ALPHA LIPOIC ACID AND LIVER MITOCHONDRIA DAMAGE

ORIGINAL RESEARCH

Adverse Effects of High Doses of Intravenous Alpha Lipoic Acid on Liver Mitochondria

静脉注射高剂量α硫辛酸对肝线粒体的不良影响

Efectos adversos de altas dosis de alfa-ácido lipoico intravenoso en las mitocondrias hepáticas

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ABSTRACT

Alpha lipoic acid (ALA, thiocic acid), among other actions, is an essential coenzyme in the conversion of pyruvate to acetyl co-enzyme A. Therefore, it is necessary for the production of energy for aerobic organisms. Scientists have found that it can be used medically to help regenerate liver tissue, reverse the complications of diabetes mellitus, slow or stop the growth of cancer cells, and chelate heavy metals, among other actions. In this article, the authors describe the cellular mitochondrial damage from excessively high doses of this beneficial agent.

SINOPSIS

El alfa-ácido lipoico (ALA, ácido tiocíclico), entre otras acciones, es una coenzima esencial en la conversión del piruvato en acetil coenzima A. Por lo tanto, es necesario para la producción de energía para los organismos aeróbios. Los científicos han descubierto que puede ser utilizado clínicamente para ayudar a regenerar el tejido hepático, invertir las complicaciones de la diabetes melito, ralentizar o detener el crecimiento de células cancerígenas y frenar la toxicidad de los metales pesados, entre otras acciones. En este artículo, los autores describen el daño mitocondrial celular causado por dosis excesivamente altas de este agente beneficioso.

INTRODUCTION

The mitochondrion converts nutrients into the energy-generating molecule adenosine triphosphate (ATP) in order to fuel aerobic respiration. Hepatocytes have exceptionally high energy demands, so they have particularly high numbers of mitochondria.

Any disruption of mitochondrial structure and/or function can lead to a wide assortment of medical disorders because the resulting oxidative stress interferes with the generation of ATP molecules. In this way, tissues are starved of the energy from electrons that normally result from the oxidation of food.

Alpha-lipoic acid (ALA, thiocic acid) was first characterized by Reed et al in 1951.1 ALA was found to play a most important role in the pyruvate dehydrogenase enzyme complex (PDC) in mitochondrial function. The PDC is composed of three enzymes: E1 (pyruvate dehydrogenase), E2 (dihydrolipoyl transacylase), and E3 (dihydrolipo dehydrogenase).

As one can see, because lipoic acid is such an essential cofactor in the conversion of pyruvate to acetyl coenzyme A, it is thought to be the rate-limiting factor for the production of energy in the eukaryotic cell. The PDC cannot operate without ALA, and all aerobic organisms would die without it. In addition, ALA is essential for several other metabolic reactions including thyroid function,2 glycine cleavage,3 and the tricarboxylic acid cycle,4 among others. Many of these reactions occur within the mitochondrion.

Bartter et al and Berkson reported in three articles, in the first large-scale human clinical study out of the National Institutes of Health (NIH), that 75 of 79 patients survived severe acute hepatic necrosis as a result of hepatotoxic mushroom poisoning on just intravenous ALA.5,7 Those articles described the original NIH protocol. The source of the intravenous ALA in the study by Bartter et al was Italian prescription-grade thiocic acid (Merrill Richardson ALA, Merrill Richardson Pharmaceuticals, Milan, Italy). In addition, encouraging results were published using oral and intravenous ALA as a component of a treatment regimen for hepatitis C,8 various cancers,9,13 and the reversal of diabetic neuropathies.14,15

Recently, ALA was listed in the Physicians’ Desk Reference as a nutraceutical rather than as an investigational drug, as it was originally listed, and many medical and naturopathic doctors have been administering ALA intravenously as a treatment for various disorders...
such as diabetic neuropathies, acute and chronic liver disease, autoimmune disease, blood vessel disease, and cancer.

It has come to the attention of the authors anecdotally that some clinicians have used extremely high doses of this agent or have not diluted it properly as the NIH protocol describes, which can lead to adverse reactions. If numerous physicians use ALA therapeutically for various disorders, it would be beneficial to know what dose might be toxic to humans.

Some clinicians follow the original NIH protocol of Bartter et al, and others have created their own variations. Drs Bartter and Berkson were originators of the US Food and Drug Administration (FDA) Investigation New Drug Application (9957), and Dr Berkson was the FDA principal investigator for 23 years. When administered properly, ALA should have only beneficial effects.

