Oral Glutathione Equivalent to IV Therapy

Michael Ash BSc DO ND F.DipION and Marty Jones PharmD review the changing face of glutathione and explore the acetylated form as an alternative to IV glutathione therapy.

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

GSH is the smallest of the intracellular thiols (a compound that contains the functional group composed of a sulphur-hydrogen bond (-SH) hence its unpleasant smell when mercaptans are released) and its high donating electron capacity combined with dense intracellular concentration provides significant oxidative reducing capacity.[3]

How can you take it and what are its suggested applications?

- **Orally:** glutathione is used for treating cataracts, glaucoma, preventing aging, treating or preventing alcoholism, asthma, cancer, heart disease (atherosclerosis and hypercholesterolemia), hepatitis, liver disease, immunosuppression (including AIDS and Chronic Fatigue Syndrome), maintaining immune function, memory loss, Alzheimer's disease, osteoarthritis, Parkinson's disease, people with ASD and detoxifying metals and drugs.
- **Inhale**d: glutathione is used for treating lung diseases, including idiopathic pulmonary fibrosis, cystic fibrosis, and lung disease in individuals with HIV disease.
- **Intramuscularly:** glutathione is used for preventing toxicity of chemotherapy and for treating male infertility.
- **Intravenously:** glutathione is used 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, 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, [5] although many studies have strongly suggested that it can be taken up by oral ingestion using a specific uptake system. [6] 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 S-Acetyl glutathione.

S-Acetyl glutathione

S-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 de-acetylation 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 require more energy expenditure to be re-constructed back to reduced glutathione (rGSH). It is known that disease states can block the re-assimilation of components into rGSH. Therefore, it is a better dietary/therapeutic decision to provide the orally active and absorbed **S-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

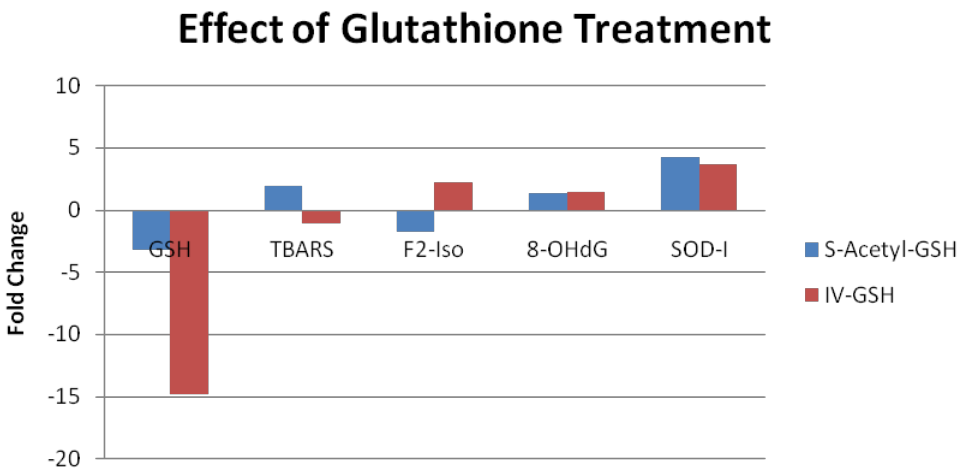
Mitochondria are the cell's fuel energy source and consume more molecular oxygen than other organelles within the cytosol. This creates Reactive Oxygen Species (ROS) which generate more oxidative stress. This is a reason why mitochondria are a main target for GSH to neutralize ROS and reduce oxidative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

Comparison of Methods of GSH assessment - 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 S-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 S-Acetyl glutathione than with the IV glutathione. [11], [12]

Study specifications:

- Oral S-Acetyl Glutathione, dosed 200mg daily for 7 days, AM
- IV 1400mg, 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



Graph comparing Oxidative Stress in S-Acetyl glutathione vs IV glutathione

- **GSH:** Blood levels are lower in the A-GSH group as compared to 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 to the IV-GSH.[14]
- **8-oxo-dG:** (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]
- **T-BARS:** T- Bars 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 T-BAR data does not show an improvement in this marker for A-GSH as compared to IV GSH.[17]

- **SOD-1:** Superoxide is one of the main reactive oxygen species in the cell, and, as such, SOD serves a key antioxidant role. Increase activity of superoxide dismutase (SOD) is shown in the A-GSH group.[16]
- **T-BARS:** T- Bars is a measurement of lipid peroxidation. A controversy is cited in the literature regarding the specificity of TBARS toward compounds other than MDA (malondialdehyde).

Comment

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

S-Acetyl glutathione provides replenishment of GSH intracellularly directly, without excess energy expenditure. The efficiency of action and ease of dosing make S-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 (<3 min) and difficulty in crossing cell membranes, so administration of high doses is necessary to reach a therapeutic value.[18]

S-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. ,[21] 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.

