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Randomized, Double-Blind, Pilot Evaluation of Intravenous Glutathione in Parkinson's Disease

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Abstract: The objective of this study was to evaluate the safety, tolerability, and preliminary efficacy of intravenous glutathione in Parkinson's disease (PD) patients. This was a randomized, placebo-controlled, double-blind, pilot trial in subjects with PD whose motor symptoms were not adequately controlled with their current medication regimen. Subjects were randomly assigned to receive intravenous glutathione 1,400 mg or placebo administered three times a week for 4 weeks. Twenty-one subjects were randomly assigned, 11 to glutathione and 10 to placebo. One subject who was assigned to glutathione withdrew from the study for personal reasons prior to undergoing any postrandomization efficacy assessments. Glutathione was well tolerated and there were no withdrawals because of adverse events in either group. Reported adverse events were similar in the two groups. There were no significant differences in changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores. Over the 4 weeks of study medication administration, UPDRS ADL + motor scores improved by a mean of 2.8 units more in the glutathione group ($P = 0.32$), and over the subsequent 8 weeks worsened by a mean of 3.5 units more in the glutathione group ($P = 0.54$). Glutathione was well tolerated and no safety concerns were identified. Preliminary efficacy data suggest the possibility of a mild symptomatic effect, but this remains to be evaluated in a larger study. © 2009 Movement Disorder Society

Key words: glutathione; Parkinson's disease; treatment; antioxidant; neuroprotection; UPDRS

Glutathione is a tripeptide of glutamate, cysteine, and glycine, that plays multiple roles in the brain.[1] It serves as an important central nervous system antioxidant, clears free radicals including superoxide radicals, hydroxyl radicals, nitric oxide, and carbon radicals,[2,3] and helps clear hydrogen peroxide.[4] In addition, glutathione helps maintain the cellular redox state of protein thiols and low-molecular-weight antioxidants such as vitamin E and ascorbate.[5] Recent evidence suggests that glutathione can also act as a neurotransmitter and neurohormone.[6]

In Parkinson's disease (PD), glutathione is reduced by 40–50%.[7–11] This reduction is specific within the brain to the substantia nigra[9] and correlates with

Additional Supporting Information may be found in the online version of this article.

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disease severity.[10] In contrast to PD, glutathione is not decreased in multiple system atrophy or progressive supranuclear palsy, despite nigral neuronal loss.[8,9] In incidental Lewy body disease, glutathione is substantially decreased even as nigral cell loss is modest, and complex I activity is not significantly decreased,[12] suggesting that the reduction of glutathione is a very early event in PD.

In vitro experiments indicate that prolonged depletion of glutathione results in selective impairment of mitochondrial complex I activity.[13] To the extent that mitochondrial dysfunction impairs dopaminergic function, it is possible that glutathione replacement could provide symptomatic benefit in PD. There is also interest in glutathione as a possible neuroprotective agent. In a genetically engineered mouse line, glutathione depletion resulted in mitochondrial complex I inhibition, followed by age-related nigrostriatal neurodegeneration.[14] In addition, deficiency of glutathione peroxidase enhanced MPTP toxicity in a mouse knockout model,[15] whereas pretreatment with glutathione reduced MPTP toxicity in mouse brain slices.[16]

There have been few studies of glutathione as a treatment for PD. Sechi et al.[17] reported a 42% decline in PD disability with 600 mg glutathione administered intravenously twice daily for 30 days. The therapeutic effect was observed to last for 2 to 4 months. We performed a randomized, placebo-controlled, double-blind, pilot evaluation of the tolerability, safety, and preliminary efficacy of intravenous glutathione (1,400 mg) administered three times a week for 4 weeks compared with placebo in PD patients. This regimen was chosen because of its anecdotal use in clinical practice.

PATIENTS AND METHODS

This was a 12-week, randomized, parallel group, double-blind, placebo-controlled pilot study. Eligible patients were those with a diagnosis of PD (with at least two of three cardinal signs—rest tremor, bradykinesia, and rigidity) whose motor symptoms were not adequately controlled on their current medication regimen. Inclusion criteria included Hoehn and Yahr Stage II–IV and Mini Mental State Examination score of >24. Subjects were on a stable regimen of antiparkinsonian medications for at least 1 month prior to study entry. Exclusion criteria included prior exposure to glutathione, atypical parkinsonism, use of neuroleptics, history of a seizure, or drug addiction. All subjects provided written informed consent prior to study participation.

