Glutathione
Use in cell repair and augmentation of parenteral glutathione before and after administration:

Rationale and formula developed for the BIORC – AMSA Clinics during the integrative oncology study.

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Neuro-regeneration

- Neurological cells (and all others) are incredibly sensitive to mitochondrial damage, cell membrane damage and other effects.
- Many oncologic therapies have deleterious effects on the cell matrix and nerve function, leading to significant decreases in quality of life.
- Supplementation and augmentation of glutathione (GSH) function can aid in the regeneration of all damaged neurological tissues.

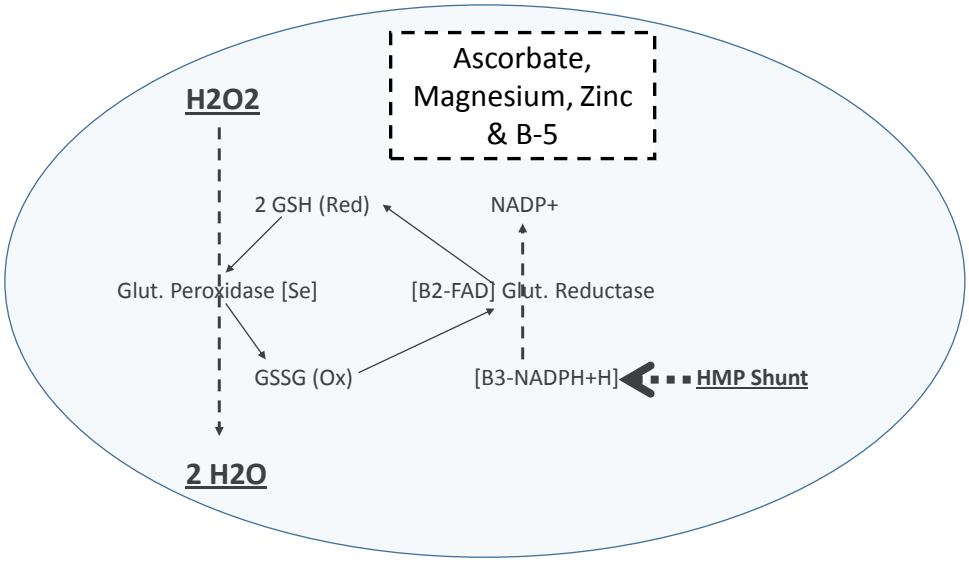
Glutathione

- Proven beneficial in pre loading doses prior to radiation.
- Studies showing further benefit post radiation treatments
- Decreases post treatment neuropathy
- Supports p53 activity through the redox modulation enhancing tumor apoptosis.

Glutathione

- Glutathione (GSH) and the augmentation of its function appear in early trials at the Bastyr Integrative Oncology Research Center and AMSA clinic to aid greatly in repair of radiation and chemotherapy induced neuropathies.
- Data are preliminary, but if general pharmacokinetic and dynamic parameters are observed GSH can be safely used in the patient with cancer.
- This presentation will look at data supporting GSH augmentation as well as the propensity for GSH depletion with standard oncologic therapies.

Glutathione and Cofactors



What does this mean?

- In most instances where glutathione is required, and particularly in those needing mitochondrial or other cell support, if one simply "pushed glutathione" they will have patient response – but it will be a diminishing effect.
- This is often seen as benefit in earlier IV's then decreased benefit as the therapy progresses – or a need for higher and higher doses of glutathione.
- Attending to the co-factors for glutathione recycling decreases the doses required for GSH as well as extends the life of the glutathione and the effectiveness of it as a therapy.

