Nevertheless, these results are important for research that recruits PD patients with borderline or MCI. They suggest the need to attend to deficits in memory and executive function, given that subtle disruption in these areas increases the likelihood that a patient is not capable of giving consent. Indeed, people with PD MCI may also have reduced awareness of executive function impairment, potentially compromising safety and judgment in naturalistic settings.[15] In such cases, study precautions should be considered, including a structured assessment of capacity and asking the patient to designate a study partner. We remind readers and investigators that a brief measure of executive function, such as the DRS-2 *Initiation-Perseveration* subscale, *Visuospatial/Executive* subscale of the MoCA, or even a brief screening instrument such as the MoCA, is not a sufficient measure of capacity. Low performance on these scales, however, may serve as a prompt to consider additional protections to guard against the possibility of mistakenly judging a patient who is not capable as capable. ■

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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.

Oral Inosine Persistently Elevates Plasma Antioxidant Capacity in Parkinson's Disease

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ABSTRACT

Introduction: Higher serum urate predicts slower progression in PD. The aim of this work was to assess whether oral inosine alters antioxidant capacity of plasma or CSF or urinary markers of oxidative injury in early PD.

Methods: We assayed plasma and CSF antioxidant capacity by ferric-reducing antioxidant power and measured DNA oxidation adduct 8-hydroxydeoxyguanosine from urine in Safety of URate Elevation in PD, a randomized, placebo-controlled trial of oral inosine assessing safety of elevating serum urate from <6 mg/dL to 6.1–7.0 or 7.1–8.0 mg/dL in patients with early PD.

Results: At 6 months, antioxidant capacity was 29% higher among mild and 43% higher among moderate group participants compared to placebo and correlated with change in serum urate ($r = 0.86$) and inversely with rate of clinical decline ($r = -0.26$). CSF antioxidant capacity and urine 8-hydroxydeoxyguanosine did not differ.

Conclusions: The findings demonstrate a dose-dependent, persistent elevation of plasma antioxidant capacity from oral inosine of potential therapeutic relevance. © 2016 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; antioxidant; uric acid/urate; inosine

Higher levels of serum urate are a predictor of decreased incidence of Parkinson's disease (PD) and slower progression in early PD.[1-6] Whether these associations reflect a causally protective role of urate is unclear. In rodent models of PD, raising or lowering urate levels protects or exacerbates PD phenotypes, respectively.[7,8] In human beings, many characteristic biochemical features of PD, such as mitochondrial dysfunction, decreased nigral glutathione levels, and increased nigral iron load, are associated with increased oxidative stress.[9-11] Urate, which has both direct and indirect antioxidant effects, is hypothesized to be neuroprotective in PD by alleviating oxidative nigral injury.[12,13]

The Safety of URate Elevation in PD (SURE-PD) study was a randomized, double-blind, placebo-controlled phase II trial testing the safety, tolerability, and feasibility of raising serum and cerebrospinal fluid (CSF) urate with inosine (an orally bioavailable metabolic precursor of urate) in patients with early PD not requiring symptomatic therapy.[14] The results showed that inosine was well tolerated and safely raised serum and CSF urate levels.[14] In this exploratory biomarker study, we report on ferric-reducing antioxidant power (FRAP; a measure of antioxidant capacity) in plasma and CSF and on 8-hydroxydeoxyguanosine (8-OHdG; a measure of nucleic acid oxidative injury) in urine.[15,16]

Patients and Methods

Biospecimens

As detailed previously,[14] the SURE-PD trial enrolled 75 patients with early PD not yet requiring symptomatic antiparkinsonian treatment (except for a stable dose of monoamine oxidase type B inhibitor) with serum urate <6 mg/dL. They were randomized at 16 sites in 1:1:1 distribution to three treatment groups: (1) placebo, or oral inosine titrated to (2) mildly elevated serum urate (6.1–7.0 mg/dL), or (3) moderately elevated serum urate (7.1–8.0 mg/dL). Inosine dosing was adjusted based on serum urate at scheduled study visits. Participants remained on study drug for up to 24 months (average, 18; range, 9–24). Plasma was collected in heparinized tubes at baseline, 6-month-visit, and final visit on drug. Urine was collected at baseline and 6-month-visit. CSF was collected once at 12-week visit. Samples were obtained with institutional review board–approved consent procedures and frozen at –80°C. Investigators were blinded to treatment assignments.

