A Double-Blind, Randomized, Placebo-Controlled Trial of Bumetanide in Parkinson's Disease

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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ABSTRACT: Background: Acting on the main target of dopaminergic cells, the striatal γ-aminobutyric acid (GABA)-ergic cells, might be a new way to treat persons with Parkinson's disease (PD).
Objective: The objective of this study was to assess the efficacy of bumetanide, an Na–K–Cl cotransporter (NKCC1) inhibitor, to improve motor symptoms in PD.
Methods: This was a 4-month double-blind, randomized, parallel-group, placebo-controlled trial of 1.75 to 3 mg/day bumetanide as an adjunct to levodopa in 44 participants with PD and motor fluctuations.
Results: Compared to the baseline, the mean change in OFF Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III score after 4 months of treatment (primary endpoint) did not improve significantly compared with placebo. No changes between participants treated with bumetanide and those treated with placebo were observed for most other outcome measures. Despite no relevant safety signals, bumetanide was poorly tolerated.
Conclusions: There was no evidence in this study that bumetanide has efficacy in improving motor symptoms of PD.

Key Words: bumetanide; GABAergic cells; NKCC1 inhibitor; Parkinson's disease

More than 6.2 million people worldwide are suffering from Parkinson's disease (PD).[1] The core of the disease is the progressive degeneration of midbrain dopamine-containing cells. The subsequent loss of brain dopamine, especially at the level of the striatum, explains most motor symptoms observed in people with PD. Effective symptomatic drug treatments aim to restore brain dopamine (levodopa), mimic its action (dopamine agonist), and, in the case of deep brain stimulation, correct basal ganglia dysfunction induced by the lack of dopamine.[2] As the disease progresses, dopamine-containing cells continue to be lost; thus, these treatments become less effective and need to be adjusted. At the same time, the duration of their beneficial effect decreases, leading to motor and nonmotor fluctuations, which may induce abnormal involuntary movements (ie, dyskinesia). Moreover, the lesion may spread more diffusely in the brain, leading to symptoms such as balance impairment, freezing-of-gait, or cognitive decline, which are poorly improved by the current symptomatic treatments.

Experimental investigations in dopamine-deprived mice revealed depolarizing actions of the inhibitory transmitter γ-aminobutyric acid (GABA) due to elevated $(Cl^-)_i$ levels.[3] The well-known loop diuretic bumetanide is a specific inhibitor of an Na–K–Cl cotransporter (NKCC1) that regulates $(Cl^-)_i$ in striatal neurons, thereby restoring GABAergic inhibition and thus the classical off response evoked by cortical stimulation, while also attenuating motor disturbances.[4,5] These observations raise the possibility that bumetanide might attenuate the severity of PD. In keeping with this, encouraging beneficial effects were observed in an open-label clinical study with PD participants.[6] Our aim was to demonstrate in a repurposing strategy the efficacy of bumetanide as a symptomatic treatment for people with PD.

Patients and Methods

Study Design and Participants

This study was a double-blind, parallel-group, randomized, placebo-controlled, multicenter trial of bumetanide in PD. Participants aged 40 to 80 years with a diagnosis of idiopathic PD (UKPDSBB criteria),[7] treated with more than 150 mg/d of L-dopa and suffering from motor fluctuations (>1 item Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part IV) were included. After a 1-month dose adjustment period, a specific formulation of bumetanide developed for this study was administrated orally twice daily at the maximal tolerated dosage (1.75 or 3.5 mg/day) for 3 months, followed up by a 1-month washout period. The full protocol (NCT03899324) was approved by an Independent Ethics Committee in France (CPP SUD EST II). All patients gave written informed consent. The study was supported by the French Clinical Research Network NS-

Park/F-CRIN (https://parkinson.network) and involved 12 of the network's 27 centers.