Glutathione and B-5

- Slyshenkov VS, Dymkowska D, Wojtczak L. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics.FEBS Lett. 2004 Jul 2;569(1-3):169-72. Source Nencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland. PMID: 15225628

- Wojtczak L, Slyshenkov VS.Protection by pantothenic acid against apoptosis and cell damage by oxygen free radicals--the role of glutathione. SourceNencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland. LWAC@nencki.gov.pl PMID: 12897429

Glutathione and RBC Mg

***Abstract*—**Recent evidence suggests that the endogenous antioxidant glutathione may play a protective role in cardiovascular disease. To directly investigate the role of glutathione in the regulation of glucose metabolism in hypertension, we studied the acute effects of in vivo infusions of this antioxidant (alone or in combination with insulin) on whole body glucose disposal (WBGD) using euglycemic glucose clamp and the effects on total red blood cell intracellular magnesium (RBC-Mg) in hypertensive (n520) and normotensive (n530) subjects. The relationships among WBGD, circulating reduced/oxidized glutathione (GSH/GSSG) levels, and RBC-Mg in both groups were evaluated. The in vitro effects of glutathione (100 mmol/L) on RBC free cytosolic magnesium (Mgi) were also studied. In vivo infusions of glutathione (15 mg/min3120 minutes) increased RBC-Mg in both normotensives and hypertensives (1.9960.02 to 2.1360.03 mmol/L, *P,0.01, and 1.6960.03 to 1.8160.03 mmol/L, P,0.01, respectively). In vitro GSH* but not GSSG increased Mgi (17963 to 21465 mmol/L, *P,0.01). In basal conditions, RBC-Mg values were related to* GSH/GSSG ratios (*r50.84, P,0.0001), and WBGD was directly, significantly, and independently related to both* GSH/GSSG ratios (*r50.79, P,0.0001) and RBC-Mg (r50.89, P,0.0001). This was also true when hypertensive and* control groups were analyzed separately. On multivariate analysis, basal RBC-Mg (*t56.81, P,0.001), GSH/GSSG* (*t53.67, P,0.02), and blood pressure (t52.89, P,0.05) were each independent determinants of WBGD, with RBC-Mg* explaining 31% of the variability of WBGD. **These data demonstrate a direct action of glutathione both in vivo and in vitro to enhance intracellular magnesium and a clinical linkage between cellular magnesium, GSH/GSSG ratios, and tissue glucose metabolism.**

Barbagallo M, et.al. Effects of Glutathione on Red Blood Cell Intracellular Magnesium : Relation to Glucose Metabolism. Hypertension. 1999;34:76-82. doi: 10.1161/01.HYP.34.1.76

Glutathione and Oxidative Stress

Abstract

To **evaluate the relationship between oxidative stress and glucose metabolism**, insulin sensitivity and intraerythrocytic reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio were measured in 10 non-insulin-dependent diabetes mellitus (NIDDM) patients and 10 healthy subjects before and after the intravenous administration of GSH. In particular, after baseline insulin sensitivity was assessed by a 2-hour euglycemic hyperinsulinemic clamp, either glutathione (1.35 g x m2 x min(-1)) or placebo (saline) were infused over a period of 1 hour.

In conclusion, our data support the hypothesis that abnormal intracellular GSH redox status plays an important role in reducing insulin sensitivity in NIDDM patients. Accordingly, intravenous GSH infusion significantly increased both intraerythrocytic GSH/GSSG ratio and total glucose uptake in the same patients.

De Mattia G, Bravi MC, Laurenti O, Cassone-Faldetta M, Armiento A, Ferri C, Balsano F. Influence of reduced glutathione infusion on glucose metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism. 1998 Aug;47(8):993-7. PMID: 9711998

Does GSH decrease after cancer treatment?

Conclusions:

A significant decline in GSH–glutathione disulfide, cysteine-cystine, and vitamin E status occurs after chemotherapy and BMT. Standard PN does not improve antioxidant status compared with administration of micronutrients alone.

Further evaluation of PN formulations to support patients undergoing high-dose chemotherapy and BMT are needed.

Am J Clin Nutr 2000;72:181–9.

GSH and Oxaliplatin

Purpose: We performed a randomized, doubleblind, placebo-controlled trial to assess the efficacy of glutathione (GSH) in the prevention of oxaliplatin-induced neurotoxicity.