FRAP Assay

Antioxidant capacity was measured by FRAP, as previously described.[17] In this colorimetric assay, when ferric tripyridyltriazine (Fe(III)-TPTZ) complex is reduced to the ferrous form by the added sample, a blue color develops—absorption at 560 nm is proportional to the degree of antioxidant power of the sample. Antioxidant capacity is expressed as equivalent concentrations of the standard ferrous (II) chloride (ranging from 0.03 to 1.0 mM). Plasma and CSF (sixth 3-mL lumbar puncture collection tube) were assayed in triplicate in three 96-well assay plates with interassay coefficient of variation (CV) <5%.

Urine 8-OHdG

The oxidative DNA adduct, 8-OHdG, was measured in urine by competitive enzyme-linked immunosorbent assay (ELISA; Japan Institute for the Control of Aging [JaICA], Fukuroi, Japan) and normalized to urinary creatinine, which was assayed using a colorimetric kit (R&D Systems, Minneapolis, MN). Each urine sample was measured in triplicate in three 96-well assay plates with CV <10%. 8-OHdG is expressed as ratio of concentrations of 8-OHdG and creatinine.

Statistical Analysis

Treatment- and visit-specific mean biomarker levels were estimated from shared-baseline linear mixed models with fixed effects for visit and treatment × postbaseline visit interaction and random participant-specific intercepts and slopes with unstructured covariance. Linear contrasts were used to test for treatment-dependent differences in mean change from baseline. Participant-specific rates of change of UPDRS III motor scores were estimated from a similar shared-baseline, random-slopes, mixed-effects model with time treated as continuous and censoring observations after initiation of dopaminergic therapy. Associations

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TABLE 1. Baseline characteristics of participants with plasma FRAP measurements

	Overall (n = 68)	Placebo (n = 23)	Mild (n = 21)	Moderate (n = 24)
Age in years (SD)	61.5 (10.7)	60.8 (11.4)	62.1 (10.1)	61.7 (10.8)
Male (n)	45.1% (32)	50.0% (12)	36.4% (8)	48.0% (12)
UPDRS Part III motor score (SD)	15.8 (7.6)	17.1 (8.3)	14.7 (7.2)	15.6 (7.4)
UPDRS Parts I–III total score (SD)	21.8 (9.7)	23.5 (10.4)	20.4 (9.1)	21.4 (9.7)
Years of symptoms (SD)	2.4 (1.8)	2.3 (1.4)	2.7 (2.0)	2.2 (2.0)
Diabetes mellitus (n)	4.2% (3)	4.2% (1)	0.0% (0)	8.0% (2)
Smoker, ever (n)	32.4% (23)	33.3% (8)	36.4% (8)	28.0% (7)
Mean systolic BP in mm Hg (SD)	130 (14.2)	127 (15.0)	131 (13.5)	132 (14.0)
BMI in kg/m^2 (SD)	27.5 (5.2)	28.1 (5.3)	27.5 (6.5)	27.0 (3.9)
Baseline serum creatinine in mg/dL (SD)	0.82 (0.14)	0.84 (0.15)	0.82 (0.13)	0.81 (0.15)
Baseline FRAP in mmol Fe(II)/L (SD)	0.84 (0.13)	0.82 (0.12)	0.84 (0.17)	0.86 (0.11)
Baseline urine 8-OHdG in ng/mg creatinine (SD)	11.0 (4.2)	10.7 (3.6)	10.9 (2.8)	11.3 (5.6)
Baseline serum urate in mg/dL (SD)	4.47 (0.76)	4.63 (0.57)	4.31 (0.92)	4.47 (0.74)
Baseline CSF urate in mg/dL (SD)	0.54 (0.18)	0.43 (0.19)	0.55 (0.15)	0.60 (0.18)

None of the characteristics differed for the mild or moderate group compared to placebo.
BMI, body mass index; BP, blood pressure; SD, standard deviation.

between baseline biomarker levels, changes in biomarkers levels from baseline, and biomarker levels and rates of change of UPDRS III motor scores were estimated as simple, unadjusted Pearson correlations. With the achieved sample size, the study had 80% power to detect correlations as small as $\rho = 0.33$ or 0.41 for blood or CSF biomarkers, respectively.

