

Parenteral Glutathione Research Progress and Expert Opinion: An Educational Article

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Abstract

Glutathione, a tripeptide consisting of cysteine, glycine, and glutamic acid is present in high level in most human cells. The cellular concentration of glutathione is similar to that of glucose, potassium, and cholesterol. Reactive oxygen species are associated with cell damage in a variety of conditions and disorders. Therefore, they have to be scavenged by antioxidants. Reduced glutathione has been increasingly considered as the most potent intracellular antioxidant. However, low levels of reduced glutathione has been observed in a variety of clinical conditions Therefore, effectively restoring the effective intracellular level of glutathione with the use of parenteral glutathione to serves as an adjuvant therapy in a variety of conditions has been increasingly reported.

Keywords: intravenous glutathione; adjuvant therapy; expert opinion

Expert opinion

There is preliminary evidence suggesting that the neuroprotective, anti-neuro-inflammatory, and reactive oxygen species neutralizing effects of glutathione make intravenous glutathione a potentially promising medication for clinical use as an adjuvant therapy in a variety of disorders.

Dr J. de Rey-Paihade (Figure-1A) named glutathione “Philothion” (Because of its sulfur-containing amino acids), when he first isolated it in 1888 while studying yeast. Metabolism.



Figure-1A: Dr J. de Rey-Paihade (1844-1928), a French chemist from Paris

In 1929, Frederick Gowland Hopkins (Figure-1B) from England performed acid hydrolysis of glutathione, and found that it is a tripeptide consisting of glutamate, cysteine, and glycine. Charles Robert Harington and Thomas

Hobson Mead were most probably the first to describe a method of the synthesis glutathione in 1935. Manufacturing of glutathione for commercial purposes began during the 1950s [1, 2].

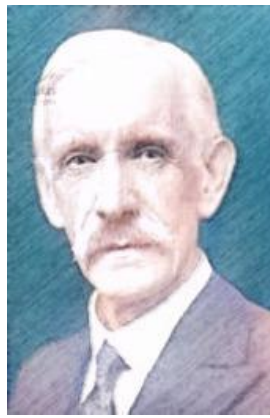


Figure-1B: Frederick Gowland Hopkins (June 1861-May 1947), an English biochemist

During the previous two decades, glutathione has been increasingly recognized as the most important antioxidant in human cells. Glutathione deficiency has been increasingly recognized as an important factor in oxidative stress which is a key contributor to the aging process and the development of a variety of clinical disorders including Parkinson disease, liver diseases, and malignancy and other conditions [3-5]. However as early as 1992, Witschi et al from Switzerland emphasized that oral glutathione is hydrolyzed by intestinal and hepatic gamma-glutamyl transferase. Therefore, oral glutathione is not an important factor in determination of circulating glutathione level. They reported a study which included seven healthy volunteers and showed that a single 3 grams dose of oral glutathione didn't increase circulating glutathione to a clinically beneficial therapeutic level in blood [6].

In 1992, Coppola et al from Italy reported a placebo-controlled study which included two groups, each of ten patients with clinical manifestations of atherosclerosis. Glutathione intravenous infusion, 600 mg daily for one week was associated a marked increase in blood filtration and a marked decrease in blood viscosity and platelet aggregation [7].

Also in 1992, Ortolani et al from Italy emphasized that the high production of oxygen radicals is associated with stressful conditions anoxia and can worsen the conditions of critical patients. The high production of oxygen radicals can be lowered by antioxidants such glutathione. They reported a placebo-controlled study which included 80 patients; 40 patients received a continuous infusion of 70 mg/Kg daily of glutathione. The control group included 40 patients who did not receive glutathione. The study showed a significant effect of intravenous glutathione on the parameters of free radical's hyper-production suggesting that glutathione reduced the production of free radicals [8].

Also in 1995, Cascina et al from Italy reported a placebo-controlled study which included 50 patients who had advanced stomach cancer treated with a weekly cisplatin regimen. Patients received glutathione 1500 mg per square meter in normal saline (100 mL) over 15 minutes just before receiving cisplatin. Glutathione 600 mg was also given intramuscularly on days 2 to 5. Control patients received normal saline solution only [9].

