MINIMUM EFFECTIVE DOSE OF REDUCED GLUTATION ADMINISTRATED INTRAVENOUSLY (Review Article)

M.D. Rita Xóchitl Hernández Alarcón.
Specialist in Human Acupuncture and Master in Science from the National Polytechnic Institute.

SUMMARY
Glutathione is the most important antioxidant molecule in animal cells; it plays a crucial role in diverse cellular functions such as the regulation of gene expression, synthesis of DNA and cellular renewal proteins and regulation of the immune response.

Physiological aging leads to the decrease of Glutathione synthesis, so its administration is recommended as preventive, treatment and adjuvant in various diseases; despite this, there is still no established dose of reduced Glutathione administered intravenously, so we conducted a review of various publications in order to know the proposals of them.

Key words: Glutathione, dose, intravenous route, antioxidant.

INTRODUCTION
Glutathione is the most important antioxidant molecule in animal cells. Studies in animals and humans that an adequate protein nutrition is crucial to maintain a homeostasis of this molecule. GSH plays an important role in the defense against of our body's oxidants, the metabolism of nutrients and the regulation of various cellular events, including the expression of genes, the synthesis of DNA and proteins, cell proliferation and apoptosis, production of cytokines and immune response, and glutathionylation of proteins, in addition to that is essential for the regeneration of other antioxidants such as tocopherol and ascorbate, so that their deficiency contributes to oxidative stress, which in turn is involved in the aging process and pathogenesis of various diseases (Kwashiorkor, Alzheimer's, Parkinson's disease, liver disease, cystic fibrosis, sickle cell anemia, HIV infection, AIDS, cancer, myocardial infarction and diabetes). For this reason, supplementation with various antioxidants has been widely studied, as a possible preventive therapy against these disorders.
1. CHEMICAL STRUCTURE
This molecule is a soluble tripeptide formed by glutamic acid, cysteine and glycine; which is in a free form and another protein bound, the first form is integrated by the reduced thiol form and is called reduced glutathione (GSH) (Fig. 1) and the oxidized or disulfide form called oxidized glutathione (GSSG). The reduced form is the active form of the molecule, the most abundant and is located in the intercellular medium in a concentration of 0.1 to 10 Mmiii.

![Chemical structure of reduced glutathione. Group SH (active group) of the Cysteine residue (circle).](image)

2. METABOLISM AND FUNCTIONS
The sulfur of the cysteine is the one that provides the functional portion to the GSH. Cysteine is an amino acid that gives flexibility in chemical reactions thanks to the sulfur atom present as a thiol group (-SH). In GSH, cysteine is oxidized when it serves as a reducer. The thiol group is also used as a detoxifier of electrophilic chemical reagents, often catalyzed by glutathione-S-transferase.

A) DETOXIFICATION OF XENOBIOTICS
The most important function of GSH is the detoxification of these compounds and their metabolites; It is conjugated with them so that they can be excreted through urine or feces.

B) ANTIOXIDANT FUNCTION
Glutathione reductase helps to maintain GSH concentrations inside the cell so that it is used by glutathione peroxidase (GPx) to eliminate H2O2; It is also important in the recovery of vitamins C and E after participating in the elimination of free radicals that are generated, either in situ or at a distance.

C) TRANSPORT AND STORAGE OF CYSTEINE
Cysteine is rapidly oxidized to cystine producing potentially toxic free radicals, glutathione helps to eliminate these radicals and to reintegrate cysteine into the intracellular medium through the γ-glutamyl cycle.

D) REGULATION OF CELL GROWTH AND DEATH
It has been shown that for cells to pass from the G1 phase to the S phase of the cell cycle, a high amount of GSH is required within them, as opposed to the presence of GSSG, which leaves the cells in the G1 phase.
Other studies have shown that the intracellular distribution of GSH is crucial for cell proliferation, mainly the distribution between the nucleus and the cytosol. Oxidation is a necessary event in the G1 phase to stimulate mitogenic pathways that control the activity of CDKs (cyclin-dependent kinases) and initiate the phosphorylation cascade including the phosphorylation of pRB (retinoblastoma protein) in order that the cell enters phase S and activates DNA replication and cell division; therefore, the reduction of the cellular medium is required to allow the cell to progress to the G2 / Mvi phases.

3. ADMINISTRATION AND INTRAVENOUS DOSE
Several investigations have shown that GSH is absorbed poorly administered orally as a consequence of the action of glutamyl transpeptidase which is an intestinal enzyme (GGT); Multiple studies have shown that supplementation with GSH in animals is effective, has benefits in the increase of immune function, protection against the carcinogenic process, and elimination of toxic chemicals; however, in humans, oral supplementation is very controversial given the presence of GGTii. Based on the evidence previously described, several researchers have proposed the intravenous administration of GSH as an alternative and a novel therapy against various diseases, such as Saitoh et al. who studied the effect of the administration of this antioxidant intravenously as a preventive of oxidative stress in the kidney after coronary angiography, based on the fact that oxidative stress is an imminent cause in the appearance of nephropathy caused by contrast mediavii. Sae-Yong Hong et al. They sought to determine the initial and maintenance dose of GSH for patients with acute damage by reactive oxygen species (ROS), as acute paraquat poisoning (herbicide), for which they conducted an experimental study with healthy volunteers who mentioned take a regular diet, free of alcohol intake and any type of medication including vitamins, for more than 3 days before the study. The researchers observed that most of the GSH after its intravenous administration, was oxidized and disappeared from the bloodstream almost immediately with a half-life of 10 minutes; Research on its pharmacokinetics has revealed that the starting and maintenance dose to ensure 1 mM as extracellular concentration, which is the minimum required to significantly reduce the ROS of the intercellular space, is 1.69 g / kg and 5.70 g / hr / kg respectively; however, they recommend determining the dose in a more specific way with each caseviii.