Results

Plasma FRAP

Baseline plasma FRAP values were available from 23 of 25 subjects in placebo, 21 of 24 in mild, and 24 of 26 in moderate groups. Baseline characteristics were balanced among the arms (Table 1). Paired baseline and follow-up plasma FRAP values were unavailable for 1 subject each in placebo, mild, and moderate groups. Inadequate sample collection or plasma separation accounted for missing values. At six months, plasma FRAP was 29% higher among mild (1.17 mM) and 43% higher among moderate (1.30 mM) group participants compared to placebo (0.90 mM) members ($P < 0.001$ for each; Fig. 1A). At the final visit on study drug (~18 months), FRAP values among mild and moderate group participants remained elevated ($P < 0.001$ for each vs. placebo). The slightly higher FRAP values at 6 months compared to final visit matches a similar spike in serum urate values at 6-month visit (caused by one-time trough measurement of serum urate at preceding visit and compensatory increase in inosine dosing). The moderate group had higher FRAP levels compared to the mild group at 6-month visit and beyond ($P = 0.025$). Change in plasma FRAP correlated strongly with change in serum urate ($r = 0.86$; $P < 0.001$; Fig. 1B). The data also indicate an inverse correlation between the extent of plasma FRAP increase and rate of clinical decline (as assessed by UPDRS Part III motor score slope estimate; $r = –0.26$; $p = 0.034$; Fig. 1C).

CSF FRAP

CSF FRAP values were available from 11 of 25 in placebo, 15 of 24 in mild, and 18 of 26 in moderate groups (lumbar puncture being optional or technically inadequate for some participants). CSF FRAP did not differ significantly among groups and did not correlate with serum urate concentration ($r = –0.04$; 95% confidence interval [CI]: –0.34 to 0.26; $P = 0.78$) or plasma FRAP ($r = 0.04$; 95% CI: –0.27 to 0.34; $P = 0.81$).

Urine 8-OHdG

Baseline and 6-month urine 8-OHdG values were available from 21 of 25 patients in placebo, 22 of 24 in mild, and 25 of 26 in moderate groups. Baseline values were similar across the groups. At 6 months, urine 8-OHdG values did not differ significantly among placebo, mild, and moderate groups (Table 2). Change in urine 8-OHdG did not correlate significantly with change in serum urate ($r = –0.11$; 95% CI: –0.34 to 0.13; $P = 0.37$).

Discussion

Long-term oral administration of inosine resulted in sustained, dose-dependent increases in plasma antioxidant capacity. This increase correlated tightly with increase in serum urate consistent with the major contribution (~60%) urate makes to plasma antioxidant capacity measured by FRAP.[16,17] The findings suggest that homeostatic mechanisms do not attenuate the increase in plasma antioxidant capacity attributed to urate elevation. Although such homeostatic control phenomena may limit the long-term effects of

