Inosine treatment safely elevates urate levels in Parkinson's disease patients

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A clinical trial assessing the potential of the nutritional supplement inosine to treat Parkinson disease has found that the studied dosages successfully raised participants' levels of the antioxidant urate without producing serious side effects. Results of the two-year phase 2 trial – conducted by a consortium led by investigators at Massachusetts General Hospital (MGH), Harvard School of Public Health, and the University of Rochester – are being published in *JAMA Neurology*. Several previous studies have suggested that urate elevation may reduce the risk of Parkinson disease or slow its progression.

"This study provided clear evidence that, in people with early Parkinson disease, inosine treatment can safely elevate urate levels in the blood and cerebrospinal fluid for months or years," says Michael Schwarzschild, MD, PhD, principal investigator of the study and an MGH neurologist. "We know that urate has neuroprotective properties in animal models, and an unusual convergence of human studies suggested its possible use as a disease-modifying strategy in Parkinson's; so the positive results of this trial are very encouraging."

Characterized by tremors, rigidity, difficulty walking and other symptoms, Parkinson disease is caused by the destruction of brain cells that produce the neurotransmitter dopamine. While current treatments can partially relieve symptoms, no therapy has been shown to alleviate the underlying loss of brain cells or the progression of the disorder. Studies by Schwarzschild's team and others have found that healthy people with naturally occurring blood levels of urate within the high normal range appear to have a reduced risk of developing Parkinson's and that the disease may progress more slowly in those with higher urate levels.

Primarily supported by a $5.6 million grant from the The Michael J. Fox Foundation for Parkinson's Research and conducted at 17 sites across the U.S., SURE-PD (Safety of URate Elevation in Parkinson's Disease) enrolled 75 recently diagnosed Parkinson disease patients with relatively low blood levels of urate (less than 6 mg/dL). Participants were randomized to three study groups – one receiving an inosine dosage designed to achieve mild elevation of blood urate (6 to 7 mg/dL), one receiving a dose designed to achieve moderate elevation (7 to 8 mg/dL) and a placebo group. Inosine is naturally converted by the body into urate as part of normal metabolism, whereas urate taken orally would be broken down in the digestive system.

Of the 75 participants only 1 did not complete the trial. During the study period, the incidence of serious adverse events was no higher among those receiving inosine than among the placebo group. Three participants receiving inosine did develop symptomatic kidney stones – a known consequence of high urate levels – but two of those were not clearly urate-related stones, and all were successfully treated. There was no increased incidence of gout or other potentially urate-related problems. After six months on the trial, 95 percent of participants reported no problems taking the drug, and while several discontinued treatment for varying periods of time during the study period, the investigators estimate that 90 percent would have tolerated the treatment if they had continued the full two years.

The tested dosages successfully increased blood and cerebrospinal fluid urate levels into the target ranges, with greater increases in the moderate-elevation group. One month after the study ended, urate levels for all participants had returned to their original levels. Additional data collected by the investigators provided preliminary effectiveness results that Schwarzschild describes as encouraging. "These results support advancing to a larger trial capable of addressing whether inosine might fill the critical unmet need for disease-

modifying treatment. The information provided by this trial is helping us design a phase 3 trial, and with guidance from the FDA, we are preparing an application for additional funding from the National Institutes of Health."

A professor of Neurology at Harvard Medical School, Schwarzschild cautions Parkinson's patients and their caregivers against attempting inosine treatment at this time. "While there is considerable evidence to support this therapy's potential, inosine is still an unproven treatment for Parkinson disease. We know that excessively high urate can lead to kidney stones, gout and possibly other untoward effects, which is why attempts to elevate urate are best pursued in carefully designed clinical trials where the risks can be reduced and balanced against possible benefits."

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