Alpha-Lipoic Acid (Thioctic Acid): My Experience With This Outstanding Therapeutic Agent

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I first became interested in alpha-lipoic acid (thioctic acid, ALA) in 1977, while I was an internal medicine resident in a Cleveland, Ohio, hospital. One October weekend, Mr. D, a patient suffering from acute hepatic necrosis, as a result of eating hepatotoxic mushrooms, was transferred to my care. The department Chief said that I was to observe the patient as a routine learning experience and I was advised that Mr. D. would probably die very soon. The Chief added that there was nothing that I could do but support him in the intensive care unit and watch.

Mr. D. was the sickest person I had ever seen. His laboratory values were several times normal and he had projectile vomiting and propulsive cholera-type diarrhea. Due to severe nausea, he could not find a comfortable position. He was miserable.

Normally, acute hepatic necrosis as a result of mushroom poisoning involves four stages. The person eats part or all of a poisonous mushroom and usually describes it as very tasty. Within 12 hours an acute and severe gastroenteritis sets in and the patient becomes dehydrated and electrolyte depleted. The third stage is an apparent recovery phase in which the patient is often released from the hospital in a weakened state. The weakness increases and within a few days, the patient falls into a coma, the fourth stage, and usually dies. I did not want this to happen to Mr. D. As a result of my Ph.D. education and my basic stubbornness, I did not accept the prognostications of the chief and began a search for a treatment that would reverse Mr. D's condition.

Fortunately, I had remembered reading an article about a European drug that had been successful in the treatment of severe liver damage while I was a mycology professor at Rutgers University. The drug, ALA, was stocked at NIH by Fred Bartter, MD who was chief of endocrin-ology. I called Dr. Bartter and he promptly shipped the ALA to me.

Thirty hours after Mr. D. had eaten the mushroom, the intravenous ALA was started. Within an hour, the patient said that he was feeling better. To everyone's surprise, the patient continued to improve rapidly and was soon discharged from the hospital feeling fine and with almost normal laboratory values. The hospital chiefs told me that the patient's recovery was an abnormality and not associated with the ALA therapy. They did not appear to be comfortable with the revival of the patient.

The following weekend, a young couple was admitted to the hospital after eating hepatotoxic mushrooms. Once again, these patients were assigned to me. I was ordered not to call NIH for more lipoic acid and to just support them medically with electrolytes and intravenous fluids. Both of the patients were deathly ill and suffered from the same symptoms as Mr. D. Their ALT and ASTs were in the hundreds of mμ/ml (showing signs of severe liver damage). I ignored the orders of the medical authorities and requested more ALA. Soon after the ALA was started, the couple showed an almost immediate improvement and within a short time they were feeling well with almost normal liver function.

Due to the amazing recoveries, NIH sent a team to Cleveland to examine my patients. I was delighted. I met Dr. Bartter and we started a long friendship and collaborative research arrangement. I was eventually awarded the FDA investigational drug permit for intravenous ALA. I thought

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the hospital chiefs would be happy with what was taking place, but they were not. Since that time I've treated over a hundred patients with intravenous or oral ALA. In most cases, I have witnessed the same amazing results.

Alpha Lipoic Acid: The Molecule

ALA is a relatively small molecule with both hydrophilic and lipophilic characteristics and a disulfide bond. It is a superb antioxidant and is an important coenzyme for the production of acetyl coenzyme Alpha dihydrolipoic acid (DHLA) is the reduced form of ALA and serves as an electron donor that recycles other important antioxidants. For example, vitamin C is directly recycled by DHLA and in turn vitamin E is recycled by vitamin C. Glutathione also appears to be recycled by DHLA.[1] In addition, both ALA and DHLA have been reported to inactivate several harmful cellular products of metabolism such as peroxyl radicals,[2] hydroxyl radicals[3] and singlet oxygen.[4]

Furthermore, lipoic acid has been reported to have metal chelating activity. Gregus, et al., demonstrated ALA's chelating activity could be used to promote the excretion of mercury by the gall bladder[5] and Jayanthi, et al., reported that ALA can prevent calcium oxalate crystals from forming in rat renal tissue.[6] In 1995, Ou, et al., described the chelation of copper by ALA[7] and veterinarians have known of ALA's use in the treatment of arsenic poisoning for many years.[8]