Outcomes

The primary outcome was to compare the efficacy of bumetanide in reducing the MDS-UPDRS[8] motor score assessed after at least a 10-hour withdrawal of antiparkinsonian drugs (OFF MDS-UPDRS motor score) and 1 hour after the morning intake of the study drug. The assessment was made at each center by an independent rater not in charge of the follow-up of the subject during the study. The secondary outcomes were the ON MDS-UPDRS motor score (ie, subject assessed 1 hour after antiparkinsonian drug intake), other MDS-UPDRS scores, the collection of adverse events (AEs), a stand–walk–sit test, and the Giladi's gait questionnaire[9]; the exploratory outcomes were the unified dyskinesia rating scale score,[10] the patient's diary records, and the patient's clinical global impression score at baseline, after 30, 60, and 120 days of study drug treatment and 30 days after study drug washout. Kalemia was assessed at each visit and at 1, 2, and 3 weeks after the inclusion; potassium was supplemented if kalemia was <3.5 mEq/l.

Statistical Analyses

The sample size calculation was based on a 25% diminution of the OFF MDS-UPDRS Part III score (8 points) after a 4-month treatment compared to baseline in the bumetanide-treated group and no change in the placebo group: a standard deviation of the score = 6, a unilateral α risk = 5%, and power = 80%. Considering these assumptions, 16 subjects per group were required. Taking into account a percentage of early discontinuation or loss to follow-up of 25%, the sample size was 40 subjects. In case of premature withdrawal for polyuria, the participant could be replaced.

Predefined statistical analyses were by intention to treat (ITT) for all included subjects and by per protocol (PP) for all subjects who completed the study with no major protocol deviations or violations thought to significantly affect the efficacy analysis. Quantitative data were analyzed by analysis of covariance with change from baseline as the dependent variable and treatment group, visit, treatment group–visit interaction, and baseline values as fixed effects (treatment group and baseline values for the primary outcome). If the residual distribution was not normal, an ln-transformation was applied to the data (before change). If the normal hypothesis was not demonstrated from ln-transformation data, rank data were retained. The level of significance was fixed at 0.05. Statistical analyses were performed by the SAS computer program (release 9.4).

Results

A total of 51 subjects were screened, and 44 of these subjects were included (4 of them replaced early-discontinuation participants) and randomly assigned in the study. Of these, 14 patients withdrew prematurely from the study (10 in the bumetanide group vs. 4 in the placebo group): 8 subjects were withdrawn by the local investigator (6 due to AEs and 2 by physician decision), and 6 subjects elected to drop out during the course of the study. Six patients had a major deviation. Twenty-four patients completed the study as per protocol (Supplementary Fig. 1). The baseline characteristics of these patients are presented in Table 1. Out of 11 participants in the bumetanide group, 7 received 3 mg/day and 4 received 1.75 mg/day, and 12 out of 13 participants in the placebo group received 3 mg/day and 1 received 1.75 mg/day during the 3 months of a stable dose.

The mean change (standard deviation [SD]) in OFF MDS-UPDRS III score was −3.0 (7.5) for bumetanide and −1.7 (6.6) for placebo after 4 months of treatment compared to baseline ($P = 0.78$ in ITT analysis; $P = 0.48$ in PP analysis) (Fig. 1). There was a significant ($P < 0.01$) worsening of the MDS-UPDRS Part IB score in the bumetanide group (mean change [SD] = 3.1 [2.7]) compared to the placebo group (−0.3 [3.5]) (bumetanide: 3.3 [2.6] vs. placebo: −0.8 [3.7]; $P < 0.02$ in PP). There was no difference between the bumetanide group and the placebo group for any of the other secondary or exploratory criteria. Of the 44 participants, 39 experienced at least one AE (22 participants in the bumetanide group vs. 17 in the placebo group), and 27 with AEs considered to be related to the study treatment (20 participants in the

