THE ROLE OF BUSPIRONE FOR THE TREATMENT OF CEREBELLAR ATAXIA IN AN OLDER INDIVIDUAL

Jayna M Holroyd-Leduc[1,3], Barbara A Liu[1,2], Brian E Maki[1], Aleksandra Zecevic[1], Nathan Herrmann[1], Sandra E Black[1]

[1]Sunnybrook & Women's College Health Science Centre, University of Toronto, Toronto, Ontario, [2]Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care, Toronto, [3]The University Health Network, Toronto

Corresponding Author: *jayna.Holroyd-Leduc @uhn.on.ca*

_____

ABSTRACT

Background
Buspirone, a 5HT-agonist and D2-dopamine antagonist/agonist, has modest beneficial effects in younger individuals with cerebellar ataxia. However, it is unclear whether it is beneficial and tolerable in older ataxic individuals.

Objective
To determine if an older individual with cerebellar ataxia would benefit from and tolerate buspirone.

Methods
We performed a single-subject, double-blinded, placebo-controlled randomized-phase study. The 80 year-old subject was to undergo six 4-week testing periods, divided randomly into three treatment and three placebo arms with a 2-week washout period between each arm. Treatment consisted of buspirone hydrochloride. Outcomes were clinical gait and balance testing, posturography testing, and subjective measurement of balance confidence.

Results
There were no statistically significant objective improvements with buspirone. The subject experienced a subjective improvement in balance confidence and tolerated treatment.

Conclusions
Single-subject studies can help when it is unclear whether drug trial results with young subjects are generalizable to an older subject. This single-subject study determined that buspirone was tolerable but not clearly beneficial for an ataxic older individual.

Key Words: *Cerebellar ataxia; buspirone; aged, 80 and over*

_____

Cerebellar ataxia is a potentially disabling condition with limited treatment options. Serotonin modulates GABA-receptors in Purkinje cells in the cerebellum.[1,2]. Purkinje cells have control over refinement of motor activities. Although the exact pharmacological mechanisms of action are unclear, buspirone hydrochloride, a 5HT-agonist and D2-dopamine antagonist/agonist, has been found to have modest beneficial effects in younger ataxic individuals, at a dose of 1mg/kg/day or 60mg/day maximum.[3,4] However, the role of buspirone for older ataxic individuals is unclear. Side effects of buspirone include dizziness and drowsiness, and the maximum recommended daily dose for older individuals is only 30mg. Our objective was to determine if an older individual with cerebellar ataxia would benefit from and tolerate buspirone 30mg/day.

METHODS

The subject was an 80-year-old male with a 14-year history of progressive ataxia and dysarthria secondary to progressive cerebellar atrophy of unknown etiology. His co-morbidities included hypertension, transient ischemic attack, falls and remote peptic ulcer disease.

His medications included clopidogrel, hydrochlorothiazide, and a variety of vitamins and herbal preparations. He was an ex-cigar smoker, and previously consumed approximately 4 alcoholic beverages per day. In the 5 years prior to the study and at the time of the study he was only rarely consuming a glass of wine. He functioned independently, used a cane, and was not cognitively impaired (Mini Mental State Examination score = 29/30). He weighed 95 kg. A previous MRI of the head revealed generalized atrophy.

The study was a single-subject, double-blinded, placebo-controlled randomized-phase design.[5] After a 6-week run-in period to adjust for the potential learning effects associated with posturography, the patient was to undergo six 4-week testing periods, divided randomly into three treatment and three placebo arms with a 2-week washout period between each arm. Treatment consisted of buspirone hydrochloride (5mg twice daily for three days, 5mg three times daily for three days, and then 10mg three times daily). The placebo tablets were physically identical to buspirone. The outcome measurements were made at baseline and at the end of each 4-week testing period. Both the patient and investigators were blinded until analysis was complete.

The Research Ethics Board of Sunnybrook & Women's College Health Science Centre approved this study, and the subject gave written informed consent. The outcomes included:
1) clinical gait and balance testing (Stops Walking when Talking;[6] Timed Get-Up and Go[7]; number of steps to make a 180° turn; and number of alternating hand movements in 15 seconds); and, 2) posturography testing (spontaneous and induced sway on a balance platform).[8]

The patient was also asked to complete the Activities-specific Balance Confidence (ABC) Scale[9] and the Hospital Anxiety and Depression Scale[10] during each testing period. He was monitored for falls throughout the study. An independent party administered a side-effects questionnaire during each testing period. Differences in mean values between treatment and placebo were compared, and Student t-test or Fisher's Exact test statistics performed (Stata 7.0).[11]

RESULTS

The subject was unable to complete the final testing period as, unrelated to the study, he became ill from acute food poisoning and required hospitalization. Therefore, only two placebo arms were completed.