MATERIALS AND METHODS

In 1996, a group of researchers at Animal Research Laboratories, White Sands Missile Range, New Mexico, led by one of the authors (MV), were concerned that physicians might inadvertently administer this normally harmless agent in excess amounts to their patients. His research group was interested in determining what dose would be excessive and harmful. The source of their intravenous ALA was Sigma-Aldrich (St Louis, Missouri). The workers performed LD50 studies on six rhesus monkeys and found that approximately 90 mg/kg to 100 mg/kg of intravenous ALA was lethal to three of the six trial specimens. Consequently, the workers considered that dose to be the LD50 (median lethal dose) for primates. The details of this study will be presented in an upcoming publication.

The authors of this article do not normally administer more than 10 mg/kg—very well below any potential lethal dose—to any patient. However, even much smaller doses might elicit hypoglycemia, so physicians must be prepared to administer intravenous sugar solution or a sweet beverage. The treated primates, including the animals that died from the lethal dose and the ones that did not die, were sacrificed and subjected to postmortem examination. All animals displayed evidence of acute hepatic necrosis. Their livers were enlarged, turgid, fragile, and markedly discolored in a pale and dark red reticulated pattern. Large waxy gray infarcts were also seen.

Other organs also were affected by the lethal and sub-lethal doses of intravenous ALA. Large necrotic areas were observed in the large muscles of their thighs, the liver, the heart, and the kidneys. At a later date, lab technicians prepared sections of the damaged liver tissues for transmission electron microscopy in order to determine the cytological basis of injury. Tissues from the necrotic regions of the liver were excised and prepared according to a generally used 2% glutaraldehyde immersion fixation preparation scheme for transmission electron microscopy. The fixed tissue was embedded and sectioned and then observed by the authors.

RESULTS

Typical rhesus monkey liver tissue demonstrates normally appearing mitochondria with numerous intact cristae and other healthy membranes (Figure 1). The normal hepatocyte mitochondrion exhibits a double membrane wall with an infolding of the inner wall to form an extensive inner surface of cristae on the surface of which ATP is generated.

Mitochondria from animals that had received excessively high doses of ALA became extremely edematous and demonstrated a disruption of all of the crucial membranes (Figure 2). These mitochondria did not
exhibit the regular double membrane wall structure but showed a coalescence of these structures with a deliquescence of other structures, thus exhibiting a complete disruption of normal ultrastructure.

**DISCUSSION**

In normal doses, intravenous ALA prevents oxidative stress—induced damage to the membranous structures of the cell including the mitochondrion. Von Zglinicki et al confirmed this by showing that rat liver cells damaged by a high iron/ascorbate solution were resuscitated by the early administration of ALA. And Li CJ et al reported that myocardial apoptosis can be suppressed by ALA through the inhibition of mitochondrial oxidative stress. ALA, if administrated early, prevented this mitochondrial cardiac damage.

One plausible mechanism for ALA’s effect in enormously high doses involves the lipids in the mitochondrial membrane. When excess amounts of the reduced intravenous ALA comes in contact with diatomic oxygen, it might form superoxide anions, a damaging free radical with a negative charge. The unsaturated double bonds in lipids of the mitochondrial membranes are prime sites for reactions with superoxide radicals.

Lipid peroxidation is common in mitochondria due to this reaction. The peroxidation of the lipids destroys the mitochondrial membranes cascading the system into apoptosis. This sequence of events is well known among the biochemical consequences of reactive oxygen species (ROS).

**CONCLUSION**

In this article, we show that exceptionally high doses of intravenous ALA can produce the same symptoms that smaller doses prevent. To prove this, the Couch and Vigil group demonstrated that the LD50 dose for primates was about 90 mg to 100 mg for IV ALA.

Kotockhina et al reported that ALA inhibits pyruvate dehydrogenase kinase. This is the enzyme that disables the pyruvate dehydrogenase complex. Consequently, ALA speeds up the conversion of pyruvate to acetyl Co A.

It is our hypothesis that ALA is the rate-limiting agent in the production of energy from carbohydrate and protein in aerobic eukaryotes. With appropriate ALA levels, the mitochondrion functions normally. If the mitochondrion does not obtain sufficient ALA, it suffers and the organism lacks energy.

Conversely, if the mitochondrion is supplied with excessive amounts of ALA, it accelerates aerobic respiration and the process runs ahead of the other necessary constituents. The mitochondrion then heats up, and its membranous components break down. Severe damage to the mitochondrion is first seen by gross swelling and then severe damage to the cristae and matrix material.

It is interesting to note that therapeutic doses of intravenous ALA help a liver regenerate, but extremely high doses of the same agent cause liver necrosis. Of course, excessive and unreasonable amounts of any substance, including water and salt, given intravenously can be lethal; however, until intravenous ALA is better studied, the authors suggest that it not be used by doctors who are not completely skilled in its chemistry and its administration. In addition, even much lower doses of intravenous ALA may cause hypoglycemia in certain individuals, so the clinician must always be prepared to counter this potentially hazardous problem.

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