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Pharmacological Interaction Between Alpha-Lipoic Acid and Propofol-Induced General Anesthesia in Rats Model

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ABSTRACT

Alpha-lipoic acid (ALA) is an endogenous antioxidant that is involved in the metabolism of energy inside the mitochondria, working as a cofactor of the enzyme-catalyzed reaction. It has strong free radical scavenging activity, which reduces all oxidative stress. The experimental study carried out the careful assessment of alpha-lipoic in adult male rats (n=29). The proposed study was undertaken to evaluate the effects of alpha-lipoic acid on Propofol-induced general anesthesia in rats. The median effective dose (ED_{50}) of alpha-lipoic acid was 45.43 mg/kg upon the intraperitoneal injection method via the up-and-down method. The paper further examined the effects of three doses of alpha-lipoic acid (30 , 60 and 120 mg/kg of 6 rats / group) on the onset, duration, and recovery periods of Propofol-induced anesthesia. The results indicated that the onset time with recovery periods was significantly reduced and the duration of anesthesia prolonged with a dose-dependent effect compared to that of the control group ($p < 0.05$). These statistics suggest that ALA can potentiate the effects of propofol and might have clinical implications in terms of improving the quality of anesthesia and recovery processes.

1. Introduction

Alpha-lipoic acid (ALA) is found in organisms naturally and protects the cells from oxidation and free radical stress. It can also be found in many foods such as leafy greens, potatoes, meats, and several organs, namely the liver, heart, and kidneys (1). ALA is an essential antioxidant, produced by the body, similar to vitamins (2). When taken as a dietary supplement, alpha-lipoic acid is produced in a synthetic manner because natural extraction is very costly (3). There are two forms of ALA, the R form and the S form; the first form is biologically active and is synthesized endogenously, whereas the latter is chemically synthesized and has a lower activity (4). The ability of ALA to directly scavenge oxidative stress and metal chelates and actively interact and renew other antioxidants such as glutathione as well as vitamins E and C are among the reasons that ALA acts as a cofactor to many mitochondrial enzymes, furthermore, ALA is anti-inflammatory (5). Another outstanding feature of ALA is that it is soluble in water and lipids, which means that it can spread all over the body with its own properties, which are unique (6). Thereby, various age-related pathologies connected with the oxidative stress, mainly cardiovascular diseases, including, e.g., ischemic heart disease, refer to the ALA as a remedy (7), hypertension (8) , heart failure (9), and atherosclerosis (7). It may decelerate ageing and extend lifetime (10). Many studies on ALA concentrate on diabetes prevention and the alleviation of diabetic neuropathy. Furthermore, some alternative healthcare practitioners have claimed that alpha-lipoic acid may prevent or ameliorate various health issues, including alcoholic liver disease (11), human immunodeficiency virus (12), rheumatoid arthritis, and preterm birth (13). Alpha-lipoic acid (ALA) is a treatment alternative for diabetic patients with neuropathy, demonstrating effective results in disease management over a continuous dosing period of six months, alongside its safety profile (14). A study on mice demonstrated ALA's capacity to lower cholesterol levels in subjects consuming a high-fat diet, suggesting its potential for treating atherosclerosis (15). Recent studies have demonstrated its therapeutic efficacy in addressing some cancer types (16) , treating Alzheimer's disease (17) and treating metal poisoning, especially arsenic (16) . ALA possesses the capability to scavenge reactive oxygen species, chelate metals, and replenish glutathione, as well as vitamins E and C (16) Administering lipoic acid elevates cellular antioxidant levels, hence diminishing the efficacy of endogenous oxidants. Consequently, ALA functions as a biological antioxidant and offers neuroprotection (18). The anti-inflammatory properties of ALA are ascribed to its inhibitory action on inflammatory cytokines, particularly nuclear factor kappa B (NF-κB) (19). Alpha-lipoic acid is deemed safe for adult consumption for a duration of up to four years. Minor adverse effects may manifest, including cephalalgia, nausea, pyrosis, and emesis (20). When utilized as a topical ointment for the treatment of diabetic neuropathy (21), it is also safe for adults for a duration of up to 12 weeks. Certain users may encounter a rash (20).

