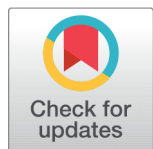


Estimation of pharmacokinetic parameters of alpha-lipoic acid in the chicks model

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Received 25-12-2021

Revised 31-03-2022

Accepted 02-04-2022

Published 02-04-2022

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DOI <https://doi.org/10.47419/bjbabs.v3i02.91>

Pages: 122-132

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ABSTRACT

Background and objective: Alpha-lipoic acid (ALA) is an organic compound with neuroprotective properties. The target of this study was to investigate the concentration of therapeutic dose of ALA in the blood plasma of broiler chicks to define the pharmacokinetic parameters.

Methods: A randomized controlled study was performed on thirty-five healthy broiler chicks of seven days old, chicks were injected into the peritoneum with a single dose of analgesic (ED₅₀) 80mg /kg b.wt., following injection of the drug, blood samples were collected at 0.25, 0.5, 1, 2, 4, 24 h (five chicks per time) from the jugular vein. Then, the blood plasma was obtained, the concentrations of ALA acid in plasma samples were estimated by using the UV-spectrometric method, and the pharmacokinetic parameters were determined by the PKSolver software. The time versus concentration curve for ALA was obtained from the software. The pharmacokinetic parameters were determined with non-compartmental models.

Results: The concentration of ALA in the blood plasma of chicks injected with ALA at a dose of 80 mg/kg were 134.6 ± 7.17 , 178.5 ± 4.10 , 192.4 ± 7.83 , 158.5 ± 11.05 , 147.1 ± 10.16 , and 122.8 ± 7.09 $\mu\text{g/ml}$ at times 0.25, 0.5, 1, 2, 4, and 24 h, respectively. The maximum plasma concentration was 192.4 $\mu\text{g/ml}$ during a period of 1 hour of injection. The terminal elimination half-life was 65 h, the terminal phase elimination rate constant was 0.011 h^{-1} , the mean residence time was 94 h, and the area under the curve from time 0 to infinity was 14960 $\mu\text{g.h/ml}$.

Conclusions: Our study suggests that the peak of the analgesic effect of ALA was one hour after treatment. In addition, it is characterized by a long elimination half-life and a poor clearance from the chick's body, which refer to longer effects of its pharmacological properties.

Keywords alpha-lipoic acid, broiler chicks, pharmacokinetic, UV spectrometric method

INTRODUCTION

Chicks model have been involved as a research model extensively during the last decade; chicks have been utilized as an animal model for pharmacology and toxicity studies.^{1,2} The

information about the pharmacokinetics of alpha-lipoic acid (ALA) in the bird is poorly studied, it is important to study all aspects of drugs and preparations in most animal models in order to develop a clear picture of the properties of the drug used. ALA is a natural product consisting of a 5-membered cyclic disulfide and a hydrocarbon tail that ends in a carboxylic acid group. ALA, as a result, is a predominantly hydrophobic particle with an amphipathic character because of the carboxylic acid group involved in the ring structure.³ It can be found in our diet, primarily in animal tissues like muscles and liver, and at low or untraceable levels in plant foods like potatoes. ALA, on the other hand, is considered desirable when used as a food additive due to its antioxidative activity, which has initially been described, and many articles have indicated its preventive properties in cases such as aging, type 2 diabetes, and neuropathy.⁴ Many studies have confirmed that ALA acid has analgesic effects for pain. It has an inhibitory effect on calcium channels type V3.2 in sensory neurons of the dorsal root ganglia of rats as well as reported that local injection of ALA reduced the sensation of heat and mechanical stimulation.^{5,6} ALA works to relieve visceral pain in rats.⁶ The analgesic mechanism was attributed to its inhibitory effects on sodium channels, blocking them, and reducing their cellular synthesis, especially sodium channels of type V1.8 located in the sensory nerves of the colon in rats with diabetes mellitus. To the best of our knowledge, there is no pharmacokinetic study of ALA in chick's model. Therefore, the aim of our study is to define the pharmacokinetic parameters of ALA in this animal model.

