Can Oral Glutathione Beat IV Therapy? (Report)

Townsend Letter: by Michael Ash, BSc, DO, ND, F. Dipion, and by Marty Jones, PharmD

Reduced glutathione, also known as glutathione or GSH, is found in all living systems. (1) Lowered GSH tissue levels have been observed in several disease conditions.
(2) The restoration of cell GSH levels in a number of these conditions has proved to be beneficial. Thus, strategies to boost cell glutathione levels are of marked therapeutic significance.

GSH is the smallest of the intracellular thiols (compounds that contain the functional group composed of a sulfur--hydrogen bond [-SH] and which has an unpleasant smell when mercaptans are released). Its high donating electron capacity combined with dense intracellular concentration provide significant oxidative reducing capacity. (3)

How Can You Take It and What Are Its Suggested Applications?

* Orally: for treating cataracts and glaucoma; preventing aging; treating or preventing alcoholism, asthma, cancer, heart disease (atherosclerosis and hypercholesterolemia), hepatitis, liver disease, immunosuppression (including AIDS and chronic fatigue syndrome), memory loss, Alzheimer's disease, osteoarthritis, and Parkinson's disease, autism spectrum disorders; maintaining immune function; and detoxifying metals and drugs.

* Inhaled: for treating lung diseases, including idiopathic pulmonary fibrosis, cystic fibrosis, and lung disease in individuals with HIV disease.

* Intramuscularly: for preventing toxicity of chemotherapy and for treating male infertility.

* Intravenously: for preventing anemia in patients undergoing hemodialysis, preventing renal dysfunction after coronary bypass surgery, treating Parkinson's disease, improving blood flow and decreasing clotting in individuals with atherosclerosis, treating diabetes, and preventing toxicity of chemotherapy.

GSH is regarded as a very valuable cell protector, via its direct effects on the quenching of reactive hydroxyl free radicals, other oxygen-derived free radicals, and DNA-damaging oxidative stressors and other biomolecules. (3)

GSH is the primary defender of the eye tissues and the skin against radiation-related damage, and supplies the key biochemical foundations for cytochrome P450 enzymatically derived detoxification in the liver, kidneys, lungs, intestinal epithelia, and other organs.

While it is employed by many rate-limiting biochemical steps in the body, our understanding of its role in the immune system management of cytokine driven inflammation is only just evolving.(4) This represents an area of increasing research as the role of the mucosal immune system becomes attributed to persistent para-inflammation and the degenerative conditions associated with it.

Possible Availability Problems

Oral consumption has been linked to questions about its subsequent biological availability, although many studies have strongly suggested that it can be taken up by oral ingestion using a specific uptake system.(5),(6) As such, patients seeking optimal exposure to the potential benefits linked to GSH have often used IV therapy. This is costly, inconvenient, and short-lived, making the investment lose its appeal after the first few infusions. An oral equivalent to IV would offer those patients easier application and no doubt increase compliance. Hence the development of acetyl-glutathione.

Acetyl-Glutathione

Acetyl-Glutathione is orally active, unlike plain glutathione, and is stable in the intestine and plasma when absorbed and delivered directly to the cells for natural deacetylation intracellularly. Plain glutathione delivered to the plasma by precursors, liposomal products, or intravenously must be broken down by enzymes to the basic amino acid components for absorption into the cell, and these require more energy expenditure to be reconstructed back to rGSH. It is known that disease states can block the reassimilation of components into rGSH. Therefore, it is a better dietary/ therapeutic decision to provide the orally active and absorbed acetyl-glutathione, which increases intracellular rGSH directly and naturally without increased energy expenditure and without being compromised from disease states. (7, 8)

Intracellular Energy Production

Mitochondria are the cell's fuel source and consume more molecular oxygen than other organelles within the cytosol. This creates reactive oxygen species (ROS), which generate more oxidative stress. This is a reason why mitochondria are a main target for GSH to neutralize ROS and reduce oxidative stress. Entry and replenishment of GSH into the mitochondria are a critical step in maintaining intracellular health. (9, 10)

Methods of GSH Assessment Compare IV vs. Oral

Markers of oxidative stress and inflammation are tools to measure the intracellular action of GSH. Reduction in oxidative stress markers is a measure of efficacy of GSH replenishment.