Materials and Methods

Ethical approval

The Scientific Ethical Committee for the research was obtained from the Research Ethics Committee at the University of Duhok, College of Veterinary Medicine, Iraq, approved this study issued on 01- 10- 2024, numbered CVM2024\0110UoD.

Laboratory Animals

This study used twenty-nine adult albino male rats weighing between 180 - 250 gram , Rats were housed in polycarbonate cages at ambient temperature (22–25°C) under a 12:12 light-dark regimen. Animals were provided unrestricted access to a regular pellet diet and water. They underwent acclimatization a seven days to commencing the trial.

Drug used

- Alpha-lipoic acid were used (600 mg/24 ml) produced in Wörwag Pharma. Company\ Germany.
- Propofol were used (10 mg/ml) produced in Fresenius Kabi company \ Austria.

Experimental design

Experiment 1: Determining the acute median effective dose (ED_{50}) of alpha-lipoic acid in rats using up-and-down method.

This experiment was conducted using the Dixon method (22) and include five healthy albino rats. An initial dose of Alpha Lipoic Acid (ALA) of 50 mg/kg of body weight was administered via the intraperitoneal method(23). The final response of ALA was characterized by an all-or-nothing analgesic effect (X denoting analgesia and O indicating absence of analgesia), evaluated for each animal 30 minutes post-administration by the tail immersion test at a

water temperature of 55–56°C. The dose was increased or decreased by a fixed step value of 15 mg/kg based on the previous animal's response, with the repeating of this method as up and down for dose value in different rats. To estimate the ED_{50} of ALA in rats, the following equation was used: $ED_{50} = Xf + Kd$, where, ED_{50} represents the median effective dose, Xf is the last dose used, and K is a constant from the Dixon table. d: Constant dose range (up and down dose) (22).

Experiment 2: Pharmacological challenge of ALA with propofol to induce general anesthesia.

To assess the enhancing effect of ALA on anesthesia induced by Propofol, twenty-four rats were used and randomly distributed to four groups. (6 animals\ group)

First group: Control (Normal saline, 5 ml/kg) i.p. daily for 2 weeks.

Second group: ALA at 30 mg/kg i.p. daily for 2 weeks.

Third group: ALA at 60 mg/kg i.p. daily for 2 weeks.

Fourth group : ALA at 120 mg/kg i.p. daily for 2 weeks.

After a 14-day regimen of (ALA), the rats received an anesthetic dose of Propofol at 100 mg/kg via intraperitoneal injection(24) . Time of induction of anesthesia was recorded; this was the time between the administration of propofol and disappearance of body righting reflex on each rat individually. The duration of the anesthesia was defined as the time between the disappearance of a reflex triggering orientation of the body and the regaining of the normal posture of the rats. The time during which the subject took to recover to the righting reflexes was recorded as the recovery period, during which it might regain movements; this was the time of reinstatement of movement.

Statistical Analysis

The data were processed with the help of the program IBM SPSS Statistics (Version 27). The data obtained regarding the effect of alpha-lipoic acid treatment on the health parameters as well as on the anesthetic response to propofol in the rat animals was compared with one- way analysis ANOVA. I averaged the scores and arrived at the interpretations that came out of the post-hoc analysis of the Tukey HSD. The results were represented as Means ± SE (standard error), and the significance was considered as $p \leq 0.05$.

Results and Discussions

In the current study, considerable information is provided on the pharmacological profile of alpha-lipoic acid as far as Propofol-induced anesthesia is concerned. These unique antioxidant properties, along with its being an amphiphilic molecule, also allow ALA to work in both the hydrophilic and lipophilic food environments (25) as well as metal-chelating (19), it supported its protective characteristics in regard to several forms of oxidative stress, cardiovascular disease and neurodegeneration (18).

The acute median effective dose (ED_{50}) of alpha-lipoic acid was 45.43 mg/kg, i.p., and the analgesic signs in the rats injected with ALA were observed within 5–15 minutes of the administration, such as a delayed tail withdrawal response during the hot water test (55–56 degrees), decreased pain sensation, sedation, and an extended time of the latency period. (Table 1). The current study demonstrates that ALA has rapid analgesic effects, with mechanisms involving antioxidant activity and neurotransmitter modulation. (2), These findings align with other studies but differ in dosing and administration routes (26 ,27).