MATERIALS AND METHODS

Animals

Ross broiler chicks of both sexes were obtained at age of one day from a local hatchery in Nineveh, Iraq. They were housed in batches of 20-25 chicks at a temperature of 25-30°C with 24 h lighting and wood shavings as floor litter. The supply of water and feed were *ad libitum*. Experiments were conducted when the ages of the chicks were at the 8 days.

The research, which is part of a master's thesis, was approved by the Scientific Committee of the Department of the Physiology, Biochemistry and Pharmacology of the College of Veterinary Medicine at the University of Mosul. The ethical approval number UM.VET.2022.6.

Dose selection

The dose was chosen according to the determination of the median effective dose for analgesia ED₅₀. The ED₅₀ of the ALA acids was calculated by the up and down method described by Dixon (1980).⁷ Hence, the selected dose of ALA was 80 mg/kg.

Calculation of the median ED₅₀ of ALA in chicks

Determination of the median effective dose (ED_{50}) corresponds to a degree of the influence of a drug, being the dose of a drug necessary to yield 50% of that drug's maximal effect of ALA for the induction of analgesia in chicks by electrical and thermal stimulation. Chicks at 7-9 days old were used.

This method is summarized by injecting a chick with a dose of ALA and then examining the analgesic effect 15 minutes after the injection. If analgesia appears, the chick is given an X mark and if it does not happen, the chick is given the mark O, and by repeating this method up and down the dose by a fixed amount (20mg/kg) after the change in effect was occurring enabling us to calculate the median effective dose (ED_{50}) of ALA based on the table mentioned⁷ and using the following equation:

$$ED_{50} = Xf + Kd$$

Whereas;

Xf = the last dose used in the experiment. K = a tabular value extracted from the table mentioned by Dixon.⁷ d = the amount of constant increase or decrease in the administered dose.

Hot water test

This test is based on the principle of thermal stimulation, where we used a water bath device and its temperature was set at 55-56 C° by the internal thermostat of the device. The chick was grabbed gently in one hand, and his left foot was placed under the fingers, and the right foot was left free to move and dipped to before the tarsal joint. The time spent per second was measured by a stopwatch, if the chick does not respond to the thermal stimulus within 20 seconds, it is immediately raised and its right foot is placed in water at room temperature for 15 seconds to quickly reduce the leg temperature and was then saw for possible heat-induced burns.⁸

Alpha-lipoic acid in blood plasma

This experiment was conducted using 30 chicks, 8 days old, and their weights ranged between 85-110 g. A dose of 80 mg/kg of body weight was used, which is represent analgesic ED_{50} . All chicks were injected with this dose and blood samples were collected to obtain Blood plasma at times 0.25, 0.5, 1, 2 and 24 hours, with 5 chicks for each time, to measure the concentration of ALA during the mentioned times (Patni and Rawat, 2018).⁹

Blood plasma samples extraction

All chicks were injected with ALA in a single dose of 80 mg/kg Ip. Then blood samples were taken through the jugular vein from the estimated time for every five chicks 0.25, 0.5, 1, 2, 4 and 24 hours after the injection. After that, blood plasma was obtained by adding heparin to blood samples in a ratio of (10:1) by diluting it with a physiological solution. The samples were placed in a centrifuge at a speed of 3000 rpm for 15 minutes, then the blood plasma was separated and the plasma samples were then frozen at -18°C for 72 hours for the purpose of conducting the analysis after that by means of a spectrophotometer.