A released pilot study following 6 patients, ahead of publication due to ongoing study, used markers of oxidative stress to evaluate GSH action from two dose forms: IV glutathione and oral acetyl-glutathione over one week at a dose of 1400 mg.

The most significant marker, considered a gold standard, was F2-isoprostane, and this was significantly more reduced by oral acetyl-glutathione than with the IV glutathione. (11, 12)

* Oral S-acetyl glutathione, dosed 200 mg daily for 7 days, AM

* IV 1400 mg, single dose

* Serum and urine tested after 1 week of administration

* N = 6, (4 female, 2 male, average age 45)

* Markers chosen are measures of antioxidants

* F2-Isoprostane is the gold standard of oxidative stress markers

* Conclusion: Oral S-A GSH compares favorably to a one-time, equivalent dose of IV-administered glutathione

Comment

Many people present at clinic with indications of altered GSH capacity, and research and clinical experiences suggest that they would benefit from increased GSH availability from sources other than food.

Acetyl-glutathione provides replenishment of GSH intracellularly directly, without excess energy expenditure. The efficiency of action and ease of dosing make acetyl-glutathione an excellent choice for the gold standard of GSH replenishment: to reduce oxidative stress and inflammation of disease progression to maintain a healthy lifestyle.

Currently, the use of GSH as a therapeutic agent is limited by its unfavorable biochemical and pharmacokinetic properties. GSH has a short life in human plasma ([Less than]3 min) and difficulty in crossing cell membranes, so administration of high doses is necessary to reach a therapeutic value.(18)

Acetyl-glutathione is more lipophilic than plain glutathione, sufficiently so to be taken up intact by cells, and has been shown to rapidly raise intracellular GSH levels. (19), (20)

S-acetyl-glutathione is able to increase intracellular-SH groups as reported by Vogel et al., is more stable in blood plasma than GSH, and enters the cells directly, where it is converted to reduced glutathione by the abundant cytoplasm thioesterases. (21)

[FIGURE 1 OMITTED]

* GSH: Blood levels are lower in the A-GSH group compared with the IV group because the A-GSH is being taken up by the cell. (13) This is substantiated by the following markers:

* F2-Iso: (F2-isoprostane) measurement of redox status and oxidative stress. A greater than 4 times reduction of F2-Iso was shown with the use of the A-GSH compared with the IV-GSH.(14)

* 8-OHdG: (8-oxo-2'-deoxyguanosine) is an oxidized derivative of deoxyguanosine. 8-oxo-dG is one of the major products of DNA oxidation. Concentrations of 8-oxo-dG within a cell are a measurement of oxidative stress. A slightly lower concentration of 8-oxo-dg was found in the A-GSH group. (15)

* SOD-1: Superoxide is one of the main reactive oxygen species in the cell, and as such, superoxide dismutase (SOD) serves a key antioxidant role. Increased activity of SOD is shown in the A-GSH group. (16)

* TBARS: TBARS is a measurement of lipid peroxidation. A controversy is cited in the literature regarding the specificity of TBARS toward compounds other than MDA (malondialdehyde). MDA formation is the result of decomposition of the unstable peroxides derived from polyunsaturated fatty acids. TBARS may not be an effective marker for GSH.

* The TBAR data do not show an improvement in this marker for A-GSH compared with IV GSH. (17)

The conclusion at this stage is that an alternative to the current oral and IV options may be found in the acetylated form of glutathione, and if further analysis and clinical experiences continue to support this as a valid clinical strategy, there will be many patients very pleased to have access to such a simple strategy to enhance GSH levels where required.

[ILLUSTRATION OMITTED]

Notes

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