Recently there has been an explosion in disease-related ALA research. The drug has been shown to inhibit HIV replication in cultured T cells,[9] prevent cataracts of the lens,[10] protect the kidney from aminoglycoside damage,[11] protect islet cells in the pancreas from inflammatory attack,[12] inhibit thymocyte apoptosis[13] and increase helper T cells in the blood.[14] Burger, et al. reported that the toxic side effects of vincristine chemotherapy could be reduced with the use of ALA[15] and Ramakrishnan, et al. showed that ALA could protect hematopoietic tissue from free-radical damage due to ionizing radiation.[16]

Numerous other studies have suggested that ALA may be useful for the treatment of diabetes mellitus. Haugaard, et al. demonstrated that ALA stimulated increased glucose utilization in rat muscle cells[17] and Jacob, et al. reported that in humans, intravenous ALA significantly reduced insulin resistance.[18] Estrada, et al., explained the increased glucose utilization by the fact that ALA stimulates glucose transport via the insulin signaling pathway.[19]

Neuropathies, a common complication of diabetes mellitus, results from a decrease in blood flow to various organs. The actual neuropathic pain is caused by increased oxidative stress and a resultant impairment of nerve function. Ziegler, et al. demonstrated that over a 3 week period intravenous ALA produced a significant reduction of neuropathic symptoms in 23 patients.[20] Nagamatsu, et al. suggested that ALA administration accomplishes this by rendering harmless the products of lipid peroxidation and by enhancing the entrance of glucose into the cell.[21]

As a result of ALA's lipophilic characteristics it can cross the blood-brain barrier quite easily and plays an important role in several neural metabolic processes. A number of authors have reported that ALA and DHLA protected animals from neuronal death following laboratory-induced cerebral ischemia and reperfusion experiments.[22-24] Nagamatsu explained that this protective effect was due to an ALA-induced rise in neuronal glutathione levels which protected the nerve cells from the harmful products of oxidation.

In Europe, ALA is often used as a treatment for all types of liver disease. However, as of yet, there is not a great amount of scientific research on this subject and some studies have not produced positive results. In the case of Marshall, et al., ALA

was not able to improve the course of the disease in 20 cirrhotic patients who did not stop drinking, but Marshall administered only 300 mg per day (very low doses) of oral ALA.[25] In contrast to Marshall's results, Loginov, et al., reported that ALA stimulated ATP production, enhanced hepatic regeneration and activated hepatic detoxification in 125 patients with chronic alcoholic and viral disease.[26]

Representative Alpha Lipoic Acid Case Histories

I have administered ALA, both oral and intravenously, to many patients, for several disease conditions, over the last twenty years. Three representative case studies are presented here.

1.Hepatitis C: Mrs. L. is a 36 year old woman who received a blood transfusion following the delivery of a normal female baby approximately three years ago. Several weeks after the transfusion, she developed a general malaise with myalgias and jaundice. She was easily fatigued and felt nauseated most of the time. Subsequent to a medical exam and blood work, she was diagnosed as suffering from hepatitis C. During the course of the disease the patient suffered pancreatic damage with resultant diabetes mellitus. These conditions were thought to be the result of multi-organ viral infection. The condition worsened and eventually a liver biopsy was performed and demonstrated acute and chronic hepatitis C with early cirrhosis. The patient's gastroenterologist discussed interferon therapy and a possible liver transplant. The patient decided to try a alternative approach to this disease prior to any more complicated treatment.

When first examined in my office, Mrs L's liver transaminases were elevated (AST was 168, ALT was 202) and she had a fasting blood sugar of 268. Her liver was tender and enlarged four finger breaths below the right costal margin and she was easily fatigued. For her diabetes, I prescribed 500mg of metforman twice a day and a low sugar and low calorie diet that was rich in vegetables. At the same time she was also started on 200mg of oral ALA three times a day, 300mg of silymarin three times a day, and 500 mg of pantothenic acid three times a day. Furthermore, an excellent multivitamin with B complex was started to supply the necessary thiamine as another coenzyme to the pyruvate dehydrogenase system.

The patient's disposition started to improve by the second week and she reported a great increase in energy. Mrs. L. started back to college and by the eighth week, her fasting blood sugar had dropped to normal (112) and her liver transaminases continued to slowly fall (AST=122 and ALT=154). I am convinced that if Mrs. L. stays on her nutritional regimen, her healthy diet and practices stress management that she will continue to improve medically.