Preparation of phosphate-buffered solution

The phosphate-buffered solution was prepared by dissolving 6.82 g of monopotassium dihydrogen phosphate KH_2PO_4 in 250 ml of distilled water in a graduated flask. For the preparation of 0.2 molarity of KH_2PO_4 . Another graduated flask was used to prepare NaOH (0.2 M) by dissolving 2 g of NaOH in 250 ml of the distilled water. Then 195.5 ml of NaOH solution was taken and added to the previously prepared solution of KH_2PO_4 , then the volume of the solution was completed to 1000 ml by adding distilled water. The pH function was checked by means of a pH meter to reach a buffer solution with a pH of 7.4 by treating the solution with an acidic substance HCl or a base substance NaOH as needed to reach a pH 7.4.

Preparation of standard solutions

Standard solutions of ALA were prepared at concentrations of 50, 100, 200, 400 and 800 $\mu\text{g/ml}$ and diluted with the prepared buffer phosphate solution. To obtain 5 ml for each concentration, then the solution was filtered by means of a filter paper, and then the pure solution was analyzed by a spectrophotometer at a wavelength of 330 nm to extract the equation of the simple regression line attached.⁹

Extraction of alpha-lipoic acid from blood plasma samples

Alpha lipoic acid was extracted from blood plasma samples using an accurate and approved method. Briefly, we added 1 ml of the previously prepared phosphate buffer solution to 1 ml of the blood plasma sample and mix them in a glass tube. Then we putted the tube in the centrifuge at 3500 rpm for 10 minutes. Then the tube was extracted and the solution was filtered by a qualitative filter paper. After that, the solution was taken and measured by means of a spectrophotometer at a wavelength of 330 nm, and the device was calibrated by means of a buffer phosphate solution.⁹

Measuring the pharmacokinetics of alpha-lipoic acid

The pharmacokinetics were calculated and measured after identifying the concentration of ALA in the blood plasma from the previous experiment and during different times using a spectrophotometer. The pharmacokinetic parameters of ALA were calculated by using the PKSolver program and Excel.⁹ While the pharmacokinetic criteria were determined and compared with the results of the program using the following equations:

Elimination rate constant (K_{el}): It is the fixed percentage of the drug that is removed from the blood plasma per hour.

Elimination half-life ($t_{1/2\beta}$): It represents the hourly time required for the drug concentration in the blood plasma to decrease by 50%.

$$t_{1/2} = \frac{0.693}{K}$$

Volume of distribution (Vd): The volume of apparent body fluids that serves to contain the drug.

$$V_d (L/Kg) = \frac{Dose_{(mg)}}{Drug\ concentration\ at\ time\ 0\ (C_0)}$$

Total Clearance (Cl): It is represented by the efficiency of the various parts of the body in filtering and excreting the drug.

$$TCI_{(L/h/Kg)} = \frac{V_d}{K}$$

Area under plasma concentration-time curve (AUC): The drug concentration in the blood plasma over different time periods.

$$AUC_{(\mu g \times h/ml)} = \frac{Dose_{(mg)}}{TC_{(L/h/Kg)}}$$

Area under Moment Curve (AUMC): It is the concentration of the drug in the blood plasma at the moment of measurement.

$$AUMC_{(\mu g \cdot h^2/ml)} = V_d \times \frac{(AUC)^2}{dose_{(mg)}}$$

Mean Residence Time (MRT): It is the expected period for the survival of ALA in the blood plasma.

$$MRT_{(h)} = \frac{AUMC}{AUC}$$

Time Maximum (T_{max}): It is the time during which the drug concentration in the blood plasma reaches its highest level.

Concentration Maximum (C_{max}) ($\mu\text{g/ml}$): It represents the highest concentration of the drug in the blood plasma during a certain time.

RESULTS

Median effective dose (ED_{50}) for analgesia of ALA

The median effective analgesic (ED_{50}) values of ALA in the chicks by hot water test was 77.6 mg/kg IP (Table 1).

Table 1 Median effective dose (ED_{50}) of ALA injected IP for generation of analgesia in chicks by using thermal stimulation.