Patients and Methods: Fifty-two patients treated with a bimonthly oxaliplatin-based regimen were randomized to receive GSH (1,500 mg/m2 over a 15- minute infusion period before oxaliplatin) or normal saline solution. Clinical neurologic evaluation and electrophysiologic investigations were performed at baseline and after four (oxaliplatin dose, 400 mg/m2), eight (oxaliplatin dose, 800 mg/m2), and 12 (oxaliplatin dose, 1,200 mg/m2) cycles of treatment.

Cascinu S, et.al. Neuroprotective Effect of Reduced Glutathione on Oxaliplatin-Based Chemotherapy in Advanced Colorectal Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Oncol 20:3478-3483.

GSH and Oxaliplatin

Conclusion: This study provides evidence that GSH is a promising drug for the prevention of oxaliplatin induced neuropathy, and that it does not reduce the clinical activity of oxaliplatin.

Cascinu S, et.al. Neuroprotective Effect of Reduced Glutathione on Oxaliplatin-Based Chemotherapy in Advanced Colorectal Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Oncol 20:3478-3483.

GSH and Oxaliplatin

Abstract

Oxaliplatin is a promising drug for cancer therapy and the oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) regimen has become the standard adjuvant treatment for colorectal cancer. However, the oxaliplatin-induced neurotoxicity still represents a clinical problem leading to a discontinuation of the therapy. Many strategies have been proposed in order to manage the neurotoxicity, but their effect on antitumoral efficacy is still unclear. In this study, we investigated the effect of reduced glutathione administration on neurotoxicity, oxaliplatin pharmacokinetics, and platinum-DNA (Pt-DNA) adduct formation in patients affected by colorectal cancer treated with FOLFOX4 adjuvant regimen.

Milla P, Airoldi M, Weber G, Drescher A, Jaehde U, Cattel L. Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. Anticancer Drugs. 2009 Jun;20(5):396-402. PMID: 19287306

GSH and Oxaliplatin

Abstract

In conclusion, this study indicates that coadministration of GSH is an effective strategy to reduce the oxaliplatin-induced neurotoxicity without impairing neither the pharmacokinetics of oxaliplatin, nor the Pt-DNA adduct formation.

Milla P, Airoldi M, Weber G, Drescher A, Jaehde U, Cattel L. Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. Anticancer Drugs. 2009 Jun;20(5):396-402. PMID: 19287306

GSH and Normal Cell Repair after Radiation

Abstract

Using a human fibroblast strain deficient in glutathione synthetase and a related proficient control strain, the role of glutathione (GSH) in repair of potentially lethal damage (PLD) has been investigated in determining survival by plating cells immediately or 24 h after irradiation. After oxic or hypoxic irradiation, both cell strains repair radiation-induced damage. However, under hypoxic conditions, the proficient cells repair PLD as well as under oxic conditions while the deficient cells repair less PLD after irradiation under hypoxic than under oxic conditions…

Midander J, Deschavanne PJ, Debieu D, Malaise EP, Revesz L. Reduced repair of potentially lethal radiation damage in glutathione synthetase-deficient human fibroblasts after X-irradiation. Int J Radiat Biol Relat Stud Phys Chem Med. 1986 Mar;49(3):403-13. PMID: 3485589

GSH and Normal Cell Repair after Radiation

The results indicate that GSH is involved in PLD repair and, in particular, in the repair of damage induced by radiation delivered under hypoxic conditions.

Midander J, Deschavanne PJ, Debieu D, Malaise EP, Revesz L. Reduced repair of potentially lethal radiation damage in glutathione synthetase-deficient human fibroblasts after X-irradiation. Int J Radiat Biol Relat Stud Phys Chem Med. 1986 Mar;49(3):403-13. PMID: 3485589