1.Diabetic Neuropathy: Mr. M, a 55 year old male, presented to my office two years ago with a fasting blood sugar of 203. He complained of burning and painful feet and paresthesias of his toes. He said that he had purchased several different types of shoes and shoe footpads, nevertheless his foot pain continued to increase. The diabetic neuropathy pain was not only interfering with Mr. M's recreational activities, but also conflicting with his daily life and business operations.

Mr. M was put on a 2000 calorie ADA diet, a hypoglycemic agent (Glyburide 10mg twice a day), a good multivitamin and 600mg of oral ALA a day. Within five weeks the foot pain and toe paresthesias were gone and Mr. M was able to resume all of his normal daily activities without any discomfort. Mr. M has continued his ALA oral therapy and healthy lifestyle regimen and has been feeling healthy and free of neuropathies for two years. His most recent fasting blood sugar was 104.

Acute Hepatic Necrosis. Mr. P consumed several large Amanita mushrooms two days prior to his presentation at the

first hospital emergency room. His symptoms were described as severe cramping with propulsive vomiting and diarrhea. He was treated with intravenous fluids, electrolytes, and an antiemetic and discharged. Twenty-four hours later, when his symptoms did not abate, he went to another hospital emergency room. Mr. P was hypotensive on presentation and was resuscitated with intravenous fluids and electrolytes. His liver function was gravely abnormal (ALT=3,125 mμ/ml) and his kidney function was poor. He was one of the majority of Amanita mushroom poisoning patients who develop acute hepatic necrosis.

Acute hepatic necrosis (massive and acute liver destruction) is a condition that may be caused by several agents such as carbon tetrachloride, fungal toxins or a large dose of an over-the-counter drug such as acetaminophen. The degree of liver damage that these poisons generate have been shown to be directly proportional to the quantity of the toxin and the period of time that the liver is exposed to the toxin. In time, if the person survives, fibrous tissue replaces the necrotic areas of the liver and transforms these regions into non-functional scar tissue.

During the course of acute hepatic necrosis, the injured liver cells release large amounts of transaminases (ALT and AST) and these laboratory values are indicative of the severity of the hepatic damage. Mr. P was admitted to the hospital and intravenous ALA was not started until his ALT was over 5,000 mμ/ml. By the third day of lipoic acid treatment, his ALT had dropped 1,500 mμ/ml and he said he was feeling much better. On the sixth post-therapy day Mr. P.s ALT was measured at 437mμ/ml and he was discharged from the hospital eighteen days later feeling normal, but weak, with an ALT of 79 mu/ml. A follow-up series of laboratory tests, one month following mushroom ingestion showed a normal ALT. Mr. P was just one example of over a hundred mushroom poisoning patients with acute hepatic necrosis who were successfully treated with intravenous ALA.

The Past and Future of Alpha Lipoic Acid

In 1980, Dr. Bartter and I published two papers describing our successes with ALA for acute hepatic necrosis using the NIH protocol.[27,28] We expected a certain amount of interest in this remarkable new type of therapy, but we were disappointed in the lack of attention from the medical community. After Dr. Bartter's death in 1985, I continued to study ALA as a therapeutic agent.

Today, in addition to my clinical practice, I am involved with a research program on the cellular effects of ALA in primates and I know of at least one well-respected medical center in the United States that is conducting a ALA research program on the treatment of diabetic neuropathies. I remain optimistic about the future of ALA and its ability to replace expensive and complicated treatments with a economical and more sensible method of treating several serious disease conditions.

References

1. Busse E, Zimmer G, et al: Influence of alpha-lipoic acid on intracellular glutathione in vitro and in vivo. *Arzneim-Forsch/Drug Res,* 1992; 42: 829-831.
2. Scott, B., Aruoma, O. et al. 1994. Lipoic acid and dihydrolipoic acid as antioxidants: A critical evaluation. *Free Rad. Res,* 1994; 20: 119-133.
3. Suzuki Y, Tsuchiya M, Packer, L: Thioctic acid and dihydrolipoic acid are novel antioxidants which interact with reactive oxygen species. *Free Rad Res Commun,* 1991; 15: 225-263.
4. Stary F, Jindal S, et al: Oxidation of alpha-lipoic acid. *J Organic Chem,* 1975; 40: 58-62.
5. Gregus Z, Stein A, et al: Effects of lipoic acid on biliary excretion of glutathione and metals. *Toxicol Appl. Pharmacol.* 1992; 114: 88-96.
6. Jayanthi S, et al: Effects of DL alpha-lipoic acid in glyoxylate-induced acute lithiasis. *Pharmacol Res,* 1975; 30: 281-288.
7. Ou P, Tritschler H, et al: Thioctic (lipoic) acid: a therapeutic metal-chelating antioxidant? *Biochem Pharmacol,* 1995; 50: 123-126.
8. Grunnert R: The effect of DL-alpha lipoic acid on heavy metal intoxication in mice and dogs. *Arch Biochem Biophys*, 1960; 86: 190-195.