Parameters	Outcome
ED_{50} (mg/kg)	77.6
Average of the doses used (mg/kg)	100-60 =40
Initial dose (mg/kg)	100
Last dose (mg/kg)	60
Increase or decrease in the dose (mg/kg)	20
Number of chicks involved	5 (XOXXO)
Dose sequence	100-80-100-80-60
Equation application: $ED_{50} = Xf + Kd$	$60 + (0.878 \times 20) = 77.6$
Heat temperature of water bath	55-56°C
Sings of nociception	Foot withdrawal

The time needed to foot withdrawal from water bath before and after 15 min of alpha-lipoic acid injection was calculated. The ED_{50} was calculated by the up-and-down method.

X: positive reaction of analgesia; O: negative reaction of analgesia.

Plasma concentration of alpha-lipoic acid

The administration of ALA at 80 mg/kg of body weight intraperitoneally led to its appearance in the blood plasma of chicks with concentrations: 134.5, 178.6, 192.4, 158.5, 147.1 and 122.8 micrograms/ml at times 0.25, 0.5, 1, 2, 4 and 24 hours, respectively, and the concentration of ALA was high at times half and an hour after injection and then decreased to reach its lowest concentration after 24 hours of administration (Figure 1).

Alpha-lipoic acid pharmacokinetics in plasma

The pharmacokinetic parameters of ALA in the blood plasma of injected chicks at a dose of 80 mg/kg are represented by the area under the curve was 14960.7 $\mu\text{g/ml} \cdot \text{h}$ and Area under the instantaneous curve was 1417579.6 $\mu\text{g h}^2/\text{ml}$, and the mean residence time

was 94.8 hours. Elimination rate constant was 0.0106 h⁻¹, the volume of distribution was 0.507 L/kg, the total clearance was 0.0054 L/hr/kg, the half-life was 65.7, the time maximum was 1 hour, and the maximum concentration was 192.4 µg/ml (Table 2).

Table 2 Pharmacokinetic parameters of alpha-lipoic acid.

Parameter	Unit	Value
K_{el}	1/h	0.010557143
$t_{1/2\beta}$	h	65.65670168
T_{max}	h	1
C_{max}	µg/ml	192.4
AUC	µg.h/m	14960.67252
AUMC	µg.h ² /ml	1417579.626
MRT	h	94.75373675
Vd	L/kg	0.506515186
Cl	ml/kg/h	0.005347353

K_{el} : elimination rate constant, $t_{1/2\beta}$: half-life elimination, T_{max} : maximum time, C_{max} : maximum concentration, AUC: area under curve, AUMC: area under moment curve, MRT: mean residence time, V_d : volume of distribution, Cl: clearance.

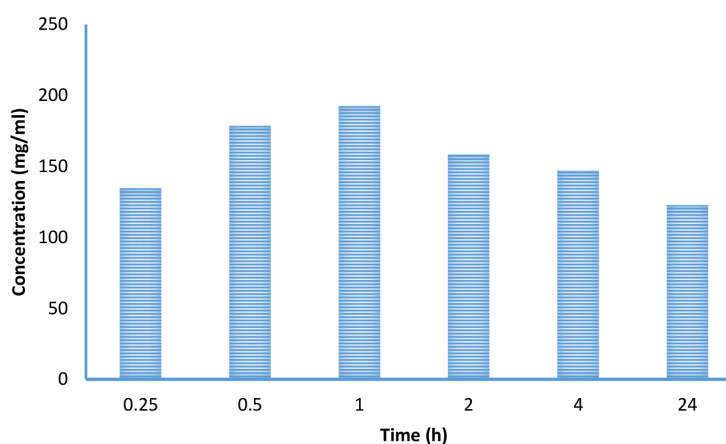


Figure 1 The concentration of the alpha-lipoic acid with time

DISCUSSION

The ALA is a reliable antioxidant agent used in oxidative stress-related clinical conditions such as diabetes mellitus, neuropathy, neurodegenerative disease, and cardiovascular disorder, obesity vertigo, and others.¹⁰⁻¹⁵