The change in clinical gait and balance test performance was not statistically significant (all $P>.05$). Although not of statistical significance, he improved by a mean of 2-3 seconds in the Timed Get-Up and Go tests on buspirone, compared to placebo (Table 1). There were no consistently significant differences in posturography testing. The subject felt more confident of his balance on buspirone compared to placebo (mean ABC score on drug 35.8 vs. placebo 30.9; $P=.04$). There was no difference in the mean depression score (placebo 3.0; buspirone 3.0; $P=1.0$) on the Hospital Anxiety and Depression Scale, however the subject had a lower mean anxiety score on buspirone (placebo 7.0; buspirone 5.3; $P=.36$).

While on buspirone, he suffered one panic attack and one brief dizziness episode. He also complained of one headache; however this was felt to be related to a temporary change in his anti-hypertension regiment to lisinopril and triamterene/hydrochlorothiazide. After his anti-hypertension regiment was changed back to hydrochlorothiazide he reported no further headaches. Unrelated to the study, he experienced an episode of Herpes Zoster. He did not report any falls. He was 92% adherent with treatment. After completing the study, the subject spent time on and time off buspirone.

TABLE 1 Results of the Clinical Gait and Balance Testing for Single-Subject Placebo-Controlled Buspirone Hydrochloride Study.

Clinical Gait/Balance Test	Buspirone	Placebo	P-value
Stopped Walking when Talking (per study arms completed)	2/3	2/2	1.00 [1]
Timed Get-Up and Go, mean (SD) in seconds • without water • carrying water	 20.9 (2.1) 24.2 (1.0)	 24.0 (2.5) 26.2 (0.5)	 .23 [2] .09 [2]
Number of steps to make 180° turn, mean (SD)	6.3 (1.5)	7.0 (1.4)	.66 [2]
Number of alternating hand movements in 15 seconds, mean (SD) • Left hand • Right hand	 16.7 (3.5) 16.0 (2.0)	 15.0 (0.0) 17.5 (0.7)	 .57 [2] .40 [2]

[1]Fisher's exact test
[2]Student t-test

DISCUSSION

Although buspirone demonstrated no statistically significant objective benefits in gait or balance, the subject reported subjective improvement in his balance confidence. Improvement in anxiety symptoms on buspirone, as reflected in a lower mean anxiety score on the Hamilton Anxiety and Depression Scale, may have contributed to this improvement in balance confidence. Although we cannot comment on long-term tolerability, buspirone was well tolerated by the subject in this 28-week study.

It is often challenging to know whether results of drug trials conducted with younger, healthier subjects are generalizable to older subjects with co-morbidities. Therefore, single-subject controlled studies may help when making uncertain treatment decisions with older individuals. Although, as demonstrated in this study, it can be difficult to find statistically significant differences given the limited power, this study design can still demonstrate clinically meaningful results.

In conclusion, this single-subject study helped determine that buspirone was tolerable but not objectively beneficial for this older individual with cerebellar ataxia.

REFERENCES
1. Strahlendorf JC, Lee MH, Strahlendorf HK. Serotonin modulates muscimol- and baclofen-elicited inhibition of cerebellar Purkinje cells. Eur J Pharmacol. 1991;201(2-3):239-242.
2. Strahlendorf JC, Lee M, Strahlendorf HK. Modulatory role of serotonin on GABA-elicited inhibition of cerebellar Purkinje cells. Neuroscience. 1989;30(1):117-125.
3. Trouillas P, Xie J, Adeleine P, et al. Buspirone, a 5-hydroxytryptamine1A agonist, is active in cerebellar ataxia. Results of a double blind drug placebo study in patients with cerebellar cortical atrophy. Arch Neurol. 1997;54(6):749-752.
4. Lou JS, Goldfarb L, McShane L, Gatev P, Hallett M. Use of buspirone for treatment of cerebellar ataxia. An open-label study. Arch Neurol. 1995;52(10):982-988.
5. Edgington ES. Randomized single-subject experimental designs. Behav Res Ther. 1996;34(7):567-574.

6. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. Lancet. 1997;349(9052):617.

7. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-148.

8. Maki BE, Holliday PJ, Fernie GR. Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. J Am Geriatr Soc. 1990;38(1):1-9.

9. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci. 1995;50A(1):M28-34.

10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.

11. Stata Statistical Software: Release 7.0 program. Stata Corporation; 2001.