GSH levels and Radiation Protection

Abstract

Endogenous thiols, especially the tripeptide-reduced glutathione (GSH), are known to play an important role in cellular defense against radiation. However, there are evidences that suggest that GSH may not be an efficient protector of DNA. The present study will determine whether modulation of endogenous GSH levels protects or potentiates the amount of chromosomal damage induced by ionizing radiation (IR). Human lymphocytes were isolated and then treated with GSH (for 1h) or buthionine sulfoximine (BSO; GSH-depleting agent for 5 h) before X-irradiation. DNA damage was analyzed by scoring chromosome aberrations (CAs) and by comet assay. The level of endogenous GSH was measured in lymphocytes treated with GSH, BSO or X-rays. A roughly 20% increase in endogenous GSH level was observed after a 3-h treatment with exogenous GSH and this reduced the frequency of all types of CA and aberrant metaphase chromosomes induced by 1 and 2 Gy of X-rays and also decreased the tail moment as determined by comet assay, suggesting radiation protection. Such uniform protection by GSH pretreatment was not visible while cells were exposed to 3 Gy or higher. Interestingly, in GSH-depleted lymphocytes, the frequency of radiation-induced CA was increased in a non-uniform manner.

Pujari G, Berni A, Palitti F, Chatterjee A. Influence of glutathione levels on radiation-induced chromosomal DNA damage and repair in human peripheral lymphocytes. Mutat Res. 2009 Jun-Jul;677(1-2):109-10. PMID: 19386243

GSH levels and Radiation Protection

Abstract

Therefore, an increase in the level of endogenous GSH in lymphocytes was unable to reduce chromosomal damage induced by 3 Gy or above, whereas decrease in the level of GSH enhanced the frequency of CA at all radiation doses in a non-uniform manner. **It seems that GSH did not act as a radioprotector against DNA damage induced by higher dose X-rays rather it acts as a modulator of DNA repair activity.**

Pujari G, Berni A, Palitti F, Chatterjee A. Influence of glutathione levels on radiation-induced chromosomal DNA damage and repair in human peripheral lymphocytes. Mutat Res. 2009 Jun-Jul;677(1-2):109-10. PMID: 19386243

References - IV AND PLASMA GSH:

- Aebi S, Lauterburg BH. Divergent effects of intravenous GSH and cysteine on renal and hepatic GSH. Am J Physiol. 1992 Aug;263(2 Pt 2):R348-52. PMID: 1510173
- Milla P, Airoldi M, Weber G, Drescher A, Jaehde U, Cattel L. Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. Anticancer Drugs. 2009 Jun;20(5):396-402. PMID: 19287306
- De Mattia G, Bravi MC, Laurenti O, Cassone-Faldetta M, Armiento A, Ferri C, Balsano F. Influence of reduced glutathione infusion on glucose metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism. 1998 Aug;47(8):993-7. PMID: 9711998
- Robinson MK, et.al. Parenteral Glutathione Monoester Enhances Tissue Antioxidant Stores. J Parenter Enteral Nutr September 1992 vol. 16 no. 5 413-418 PMID: 1433773 doi: 10.1177/0148607192016005413
- Ortolani O, et.al. The Effect of Glutathione and N-Acetylcysteine on Lipoperoxidative Damage in Patients with Early Septic Shock. Am J Respir Crit Care Med Vol 161. pp 1907–1911, 2000
- Cascinu S, Cordella L, Del Ferro E, Fronzoni M, Catalano G. Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: A randomized double-blind placebo-controlled trial. J Clin Oncol 1995 Jan;13(1):26-32.
- LIU, H., WANG, H., SHENVI, S., HAGEN, T. M. and LIU, R.-M. (2004), Glutathione Metabolism during Aging and in Alzheimer Disease. Annals of the New York Academy of Sciences, 1019: 346–349. doi: 10.1196/annals.1297.059

References - OTHER GSH SUPPORTS:

Vitamin C and GSH augmentation:

- Johnston CS, Meyer CG, Srilakshmi JC. Vitamin C elevates red blood cell glutathione in healthy adults. Am J Clin Nutr. 1993 Jul;58(1):103-105.

Cell magnesium – GSH and reciprocal augmentation:

- Barbagallo M, et.al. Effects of Glutathione on Red Blood Cell Intracellular Magnesium Relation to Glucose Metabolism. Hypertension. 1999;34:76-82.