Our study determines the pharmacokinetic parameters of the intraperitoneal dose ALA at 80mg/kg b.wt. in broiler chicks. Our findings are in agreement with studies carried out on rats and humans.^{16,17}

When ALA is given orally or intravenously, it is metabolized in the body after absorption from the stomach and small intestine and spreads to the liver through the portal circulation and to the rest of the body through the systemic circulation.¹⁸ ALA is soluble in water, hydrophilic and lipophilic,¹⁹ so it can cross the blood-brain barrier and can exist both inside and outside the cell and inside mitochondria. The half-life in plasma is about 30 minutes after oral dosing in dogs,²⁰ and the LD50 was about 400-500 mg/kg body weight. Gastrointestinal absorption is variable and decreases with food so it is recommended that ALA be taken 30-60 minutes before or at least 120 minutes after the meal. ALA reaches its maximum levels in the blood plasma 30-60 minutes after ingestion and is believed to be metabolized in the liver. It is recommended to take ALA on an empty stomach in order to take advantage of the acidic environment of the stomach, which is necessary to enhance gastric absorption of a weak acid such as ALA and to reduce competition with nutrients. Others during intestinal absorption.^{13,21} Despite this and the progress that has been made with different solid pharmaceutical formulations (tablets, coated granules, delayed-release, and rapid release),^{22,23} increasing plasma concentration and stabilizing ALA remains an objective. It must be achieved. Studies accumulated over the past years have confirmed the fact that ALA is poorly soluble in an aqueous and acidic environment such as that of the stomach. This affects the concentration available for absorption, and thus represents an important concomitant cause of low bioavailability after oral administration. Moreover, the first section of the intestine is involved in the absorption of the remainder of ALA through specific carrier proteins.²⁰ ALA is absorbed in low concentrations by active transport and mediated by carriers, and certainly in competition with short-chain fatty acids, but if it is present in high concentrations, it is absorbed by diffusion.²⁴

A pharmacokinetic study conducted in humans showed that the salt-bound form of ALA, which is sodium ALA, has a pharmacokinetic difference from that of the free form of ALA with freeform.²⁵

A study conducted on rats to measure the kinetic parameters of ALA using subcutaneous injections at doses of 20, 50, and 100 mg/kg body weight revealed the following kinetic parameters: the maximum plasma C_{max} and AUC were 3.8 and 443.1 µg/ml for the group The first and 9.9 and 745.2 µg/ml for the second group and 10.3 and 848.8 µg/ml for the third group, respectively,²⁶ and another study conducted on rats indicated that the pharmacokinetics of the racemic mixture of ALA are R_ALA and S_ALA when given them This study showed that the concentration of R_ALA in the plasma was higher than the concentration of S_ALA in the plasma, and the area under the curve for R_ALA was 1.26 greater than S_ALA, and when they were given together in the same proportion by intravenous administration, there was no significant change between the kinetic parameters of both R_ALA and S_ALA.¹⁷ The practical application of the pharmacokinetics criteria that we obtained may be of clinical benefit to determine the therapeutic doses and not to reach the toxic doses. To our knowledge, this study is the first study of the pharmacokinetics of ALA in an avian model.

CONCLUSIONS

Our findings suggest that the intraperitoneal administration of ALA to chicks has an analgesic effect, and the pharmacokinetics parameters for it after one hour are characterized by the relatively long duration of its effect, long elimination half-life and a poor clearance from the chick's body tissues.

DECLARATIONS

Authors' contributions

Both authors have equally contributed to this work.

Conflict of interest

The authors declare that they have no competing interests.

Ethical approvals

The authors obtained the official approval for the study protocol from the Committee of Postgraduate Studies at the College of Medicine, University of Mosul (Mosul, Iraq) according to institutional regulations on animal handling and use in research.

Data availability

Data are available from corresponding author upon reasonable request.

Funding

The authors declare that this research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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