At 9th week, no patients received glutathione therapy developed clinically obvious neuropathy. However, 16 control patients developed clinically obvious neuropathy. After 15 weeks, 4 of 24 patients who received glutathione therapy developed neurotoxicity, 16 of 18 control patients developed neurotoxicity ($P = 0001$). Neuro-physiological studies of median, ulnar, and sural sensory nerve conduction confirmed significant neuroprotective effect of glutathione therapy. Therefore, this study suggested that glutathione therapy can help in preventing of cisplatin-induced neuropathy. In 1996, Sechi from Italy emphasized the available evidence

suggesting that reduced glutathione deficiency in the nigra of Parkinson disease patients is correlated with the severity of the condition. They reported the use of intravenous glutathione (600 mg two times daily) for one month in the treatment of nine patients with early, untreated Parkinson disease. Thereafter, intravenous glutathione discontinued. After that, the patients

were treated with carbidopa-levodopa. Intravenous glutathione was associated with marked improvement in all patients, and resulted in a 42% reduction in disability [10].

In 2002, Enrico Arosio from Italy and his research group reported a placebo-controlled study which included 40 patients with peripheral arterial disease. Twenty patients received intravenous glutathione two times daily, and 20 patients received placebo (Saline solution) two times daily for five days. Intravenous glutathione treatment was associated with increased in pain-free walking distance ($P < .04$), increased macro-circulatory flow following treadmill test with plethysmography ($P < .002$), and increased post-ischemic hyperemia with laser Doppler flowmetry. Therefore, suggested that intravenous glutathione can be beneficial in peripheral arterial disease by prolonging pain-free walking distance and improving macro- and micro-circulation parameters [11].

In 2004, Bu-Dong Zhu from China and his research group reported a study which included 62 patients with cancer receiving chemotherapy. The patients were divided into two groups. The first group received chemotherapy plus intravenous infusion of reduced glutathione at the dose 1500 mg / square meter daily (Over 15 minutes) for one week. Thereafter, patients in this group received chemotherapy for three to four weeks.

Chemotherapy was associated with marked reduction in serum malondialdehyde level. Glutathione therapy helped in restoring serum malondialdehyde level suggesting that in can prevent lipid peroxidation and depletion of antioxidants by chemotherapy [12].

In 2005, Zhong-wei Huang from China and his research group reported a study which included forty-five patients with acute pancreatitis receiving the same treatments. 22 patients received intravenous reduced glutathione 1200 mg daily for one week, and 23 patients didn't receive intravenous reduced glutathione (Controls).

All patients experienced marked reduction of TNF-alpha and IL-6 levels ($P < .05$) after treatment. However, glutathione therapy was associated with much more reduction in TNF-alpha and IL-6 levels ($P < .05$). Glutathione therapy was also associated with much more reduction in plasma alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen, lactate dehydrogenase, creatine kinase, and MB isoenzyme of creatine kinase ($P < .05$). Therefore, this study suggested that intravenous reduced glutathione can help in maintaining visceral organ functions in acute pancreatitis [13].

2009, Robert A Hauser from the United States and his research group reported a placebo-controlled study which included 20 patients Parkinson disease who had unsatisfactory response to current medications. 10 patients received glutathione 1400 mg intravenous 3 times weekly for one month, and ten patients received placebo. Patients tolerated glutathione well and it was associated with mild symptomatic effect [12].

In 2020, Bjørklund from Norway and his international research team reviewed the literature and emphasized that glutathione has an important role in neuro-immune and neuro-oxidative processes, and also has

neuroprotective, anti-neuro-inflammatory, and reactive oxygen species neutralizing effects. Therefore, glutathione has the potential to have a beneficial therapeutic efficacy in Parkinson disease [15].

Expert opinion There is preliminary evidence suggesting that the neuroprotective, anti-neuro-inflammatory, and reactive oxygen species neutralizing effects of glutathione make intravenous glutathione a potentially promising medication for clinical use as an adjuvant therapy in a variety of disorders.

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The author has the copyrights of the sketches in this paper.

Conflict of interest: None.

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