After screening and baseline evaluations, subjects were randomly assigned 1:1 to receive 1,400 mg glutathione or placebo diluted in 10 mL of normal saline and administered by intravenous push over 10 minutes on Monday, Wednesday, and Friday of each week for a 4-week period. Attempts were made to administer study medication at the same time of day for each subject, usually in the morning. Glutathione and placebo were supplied by Wellness Health and Pharmaceuticals (Birmingham, Alabama). Antiparkinsonian medications were kept stable throughout the study.

All adverse events were recorded. Safety assessments included vital signs and ECGs. Supine and standing blood pressures were obtained at baseline and 10 minutes after the completion of each intravenous infusion. ECGs were obtained before the first infusion and $\sim$10 minutes after the completion of each infusion. Efficacy assessments were performed at baseline and at the end of weeks 1, 2, 3, 4, 8, and 12. Assessments at the end of weeks 1, 2, 3, and 4 (treatment phase) were performed 1 hour following study medication infusion. Assessments at weeks 8 and 12 were performed at approximately the same time of day as during the treatment phase to evaluate changes after study medication discontinuation. Assessments included Unified Parkinson's Disease Rating Scale (UPDRS, parts I–III), timed walking, tapping, and clinical global impression of change (CGI-C). For patients with motor fluctuations, motor assessments were obtained when subjects were in the "ON" state. The predefined efficacy outcome measure of greatest interest was the change in UPDRS ADL + motor scores from baseline to week 4.

Randomization was performed using a computer-generated randomization schedule. The sample size selected for the study was 20 subjects. Because this was a pilot study, no efficacy power analysis was performed. Adverse events and discontinuations were to be reported descriptively. Efficacy measures were compared across groups using Wilcoxon-signed rank comparisons and analysis of variance for nonparametric data, with no correction for multiple analyses and significance set at $P < 0.05$. Total levodopa (L-dopa) dose equivalents were calculated as follows: (regular L-dopa dose $\times$ 1) + (L-dopa controlled-release dose $\times$ 0.75) + (pramipexole dose $\times$ 67) + (ropinirole dose $\times$ 16.67) + (pergolide dose $\times$ 100) + (bromocriptine dose $\times$ 10) + ([regular L-dopa dose + (L-dopa controlled-release dose $\times$ 0.75)] $\times$ 0.25 if taking tolcapone) + ([regular L-dopa dose + (L-dopa controlled-release dose $\times$ 0.75)] $\times$ 0.1 if taking entacapone).[18]

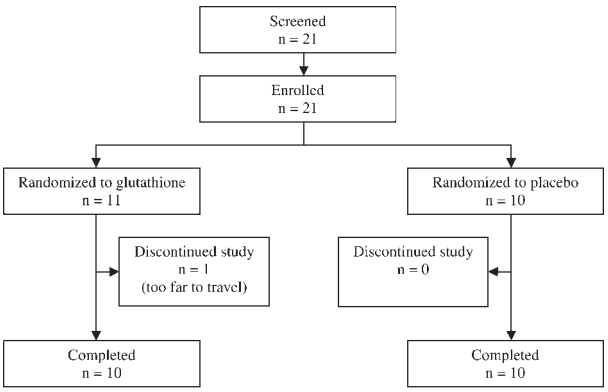

FIG. 1. Subject flowchart.

RESULTS

Subjects were enrolled in the study from September 2003 to January 2007 (Fig. 1). One subject enrolled in the study underwent baseline evaluations, was randomized, received two doses of glutathione, and withdrew prior to any post–dose efficacy assessments, because he felt it was too difficult to continue to drive to the study site. This subject was a 69-year-old man with a 7-yr duration of PD. He did not report any adverse events and is not considered here further. For the remaining 20 subjects, mean age (SD) was 64.3 (10.4) years, with a range of 43 to 84 years. Mean disease duration was 7.6 (4.6) years, with a range of 2 to 18 years. Eleven subjects were men and nine were women. There were no significant differences in baseline characteristics between the two groups (Table 1).

Mean daily L-dopa equivalents in the placebo group were 483.7 (256.2) mg and in the glutathione group were 611.0 (317.4) mg ($P = 0.34$). Individual daily L-dopa equivalents, daily L-dopa dosages, and other medications taken are delineated in Supporting Table 1. Of the 10 subjects in the placebo group, nine were receiving L-dopa at a mean dose of 467 mg/day (203 mg/day). The one subject in this group not receiving L-dopa was receiving pramipexole 1.5 mg/day. Of 10 subjects in the glutathione group, 7 were receiving L-dopa at a mean dose of 629 mg/day (263 mg/day). Of 3 subjects not receiving L-dopa in this group, 1 was receiving ropinirole 22.5 mg/day and selegiline 10 mg/day, 1 was receiving pergolide 4 mg/day, pramipexole 6 mg/day, amantadine 400 mg/day, and trihexyphenidyl 8 mg/day, and 1 was receiving pramipexole 2.5 mg/day. Five of ten subjects who were assigned to placebo were experiencing motor fluctuations and 7 of 10 who were assigned to glutathione were experiencing motor fluctuations.