Glutamine and GSH augmentation:

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Pantothenic acid and GSH augmentation:

- Slyshenkov VS, Dymkowska D, Wojtczak L. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. FEBS Lett. 2004 Jul 2;569(1-3):169-72. PMID: 15225628
- Wojtczak L, Slyshenkov VS. Protection by pantothenic acid against apoptosis and cell damage by oxygen free radicals--the role of glutathione. BioFactors Volume 17, Issue 1-4, pages 61–73, 2003. PMID: 12897429

Zinc and GSH:

- Omata Y, Salvador GA, Supasai S, Keenan AH, Oteiza PI. Decreased zinc availability affects glutathione metabolism in neuronal cells and in the developing brain. Toxicol Sci. 2013 May;133(1):90-100. doi: 10.1093/toxsci/kft022. Epub 2013 Feb 1. PMID: 23377617

NOTE:

- The following formula was used in the actual trial with radiation damaged patients.

- One DOES NOT generally need as much added nutrition to support patients receiving glutathione for less damaging conditions – BUT – in our experience it is critical to pre-load the patient with the requisite cofactors in order for the glutathione to not have a "diminishing return" effect.

Augmented Glutathione (Radiation Recovery) Formula * Used in the radiation injured patients

Rx: GSH (Glutathione) Preload

	500 mL	Sterile Water for Infusion			
	5 - 50 mL	C-500 (2.5 to 25 Gram)			
	10	Calcium Gluconate (1 gram)			(May sub 3mL CaCl)
	4	Magnesium Sulfate (2 gram)			(May sub 10mL MgCl)
	5	Zinc Chloride (25 mg)			
	2	Selenium (400 mcg)			[OPTIONAL:]
	3	B-100		1 mL	Methyl B-12 (5 mg)
	2	B-5 (500mg)		1 mL	5-Methylfolate (5 mg)
	2	B-6 (100mg)			
	25	8.4% Bicarbonate Na			(Omit in central line)

FOLLOW WITH 2 - 4 GRAMS GSH IN 30 - 100 ML NS
Total Volume: 630 Ml - Osmolarity: 611 mOsm/L

Notes about the prior slide and "What is the minimum I can infuse to gain this benefit?":

- The above formula was used in the worst radiation injured patients.
- The more minimal formula which could include the Vit: C, B100, B5, Mg, Se, Zn … should be used as a base to make the GSH active and maximally useful.
  - A minimal push of 1000 mg Ascorbate, 250 mg B-5, 1 mL B-100 (complex), 500 mg magnesium, 5-10 mg zinc (mixed in an appropriate carrier solution) and a separate push or IM of 500-2000 mcg folinate and B12 (forms below) would likely be the very minimum required to get optimal GSH cycling support.
    - Of course somewhere between the "big" IV formula and the push above is a good idea too.
  - The glutathione (1-4 grams) would then be pushed after the above.
  - The active forms of B12/Folate (5-MTHF or Calcium Folinate ["folinic acid"] and Methyl B12 or Hydroxo B12) should also be in the formula unless contraindicated.

General Outcomes and Dosing:

- The above formula was successfully used in the BIORC and AMSA clinics for people following radiation therapy in an effort to speed nerve recovery.
- Observed benefits were improved tissue healing, patient reported increased energy and quality of life, and apparently faster nerve function recovery than without therapy.
- The formula **ideally is dosed** twice a week for 4 weeks, then once a week for 4-8 weeks (based on response) and then every 2-3 weeks.
- The IV formula was **always augmented by oral nutrients** (B-vitamins, carnitine, ALA or NAC, Silymarin …) between the IV's.

Additional references – GSH IV and Plasma Data

- Aebi S, Lauterburg BH. Divergent effects of intravenous GSH and cysteine on renal and hepatic GSH. Am J Physiol. 1992 Aug;263(2 Pt 2):R348-52. PMID: 1510173
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GSH Augmentation – other agents:

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