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.

References

[1] Sen,CK. Nutritional biochemistry of cellular glutathione. Nutri Biochem, vol 8, 12 660-672. 1997.View Abstract

[2] Gul M, Kutay FZ, Temocin S, Hanninen O. Cellular and clinical implications of glutathione. Indian J Exp Biol. 2000 Jul;38(7):625-34 No Abstract

[3] Kidd PM. Glutathione: Systemic protectant against oxidative and free radical damage. Altern Med Rev 1997;1:155-176 View Full Paper

[4] Peterson JD, Herzenberg LA, Vasquez K, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):3071-6. View Abstract

[5] Witschi A, Reddy S, Stofer B, Lauterburg BH. The systemic availability of oral glutathione. Eur J Clin Pharmacol. 1992;43(6):667-9. View Abstract

[6] Hagen TM, Wierzbicka GT, Sillau AH, Bowman BB, Jones DP. Bioavailability of dietary glutathione: effect on plasma concentration. Am J Physiol. 1990 Oct;259(4 Pt 1):G524-9. View Abstract

[7] Lomaestro BM and Malone M. Glutathione in Health and Disease: Pharmacotherapeutic Issues. Annals of Pharmacotherapy 1995; 29:1263-73. View Abstract

[8] Kretzschmar M. Regulation of hepatic glutathione metabolism and its role in hepatotoxicity; Exp Toxicol Pathol. 1996 Jul;48(5):439-46. View Abstract

[9] Fernández-Checa JC, Kaplowitz N, García-Ruiz C. GSH transport in mitochondria: defense against TNF-induced oxidative stress and alcohol-induced defect; Am J Physiol. 1997 Jul;273(1 Pt 1):G7-17. View Abstract

[10] Fernández-Checa JC, García-Ruiz C, Colell A, Morales A, Marí M, Miranda M, Ardite E. Oxidative stress: role of mitochondria and protection by glutathione. Biofactors. 1998;8(1-2):7-11. Review. View Abstract

[11] Milatovic D and Aschner M. Measurement of Isoprostanes as Markers of Oxidative Stress in Neuronal Tissue. Curr. Protoc Toxicol 2009; 39:12.14 View Abstract

[12] Montuschi P, Barnes P and Roberts L. Isoprostanes: markers and mediators of oxidative stress; The FASEB Journal. 2004;18:1791-1800. View Abstract

[13] Vogel JU, Cinatl J, Dauletbaev N, Buxbaum S, Treusch G, Cinatl J Jr, Gerein V, Doerr HW. Effects of S-acetylglutathione in cell and animal model of herpes simplex virus type 1 infection. Med Microbiol Immunol. 2005 Jan;194(1-2):55-9. Epub 2003 Nov 18. View Abstract

[14] Greco A, Minghetti L, Levi G. Isoprostanes, novel markers of oxidative injury, help understanding the pathogenesis of neurodegenerative diseases. Neurochem Res. 2000 Oct;25(9-10):1357-64. Review. View Abstract

[15] de Souza-Pinto NC, Eide L, Hogue BA, Thybo T, Stevnsner T, Seeberg E, Klungland A, Bohr VA. Repair of 8-oxodeoxyguanosine lesions in mitochondrial dna depends on the oxoguanine dna glycosylase (OGG1) gene and 8-oxoguanine accumulates in the mitochondrial dna of OGG1-defective mice. Cancer Res. 2001 Jul 15;61(14):5378-81. View Abstract

[16] http://tinyurl.com/4fzcfo8

[17] Armstrong D, Browne R. The analysis of free radicals, lipid peroxides, antioxidant enzymes and compounds related to oxidative stress as applied to the clinical chemistry laboratory. Adv Exp Med Biol. 1994;366:43-58. Review No Abstract

[18] Lu, S.C. Regulation of hepatic glutathione synthesis: current concepts and controversies. FASEB J. 1999, 13, 1169–1183 View Abstract

[19] Anderson, M.E.; Powrie, F.; Puri, R.N.; Meister, A. Glutathione monoethyl ester: uptake by tissues and conversion to glutathione. Arch. Biochem. Biophys. 1985, 239, 538–548. View Abstract

[20] Anderson, M.E.; Nilsson, M.; Sims, N.R. Glutathione monoethyl ester prevents mitochondrial glutathione depletion during focal cerebral ischemia. Neurochem. Int. 2004, 44, 153–159. Molecules 2010, 15,1260 View Abstract

[21] Vogel, J.U.; Cinatl, J.; Dauletbaev, N.; Buxbaum, S.; Treusch, G.; Cinatl, J.; Gerein, V.; Doerr, H.W. Effects of S-acetylglutathione in cell and animal model of herpes simplex virus type 1 infection. Med. Microbio. Immunol. 2005, 194, 55–59. View Abstract