

Intravenous Glutathione for Parkinson's Disease



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Parkinson's disease (PD) is a progressive, neurodegenerative disorder associated with a loss of dopamine neurons in the substantia nigra (SN). Although the exact cause of cell death in PD is unknown, there is evidence that oxidative stress plays a key role. Oxidative stress occurs as a result of cellular aerobic metabolism. By-products of aerobic metabolism, such as reactive oxygen species (ROS), can damage cells including neurons, and the brain may be especially sensitive to damage from free radicals. The body attempts to avoid potential adverse consequences of oxidation reactions through the use of specific protective chemical reactions and antioxidants. When the balance between normal oxidative by-products and the body's natural defenses is upset, oxidative stress occurs and tissue damage may ensue.

Glutathione is an important antioxidant. It functions as a scavenger of toxic chemicals and plays a role in multiple cellular processes. One of the earliest known biochemical changes in PD is a reduction in total glutathione levels in affected dopamine neurons. A reduction in glutathione occurs prior to impairment of mitochondrial complex I activity, dopamine loss, and cell death (Perry and Yong 1986, Sian et al 1994). Reduced glutathione levels have been demonstrated in cases of "presymptomatic PD," where incidental Lewy bodies were observed on autopsy of apparently normal individuals (Sian et al 1992). In PD patients, the extent

of glutathione reduction appears to parallel the severity of disability (Reiderer et al 1989). Moreover, it was recently demonstrated that glutathione depletion in cells *causes* a selective inhibition of mitochondrial complex I function (Hsu et al 2005) as is observed in PD. PD patients have decreased mitochondrial complex I activity in brain and peripheral tissues, and complex I inhibitors such as MPTP and rotenone cause a PD-like syndrome in humans and animals (Sherer et al 2002).

Mutations in the parkin gene are a major cause of early-onset PD. Whitworth et al (2005) recently explored the effects of glutathione function on the loss of dopamine neurons in fruit flies (*Drosophila*) with the parkin mutation. Glutathione S-transferases help glutathione neutralize a variety of substrates including reactive oxygen species. In parkin fruit flies, reduction of glutathione activity by the addition of a loss-of-function mutation in the glutathione S-transferase S1 (*GstS1*) gene increased loss of dopamine neurons. Conversely, augmentation of glutathione activity by overexpression of *GstS1* decreased dopamine neuron loss. These observations suggest that enhancing glutathione activity might provide neuroprotection by preventing or slowing loss of dopamine neurons in PD. Glutathione might also provide symptom benefit by improving mitochondrial activity and function of remaining dopamine neurons. In the rat, glutathione is transported

across the blood-brain barrier by a saturable and specific mechanism (Kannan 1990), suggesting that glutathione can enter the brain and that glutathione administration might be a plausible treatment for PD patients.

Sechi et al (1996) conducted an open label trial of intravenous (IV) glutathione. Nine patients with early PD and not taking antiparkinsonian medications received 600 mg of glutathione administered twice a day for 30 days. Patients were assessed at baseline, after one month of treatment, and monthly until observed benefit was lost. They were then treated with carbidopa/levodopa 25/250, one half tablet three times a day and again assessed after 30 days. Patients were evaluated using a modified Columbia University Rating Scale (CURS) (scoring speech, hypomimia, rest tremor, action or postural tremor of the hands, rigidity, finger taps, hand movements, pronation/supination of the hands, foot tapping, arising from a chair, posture, gait, balance, and hypokinesia).

All patients were reported to improve with glutathione therapy. There was a 42 percent improvement in modified CURS scores ($p < 0.007$). Significant improvement was noted for speech, hypomimia, rigidity, pronation/supination of the hands, foot tapping, posture, gait, balance, and hypokinesia. Once glutathione was stopped, the therapeutic effect was lost over two to four months. Carbidopa/levodopa improved modified CURS scores similarly (45 percent, $p < 0.01$). Patient Global Impression scores were significantly improved with treatment with either glutathione or carbidopa/levodopa. Safety data indicated that glutathione was well tolerated, with few side effects. Two patients



experienced transient infusion site thrombophlebitis that responded to antibiotic treatment. Sechi et al concluded that in untreated PD patients, glutathione improves symptoms and possibly retards the progression of the disease.

While the above study is interesting, it certainly is not conclusive. Because it is an open label study, some or all of the observed benefit could be due to a placebo effect. In addition, given the short time frame of the study, it seems that any actual benefit would more likely be symptomatic than neuroprotective. A longer study would be required to assess any possible effect on slowing of disease progression.

The University of South Florida Parkinson's Disease and Movement Disorders Center is currently conducting a short-term, double-blind study of intravenously

administered glutathione. Twenty patients who are inadequately controlled on their current PD medications will be enrolled and randomized equally to treatment with IV glutathione or placebo. Patients receive IV glutathione 1400 mg (or placebo) administered three times a week for four weeks. Neither the investigators nor the patients know who is receiving the glutathione. Assessments are conducted weekly for four weeks and monthly for an additional two months. The study is funded in part by The Florida Coalition to Cure Parkinson's Disease and Wellness Health Pharmacy. Results are expected in 2006. This study will evaluate the safety and tolerability of intravenous glutathione and may provide a preliminary indication of whether glutathione might provide short-term symptomatic benefit. ▲