Adverse events reported during the 4 weeks of study medication administration are listed in Table 2. The adverse events reported by more than one subject in the glutathione group were headache (three glutathione, two placebo), muscle soreness/cramps (three glutathione, three placebo), nausea (two glutathione, 0 placebo), and dizziness/lightheaded (two glutathione, two placebo). One subject in the glutathione group reported mild nausea 2 days after her fourth medication administration, and another reported mild nausea 1 day after her third medication administration. Five subjects in the placebo group reported fatigue/tiredness compared with one in the glutathione group, and three subjects in the placebo group reported cold symptoms/cough compared with none in the glutathione group. No subjects in either group withdrew from the study because of adverse events and there were no serious adverse events. Analysis of vital signs and ECGs revealed no significant differences between groups.

TABLE 1. *Baseline characteristics*

	Placebo (n = 10) [mean (SD), range]	Drug (n = 10) [mean (SD), range]	*P*
Age (yr)	65.9 (12.6), 43–84	62.6 (7.9), 49–73	0.49
Disease duration (yr)	5.8 (3.1), 2–10	9.4 (5.2), 3–18	0.08
Gender	6 M, 4 F	5 M, 5 F	
Levodopa equivalents (mg)	483.7 (256.2), 50–825	611.0 (317.4), 168–1200	0.34
UPDRS mentation	2.2 (1.6), 0–4	1.8 (1.7), 0–5	0.59
UPDRS ADL	11.7 (6.4), 3–27	12.1 (3.9), 7–19	0.87
UPDRS motor	23.4 (9.5), 8–40	25.5 (6.2), 17–39	0.57
UPDRS ADL + motor	35.1 (14.8),13–67	37.6 (9.5), 28–58	0.66
UPDRS total	37.3 (16.0),13–71	39.4 (9.5), 28–58	0.73
HY	2.0 (0), 2.0	2.1 (0.3), 2.0–3.0	0.33
SE	81.5 (15.3), 40–90	83.0 (9.5), 60–90	0.80
MMSE	29.7 (0.5), 29–30	29.6 (0.7), 28–30	0.71

UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; HY, Hoehn and Yahr staging; SE, Schwab and England; MMSE, Mini Mental State Examination.

TABLE 2. *Adverse events during treatment phase (baseline through week 4)*

	Glutathione (n = 10)	Placebo (n = 10)
Headache	3	2
Muscle soreness/cramps	3	3
Dizziness/orthostatic hypotension	2	2
Nausea	2	0
Erythema at infusion site	1	0
Falling/unbalanced gait	1	2
Fatigue/tired	1	5
Hair loss	1	0
Pain (knee, foot)	1	2
Sleep difficulties	1	0
Sweating increased	1	0
Upper respiratory infection	1	0
Vivid dreaming	1	0
Cold symptoms/cough	0	3
Difficulty breathing	0	1
Dyskinesia increased	0	1
Edema	0	1
Hot flashes	0	1
Mouth tremor increased	0	1
Numbness	0	2
Strep throat	0	1
Vision problems worsening	0	1

There was no significant difference between groups in change in UPDRS ADL + motor scores from baseline to week 4 ($P = 0.32$; Fig. 2, Supp. Table 2). UPDRS ADL + motor scores improved from 37.6 (9.5) at baseline to 34.8 (8.1) at week 4 in the glutathione group and were unchanged in the placebo group, 35.1 (14.8) at baseline and 35.1 (14.2) at week 4. Also, there was no significant difference between groups in change in UPDRS ADL + motor scores from weeks 4 to 12 (evaluating possible loss of symptomatic benefit; $P = 0.54$). UPDRS ADL + motor scores worsened from 34.8 (8.1) at week 4 to 36.3 (8.3) at week 12 in the glutathione group and improved in the placebo group from 35.1 (14.2) at week 4 to 33.1 (15.2) at week 12. Significant differences across groups were also not observed for other outcome measures (Supp. Table 2). In the glutathione group, CGI-C indicated that at 4 weeks (end of treatment phase) compared with baseline, four were mildly improved and six were unchanged. At 12 weeks (8 weeks after study medication discontinuation) compared with baseline, seven were unchanged and three were mildly worse. In the placebo group, at week 4, 1 subject was moderately improved, 7 were unchanged, and 2 were mildly worse. At week 12, 1 was still moderately improved, 4 were unchanged, 4 were mildly worse, and 1 was moderately worse compared with baseline.

