 6 for this particular endpoint. This data is also exhibited in Table 2. However, the improvement scores according to CGI for patient's self ratings only had a p score of 0.384.[6]

The second study, conducted by Hauser, et al, utilized 8 weeks of treatment maintenance at the optimized dose of droxidopa, ranging between 100-600mg TID.[7] Non-responders were not removed from the study prior to randomization, unlike the other two studies included in this analysis. Patient reported scores for item 1 of the OSHA score were then measured as the primary endpoint, with data taken at weeks 1, 2, 4 and 8 and compared to baseline.[7] Mean improvement at week 1 was 2.3, with a standard deviation of 2.95, compared to 1.3 with standard deviation of 3.16 in the control group, with a p-value of 0.018.[7] Improvement in weeks 2, 4 and 8 also favored droxidopa, but not to a statistically significant degree.

In the final study, conducted by Kaufmann, et al, 263 patients participated in open label droxidopa optimization, with 162 responders subsequently randomized into double blind placebo or droxidopa.[8] Following a 1 week washout period, patients were either continued at their optimized dosage of droxidopa, 100-600mg TID, or provided placebo.[8] The primary endpoint was determined as improvement from baseline in mean composite OHQ score, with specific attention paid to improvement of greater than 3 points from baseline.

Droxidopa patients had a mean change of -1.83 units in OHQ score, compared to a -0.90 in the placebo group, favoring droxidopa with a p score of 0.003.[8] In addition, improvement was greater than 3 units in 27.2% of droxidopa recipients compared to 11.4% of placebo recipients, with a p score of 0.016.[8] This particular endpoint results in a relative benefit increase of 139%, an absolute benefit increase of 15.8%, and a numbers needed to treat of 7 for droxidopa. This data is also exhibited in Table 2.

Table 2: Efficacy of Treatment, Experiment vs Control

Study	Control event rate (CER)	Experimental event rate (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Numbers needed to treat (NNT)
Biaggioni[6]	27.5%	46%	67%	18.5%	6
Kaufmann[8]	11.4%	27.2%	139%	15.8%	7

In all three studies, droxidopa was generally well-tolerated, as evidence by the data provided in table 3. During double blind treatment in the study conducted by Biaggioni, et al, 30% of droxidopa recipients reported at least one adverse effect, compared to 37.3% of those who received placebo treatment.[6] In the study conducted by Hauser, et al, 82% of droxidopa recipients reported adverse effects during treatment, compared to 79.3% of the placebo group.[7] And during double blind treatment in the study conducted by Kaufmann, et al, 18.5% of

droxidopa recipients reported adverse effects to treatment compared to 14.8% of placebo recipients.[8] A complete collection of this data, including relative risk increase, absolute risk increase, and the numbers needed to harm (NNH) are provided in Table 3.

Table 3: Adverse Effects of Treatment, Experimental vs Placebo

Study	Control event rate (CER)	Experimental event rate (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Numbers needed to harm (NNH)
Biaggioni[6]	37.3%	30%	-20%	-7.3%	-13
Hauser[7]	79.3%	82%	3.4%	2.7%	38
Kaufmann[8]	14.8%	18.5%	25%	3.7%	28

Discussion

This systemic review analyzed 3 randomized, placebo-controlled trials to evaluate the efficacy and safety of droxidopa as a treatment for the symptoms of neurogenic orthostatic hypotension. Patients were over the age of 18 in all studies, and any studies attempting to evaluate the effect of droxidopa on a pediatric population would likely be very difficult and largely unnecessary, as the conditions that most often cause neurogenic orthostatic hypotension have a predominance in the older population. Each study analyzed a relatively large group of patients, with each over 100 participants, and the age ranges were relatively varied for each study. Every study included in the review did exclude patients who take long-acting antihypertensive medications, which is reasonable to isolate the adverse effects of the medication but could pose issues as a relative or total contraindication in the future. Hypertension is a relatively common issue, especially as age increases, and could be a relatively common comorbidity in patients that would otherwise benefit from droxidopa treatment.

Two of the studies utilized in this review, Biaggioni, et al, and Kaufmann, et al, only included patients that were identified as responders in their randomization and subsequent study. In Kaufmann, et al, 263 patients participated in open-label droxidopa optimization, but only 162 responders, or 61.6%, continued to the randomization phase of the trial.[8] This certainly poses an issue when considering the efficacy of droxidopa, as any statistics measuring the drug's effects compared to placebo has already not included many patients who the drug would not work for. This indicates that the numbers of patients who would benefit from its use in clinical practice is actually lower than the study would indicate. In Biaggioni, et al, a similar trend was seen, as 181 patients entered open-label droxidopa optimization but only 101 entered the randomized and double-blind portion of the trial, with 24 reported as not meeting responder criteria.[6] Of particular concern here are the 43 patients who did not progress due to adverse effects, including 21 who had a blood pressure elevation. This not only casts doubt on the efficacy of the drug in clinical practice, but also indicates that this particular study may overstate the safety of droxidopa by excluding patients with adverse reactions before the randomized trial has begun. This helps to explain the negative numbers needed to harm seen in this study, and shows that this study may both overstate droxidopa's safety and efficacy.