9. Bauer A, Harrer T, et al: Alpha lipoic acid is an effective inhibitor of human immunodeficiency virus replication. *Klin Wochenzchr,* 1991; 69: 722-724.
10. Maitra I, Serbinova E, et al: Alpha lipoic acid prevents butathione sulfoximine-induced cataract formation in newborn rats. *Free Rad Biol Med,* 1995; 18: 823-829.
11. Sandhya P, et al: Role of DL alpha-lipoic acid in gentamycin-induced nephrotoxicity. *Mol Cell Biochem* (Netherlands) 1995; 145: 11-17.
12. Burkhart V, Koike T, et al: Dihydrolipoic acid protects pancreatic islet cells from inflammatory attack. *Agents and Actions,* 1993; 38: 60-65.
13. Bustamante J, Slater A. et al: Antioxidant inhibition of thymocyte apoptosis by dihydrolipoic acid. *Free Rad Biol Med,* 1995; 19: 339-349.
14. Fuchs J, Schofer H, et al: Studies on lipoate effects on blood redox state in human immunodificiency virus infected patients. *Arzneimittel-Forschung,* 1995; 431: 359-1362.
15. Berger V, et al: Influence of thioctic acid on the chemotherapeutic efficacy of cyclophosphamide and vincristine sulfate. *Arzneim Forsch,* 1983; 33: 1286-1288.
16. Ramakrishnan N, Wolfe N, Catravas G: Radioprotection of hematopoietic tissues in mice by lipoic acid. Radiation Research, 1992; 130: 360-365.
17. Haugaard N, Haugaard E, et al: Stimulation of glucose utilization by thioctic acid in rat diaphragm incubated in vitro. *Biochem Biophys Acta,* 1970; 222: 583-586.
18. Jacob S, Henriksen E, et al: Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. *Arzneim-forschung/ Drug Research,* 1995; 45: 872-874.
19. Estrada D, Ewart H, et al: Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid /thioctic acid *Diabetes,* 1996; 45: 1798-1804.
20. Ziegler D, Mayer P, et al: Effekte einer Therapie mit alpha-liponsaure gegenuber vitamin B1 bei der diabetischen. *Neuropathie Diab Stoffw,* 1993; 2: 443-448.
21. Nagamatsu M, Nickander K, et al: Lipoic acid improves nerve blood flow, reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy. *Diabetes Care,* 1995; 18: 1160-1167.
22. Greenamyre JT, Garcia-Osuna M, Greene J: The endogenous cofactors, thioctic acid and dihydrolipoic acid are neuroprotective against NMDA and malonic acid lesions of striatum. Neuroscience Letters, 1994; 171: 17-20.
23. Cao X, et al: The free radical scavenger alpha-lipoic acid. Protects against cerebral ischemia-reperfusion injury in gerbils. *Free Radical Research,* 1994: (Switzerland) 23: 365-370.
24. Prehn J, Karkoutly C, et al: Dihydrolipoic acid reduces neuronal injury after cerebral ischemia. *J Cereb Blood Flow Metab,* 1992; 12: 78-87.
25. Marshall E, Graul R, et al: Treatment of alcohol related liver disease with thioctic acid. *Gut,* 1982; 23: 1088-1093.
26. Loginov A, Nilova T, et al:Pharmacokinetics of lipoic acid preparations and their effects on ATP synthesis, processes of microsomal and cytosole oxidation in human hepatocytes during liver damage. *Farmacol Toksikol,* 1989; 52: 78-82.
27. Bartter FC, Berkson B, et al: Thioctic acid in the treatment of poisoning with alpha-amanitin. In eds. Faulstich H, Kommerell B, Wieland, T: *Amanita Toxins and Poisonings,* Witzstrock, Baden Baden, 1980. 197-202.
28. Berkson B: Treatment of four patients with thioctic acid. In eds. Faulstich H, Kommerell B, Wieland, T: *Amanita Toxins and Poisonings,* Witzstrock, Baden Baden, 1980. 203-207.