DISCUSSION

In this pilot study, glutathione was well tolerated and there were no withdrawals because of adverse events. Reported adverse events were similar in the glutathione and placebo groups, with the possible exception of nausea, which was reported in 2 of 10 glutathione patients and 0 of 10 placebo patients. In both cases, nausea occurred once, did not occur on the same day as medication administration, and was mild and transient. No safety concerns were identified regarding vital signs or ECGs.

We did not observe a significant improvement in parkinsonian signs and symptoms in the glutathione group when compared with the placebo group. However, this was a pilot study and was not powered to definitively evaluate efficacy. In addition, efficacy observations may be further limited by the heterogeneity of the study population. Nonetheless, during the 4-week course of study medication administration, the glutathione group was observed to improve a mean of 2.8 units more than the placebo group as assessed by UPDRS ADL + motor scores. In the 8 weeks following study medication discontinuation, the glutathione group was observed to worsen a mean of 3.5 units more than the placebo group as assessed by UPDRS ADL + motor scores. These observations suggest the possibility that glutathione may provide a mild symptomatic benefit, but this would have to be evaluated in a larger clinical trial.

In an open-label study of nine PD subjects, Sechi et al.[17] reported that intravenously administered glutathione (600 mg) twice daily for 30 days reduced disability by 42% as assessed using a modified Columbia University Rating Scale. We did not observe improvement of this magnitude. This could be because their study was open label whereas ours was placebo-

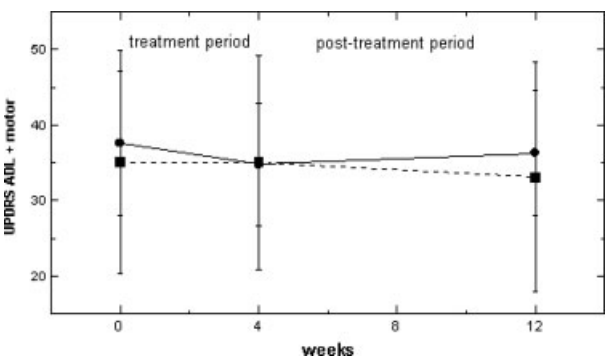

FIG. 2. Mean UPDRS ADL + motor scores for placebo (squares, dashed lines) and glutathione groups (circles, solid lines) at baseline, week 4, and week 12.

controlled and double-blind. However, their patients received a total of 36,000 mg of glutathione over 1 month, whereas our patients received 16,800 mg over 1 month and we cannot exclude the possibility that higher or more frequent doses might provide greater benefit. In addition, patients in their study had early PD and were otherwise untreated, whereas ours were all receiving antiparkinsonian medications and most were receiving L-dopa.

A critical question regarding glutathione as a potential treatment for PD is whether it crosses the blood-brain barrier (BBB). Studies have demonstrated that glutathione is transported across the BBB in the rat and guinea pig.[19,20] More recently, human cerebrovascular endothelial cells were demonstrated to exhibit glutathione uptake and efflux.[21] Both sodium-dependent and sodium-independent uptake mechanisms were identified. Sodium-dependent transport was localized to the luminal membrane consistent with the notion that this transporter effects uphill glutathione transport from low plasma to higher endothelial cellular concentrations. There was also evidence for the presence of an efflux mechanism from the abluminal surface of the endothelial cells. These observations suggest that there is a BBB transporter system for glutathione. The degree to which administered glutathione actually crosses the BBB in humans remains to be determined.

Our pilot study addressed the short-term tolerability, safety, and preliminary efficacy of glutathione. It is important to recognize that our study was not designed to evaluate a potential neuroprotective effect of glutathione. During 4 weeks of administration, glutathione appeared to be well tolerated and we did not identify any safety concerns. This suggests that glutathione might be considered for longer trials to evaluate potential slowing of clinical disease progression.

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Author Roles: Robert Hauser participated in study design, acquisition of data, and interpretation of data, wrote the first draft and revised it based on critical review by coauthors. Kelly Lyons participated in study design, performed statistical analyses, participated in interpretation of data, and critically revised the draft. Terry McClain participated in data acquisition and critically revised the draft. Summer Carter participated in data acquisition and critically revised the draft. David Perlmutter participated in study design and critically revised the draft. There were no ghost writers and this manuscript complies with the *Movement Disorders* policy on ghost writing.

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