In a review of the website: RMI Aesthetics, different doses are referred intravenously for different pathologies such as liver disorders,
cardiovascular, urological and neoplastic. A dose of 1.5 g / m² has shown protection against the toxicity of cisplatin in the weekly treatment of it in gastric carcinoma; and from 2500 to 5000 mg or 1500 mg / m² in ovarian carcinoma with the same effect. As mentioned above, the dose should be chosen according to the patient's state, imbalance or pathology. RMI Aesthetics breaks down a series of these conditions with the dose proposed for each case:

- Acute myocardial infarction: 67 patients were treated with 1800 mg of glutathione in bolus, followed by an infusion of 20 mg / kg / min for 24 hours, significantly improving the incidence of arrhythmias, as well as the decrease in plasma of malondialdehyde (MDA) and CPK.

- Alcoholic liver cirrhosis: the effects of high doses of glutathione (2400 mg) daily intravenously for 15 days were investigated by Bardellini et al., Finding a statistically significant decrease in total bilirubin.

- Chemoprotection in cancer: with effective doses from 1500 mg / m² to 2500 mg / m² according to the type of cancer in question.

- Chronic renal failure: the effect of the application of 1200 mg at the end of each hemodialysis session was evaluated during 120 days, the erythrocyte levels increased as well as the hematocrit and hemoglobin.

- HIV infection: an open study was carried out with 14 seropositive patients, 600 mg of glutathione was administered intranasally twice a day, resulting in the increase of glutathione in the nasal epithelium after 3 days.

**ANALYSIS**

As can be seen in the previous paragraphs, we have tried to establish effective doses of reduced glutathione administered intravenously in various conditions, recommending such dosages in various units, so we will try to unify this information.

<table>
<thead>
<tr>
<th>PATHOLOGICAL IMBALANCE</th>
<th>BOLUS</th>
<th>MAINTENANCE</th>
<th>UNIFIED DOSE (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protective effect vs ROS</td>
<td>1.69 g/kg</td>
<td></td>
<td>118 g</td>
</tr>
<tr>
<td>Protective effect vs ROS</td>
<td>5.70 g/hr/kg</td>
<td></td>
<td>399 g/hr</td>
</tr>
</tbody>
</table>

1 Unified taking into account a Mexican physiological male subject (weight 70 kg, height 1.60 m) and using the Dubois formula in m² = (weight (kg) x (size [cm]) 0.425 x 0.725 x 0.7184) / 100 to obtain the body surface.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage Description</th>
<th>Intravenous Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoprotector in gastric Ca</td>
<td>1.5 g / m2 weekly</td>
<td>1.5 g / m2 weekly</td>
</tr>
<tr>
<td>Chemoprotector in ovarian Ca</td>
<td>2500-5000 mg</td>
<td>2.5 – 5 g</td>
</tr>
<tr>
<td>Chemoprotector in ovarian Ca</td>
<td>1500 mg/m²</td>
<td>2.6 g</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1800 mg</td>
<td>1.8 g</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>20 mg / kg / min in 24 hrs</td>
<td>1.4 g / min in 24 hrs</td>
</tr>
<tr>
<td>Alcoholic liver cirrhosis</td>
<td>2400 mg / day for 15 days</td>
<td>2.4 g / day for 15 days</td>
</tr>
<tr>
<td>Chemoprotective in Ca</td>
<td>1500 – 2500 mg/m²</td>
<td>2.6 - 4.3 g</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1200 mg after each hemodialysis session</td>
<td>1200 mg after each hemodialysis session</td>
</tr>
</tbody>
</table>

Table 1. Summary of applications and intravenous doses (compilation of various studies)

**CONCLUSIONS**

Several essential functions in the cell that are carried out by glutathione have been described, and for this reason, supplementation with said antioxidant is nowadays almost essential in some diseases such as cancer, AIDS or HIV infection, diabetes, infarction, to the myocardium, Parkinson's disease and Alzheimer's, among other processes. However, given its metabolism, it is not possible to obtain an adequate bioavailability with oral administration, so its intravenous administration has been recommended. As can be seen, the recommended doses range from 1.2g to 2016g a day in a severe and acute process, there is a wide difference between one dose and another, which suggests that each patient should be assessed and dosed individually.


ix Glutathione IV, Overview; RMI Aesthetics, https://www.riordanwellness.com/services/glutathione-iv/, 22/06/2018