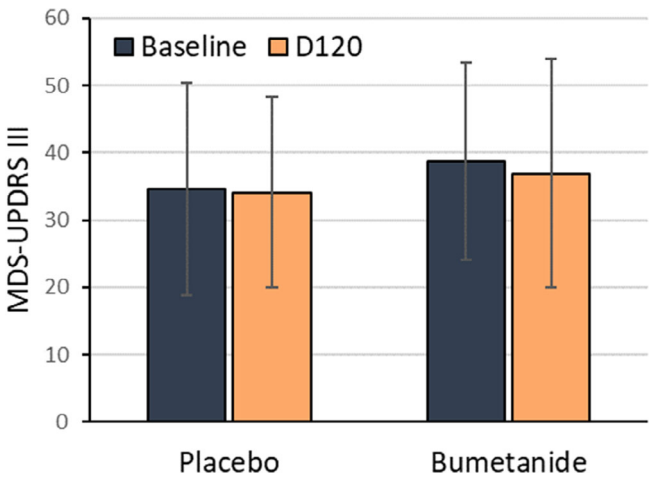

FIG. 1. Change in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score in the OFF stage (primary outcome) at baseline and after 4 months of bumetanide or placebo treatment. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 *Baseline characteristics of randomized participants*

Characteristic	No (%)		
	Placebo (n = 21)	Bumetanide (n = 23)	Total (n = 44)
Age, mean (SD) (y)	62.2 (8.9)	64.9 (9.9)	63.6 (9.4)
Sex, n (%)			
Female	7 (33.3)	5 (21.7)	12 (27.3)
Male	14 (66.7)	18 (78.3)	32 (727)
Disease duration, mean (SD) (y)	10 (4)	9 (3)	10 (4)
MDS-UPDRS III, in OFF stage (SD)	34.6 (15.8)	38.8 (14.6)	36.8 (15.2)
MDS-UPDRS III, in ON stage (SD)	18.2 (8.1)	24.0 (9.7)	21.3 (9.4)
Hoehn and Yahr stage (SD)	2.1 (0.7)	2.3 (0.7)	2.2 (0.7)
Levodopa equivalent dosage (SD) (mg)	1162 (506)	981 (312)	1072 (425)

Abbreviations: MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III score; SD, standard deviation.

bumetanide group vs. 7 in the placebo group). The most frequent AEs were urinary disorders (19% of AEs), 61% of them being pollakiuria, followed by episodes of fatigue (14% of AEs). Among the six serious AEs observed in the trial (three in each group), only one (coronary syndrome) was considered to be possibly linked to bumetanide treatment. The comprehensive results and analyses are available in the Supplementary Data.

Discussion

This randomized, double-blind, placebo-controlled trial failed to show any beneficial symptomatic effect of 4-month treatment with 1.75–3.5 mg/day bumetanide on PD. It also highlighted the poor tolerability of bumetanide in PD subjects, with frequent side effects, some of which led the participant to prematurely withdraw from the study, and a worsening of the MDS-UPDRS Part IB score (which assesses the nonmotor aspects of experiences of daily living and notably includes urinary problems and fatigue) in the active treatment group compared to the placebo group. The large dropout rate (24 patients analyzed out of 44 randomized) decreased the power of the analysis. Nonetheless, the absence of effects observed in PP analyses indicates that bumetanide at the dosage used in this study does not have a strong symptomatic effect on PD.

Despite poor brain penetration, bumetanide has led to some beneficial effects in children with autism spectrum disorder and in patients with tuberous sclerosis complex,[10-13] suggesting a cerebral action of this drug. In contrast, in PD adults, the NKCC1 inhibition by bumetanide at the dosage used in our study might be insufficient to restore the GABAergic transmission satisfactorily. Earlier-stage PD subjects might have had a better response to bumetanide and been less prone to the side effects of the diuretic. Despite our negative results, we cannot exclude the possibility that other agents acting on NKCC1, either with better brain penetration or with better tolerability, might be found to improve PD symptoms.

Data Availability Statement

Deidentified participant data are available upon reasonable request to the corresponding author.

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Supporting Data

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