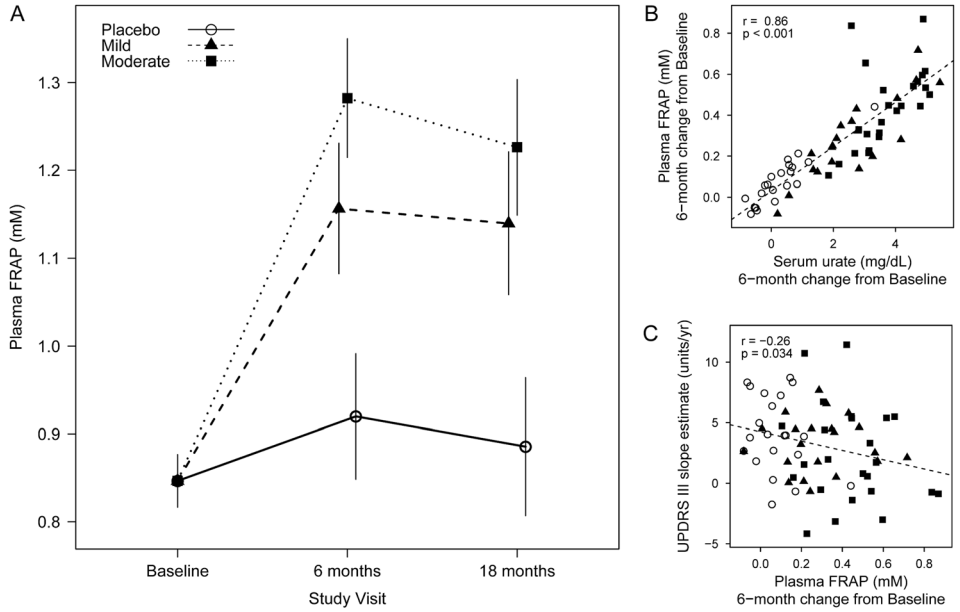

FIG. 1. (A) Plasma FRAP increased in mild (triangle) and moderate (square) groups compared to placebo (circle). (B) Plasma FRAP and serum urate changes are correlated. (C) Increase in plasma FRAP correlated with slower progression of motor symptoms of PD.

treatment with other specific antioxidants like ascorbate,[18,19] oral inosine titrated to a urate level can produce long-term elevations in peripheral antioxidant capacity.

Whereas many assays measure total antioxidant capacity, FRAP has been assessed in multiple relevant clinical studies. Decreased FRAP levels have been found in diseases with increased oxidative stress, such as cardiovascular disease,[20] chronic kidney disease,[21] and Alzheimer's disease.[22] In the PREDIMED diet trial, Mediterranean diet supplemented with olive oil or nuts resulted in early increased plasma FRAP level at 1 year and improved cardiovascular outcome in longer follow-up.[23,24] Taken together, plasma antioxidant levels measured by FRAP may be of potential therapeutic significance.

The lack of apparent effect of inosine on CSF FRAP may suggest that the antioxidant actions of inosine dosing do not extend to the CNS, or at least to its CSF compartment. Alternatively, an inosine-induced increase in CSF FRAP may have been more difficult to detect. Urate concentration in the CSF is 8- to 10-fold lower than in serum and comprises a smaller fraction of CSF antioxidant power.[14,25,26] Thus, a proportional increase in urate in both compartments would have a smaller impact on CSF FRAP. Our study was also markedly limited by lack of baseline CSF samples and a small number of subjects consenting for lumbar puncture.

We attempted to assess systemic antioxidant effect by measuring urine 8-OHdG, which is produced by hydroxyl radical attack on nucleosides in DNA. Urine 8-OHdG in a cross-sectional study increased with progression of PD, suggesting that progressive nucleic acid oxidative injury accompanies disease progression.[27] At 6 months, we did not detect differences in urine 8-OHdG among the three groups. This may indicate that increased antioxidant *capacity* does not result in greater antioxidant *effects*, and urate may not confer neuroprotection in PD or may do so by another mechanism. Alternatively, 8-OHdG in urine may inadequately reflect antioxidant effects in remote organs such as the brain. Finally, different methods of measuring 8-OHdG (such as high-performance liquid chromatography vs. ELISA) can yield values orders of magnitude apart, limiting comparison of studies.

The finding that rates of clinical decline (in the motor UPDRS Part III) were slower among participants with larger increases in plasma FRAP suggests a role for plasma FRAP as biomarker of target engagement.[28] There are several limitations of this interpretation. First, this is an exploratory analysis and requires replication in a study powered for treatment-dependent differences in rates of disease progression. Second, mechanistic significance is tempered by the absence of demonstrable CSF FRAP elevation. Last, serum urate itself is simpler and less expensive to measure than FRAP and is more directly relevant to safety than FRAP for titrating inosine dose to avoid hyperuricemic adverse events.[11]

In conclusion, chronic oral inosine administration in people with early PD patients produced a substantial, dose-dependent, persistent elevation of plasma antioxidant capacity in parallel with its urate elevating effects. The findings provide additional evidence for a

possible antioxidant mechanism of inosine and suggest a potential therapeutic benefit from urate's antioxidant properties. ■

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