All studies used, once they had reached the randomization stage, were generally well conducted. All were placebo-controlled and double blind and had relatively few discontinuations or withdrawals. However, all were conducted utilizing the optimized dose of droxidopa for each individual patient, defined as between 100-600mg TID. This does exhibit a potential complication with droxidopa's use in clinical practice, as this stipulation indicates that it is not a drug with an easy dosing formula. Optimizing the dosage for each patient may be time consuming and require a higher amount of office visits than may at first be apparent. In addition,

the timing of dosing at three times a day may be inconvenient for some patients if continued in clinical practice. This could decrease the amount of patients who are compliant with treatment and therefore further decrease the efficacy of droxidopa as a clinical treatment option.

In the study conducted by Hauser, et al, droxidopa did show a significant improvement in symptoms compared to placebo according to its primary endpoint, OSHA item 1.[7] However, this statistically significant improvement was only seen from baseline to week 1, and a similar improvement was not exhibited at week 2, 4, and 8, although numerical improvement still was present compared to placebo.[7] This does raise questions on the long-term efficacy of droxidopa as a treatment for nOH, as it is unclear why this statistical improvement was not continued throughout the trial. As neurogenic orthostatic hypotension often occurs as a result of chronic conditions, it is important that any treatment utilized be able to be continued long-term, which this trial was unable to exhibit.

Finally, it is important to note that droxidopa currently carries a black-box warning issued by the Food and Drug Administration regarding the risks of supine hypertension with its use.[9] It is therefore recommended that patients must sleep with their head and upper body elevated, in order to alleviate this potential issue. Although this may be an annoyance to some patients and could lead to some issues with clinical use, it is important to consider that the only other FDA-approved medication for nOH, midodrine, carries a similar black-box warning.[9] As such, there are not any pharmacologic options that avoid this complication, and given the nature of the disorder it may be very difficult to develop one that does not carry such a risk.

Conclusion

The use of droxidopa was exhibited to be effective and safe in each of the studies analyzed in this review. However, efficacy over placebo was only shown in some of the endpoints measured to a statistical significance, with others only showing numerical improvement if any at all. One study also only showed statistical improvement after 1 week, and was unable to show a continuation of this throughout the study.[7] The other two studies also both selected for responders to droxidopa before randomizing, casting doubt on both their efficacy and safety data. As such, more studies would need to be conducted before being able to make any strong recommendations for or against the use of droxidopa in treatment of neurogenic orthostatic hypotension.

In future studies, it would be important to include patients who pass screening, including those who may be droxidopa non-responders, in order to fully capture the potential of the drug to be efficacious in clinical practice. This would also prevent those who experience adverse effects from being removed before data is collected, so that accurate safety data can be collected. Studies would also need to be extended long enough to exhibit whether droxidopa can be expected to improve symptoms in patients long-term, as the data is not strong in this aspect. Considering the paucity of pharmacologic options for the treatment of neurogenic orthostatic hypotension, and the efficacy that was exhibited in some of the endpoints measured in the studies included in this review, droxidopa remains a promising treatment option and would continue to benefit from further analysis and study.

References

1. Metzler M, Duerr S, Granata R, Krismer F, Robertson D, Wenning GK. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. Journal of Neurology. 2013;260(9):2212-2219. doi:10.1007/s00415-012-6736-7.
2. What is neurogenic orthostatic hypotension? The MSA Coalition Web site. https://www.multiplesystematrophy.org/what-is-noh. Accessed December 11, 2016.
3. Low PA. Prevalence of orthostatic hypotension. Clin Auton Res. 2008;18 Suppl 1:8-13. doi: 10.1007/s10286-007-1001-3 [doi].
4. Francois C, Hauser RA, Aballea S, Dorey J, Kharitonova E, Hewitt LA. Cost-effectiveness of droxidopa in patients with neurogenic orthostatic hypotension: Post-hoc economic analysis of phase 3 clinical trial data. J Med Econ. 2016;19(5):515-525. doi: 10.3111/13696998.2015.1136827 [doi].
5. What is neurogenic orthostatic hypotension (nOH)? nOH matters Web site. https://www.nohmatters.com/neurogenic-orthostatic-hypotension-causes. Accessed December 12, 2016.
6. Biaggioni I, Freeman R, Mathias CJ, et al. Randomized withdrawal study of patients with symptomatic neurogenic orthostatic hypotension responsive to droxidopa. Hypertension. 2015;65(1):101-107.
7. Hauser RA, Isaacson S, Lisk JP, Hewitt LA, Rowse G. Droxidopa for the short-term treatment of symptomatic neurogenic orthostatic hypotension in parkinson's disease (nOH306B). Mov Disord. 2015;30(5):646-654.\
8. Kaufmann H, Freeman R, Biaggioni I, et al. Droxidopa for neurogenic orthostatic hypotension: A randomized, placebo-controlled, phase 3 trial. Neurology. 2014;83(4):328-335.
9. Kaufmann H, Norcliffe-Kaufmann L, Palma J-A. Droxidopa in neurogenic orthostatic hypotension. Expert review of cardiovascular therapy. 2015;13(8):875-891. doi:10.1586/14779072.2015.1057504.