The observations indicate that alpha-lipoic acid (ALA) considerably influences Propofol-induced anesthesia in a dose-dependent manner relative to the control group administered Propofol with normal saline. Administration of ALA at dosages of 60 and 120 mg/kg markedly reduced the onset of anesthesia, with the highest dose (120 mg/kg) resulting in the swiftest induction time (2.2 ± 0.26 min) in comparison to the control group and the second group (5.3 ± 0.30 and 4.9 ± 0.44, respectively). The duration of anesthesia was significantly extended in the 120 mg/kg group (237.3 ± 15.8 min) compared to the control, second, and third groups (184.6 ± 12.9, 187.0 ± 24.1, and 211.8 ± 8.0, respectively). Table II. The recovery period was markedly reduced due to the dose-dependent effects of ALA treatment across all treated groups compared to the control group (Table 2). ALA markedly improved the effectiveness of Propofol anesthesia in a dose-dependent fashion by diminishing the onset time, extending the duration of anesthesia, and expediting recovery. This finding indicates a synergistic interaction between ALA and propofol, a phenomenon corroborated by other studies in which antioxidants influenced anesthetic outcomes. Administration of ALA at doses ranging from 50 to 200 mg/kg has been documented to mitigate isoflurane-induced cognitive deficits and oxidative damage in aged

rat models (28), While it was proven that perioperative ALA treatment mitigated oxidative brain injury and enhanced cognitive outcomes in patients receiving sevoflurane anesthesia (29). The concurrent administration of ALA and propofol may provide additive or synergistic neuroprotection by addressing mitochondrial malfunction and reactive oxygen species production, which are significant factors in anaesthesia-induced neurotoxicity (30). The modification of anesthetic properties by ALA presumably involves many mechanisms. Its direct reactive oxygen species scavenging and metal chelation mitigate oxidative damage during anaesthesia, while its facilitation of mitochondrial activity bolsters neural resilience and recovery (31). By maintaining mitochondrial integrity and diminishing oxidative stress, ALA may stabilize brain networks, promoting expedited induction and recovery from anesthesia. The augmentation of Propofol anesthesia by ALA indicates possible uses in enhancing anesthesia quality and safety, decreasing aesthetic dosages, and mitigating postoperative cognitive impairment. This study adds to the increasing evidence that ALA is a potential adjunct in anaesthesia, enhancing efficacy while improving clinical trials.

Table (1): Determination of ED_{50} of Alpha Lipoic Acid in Rats by Intraperitoneal Route

Measures	Result
Median effective dose (ED_{50})	45.43 mg/kg
Dose range used	30–75 mg/kg
Initial dose	50 mg/kg
Last dose	50 mg/kg
Up and down dose	15 mg/kg
Number of rats	5 (OXOXO)
Onset of action	5–15 minutes
Analgesic signs	Delayed tail withdrawal, reduced pain response, calmness
X:	Presence of analgesia (increased latency > pre-injection)
O:	Absence of analgesia (latency same or less than baseline)

Table (2): Pharmacological challenge of ALA with propofol to induce general anaesthesia

Groups	Onset (min)	Duration (min)	Recovery (min)
Control (Propofol+ N.S)	5.3 ± 0.30	184.6 ± 12.9	96.17 ± 18.5
ALA 30 mg/kg	4.9 ± 0.44	187.0 ± 24.1	27.67 ± 7.1*
ALA 60 mg/kg	3.0 ± 0.08*a	211.8 ± 8.0	25.17 ± 2.2*
ALA 120 mg/kg	2.2 ± 0.26*a	237.3 ± 15.8*a	17.50 ± 2.8*

The values represent the Mean ± SE for (6) rats\ group.
*: Denote a significant difference compared with the control group at ($p \leq 0.05$)
a: Denote a significant difference compared with the 30 mg/kg group at ($p \leq 0.05$)

Conclusions

The observed synergistic interaction in this study between ALA and propofol indicates that ALA may function as a beneficial adjunct in clinical anaesthesia, potentially enhancing the quality of induction, prolonging the effective duration of anaesthesia, and promoting expedited postoperative recovery. The ALA exhibits considerable potential to improve anesthetic results when delivered alongside propofol, enhancing both efficacy and recovery profiles. Further research is necessary to clarify the specific molecular pathways responsible for these effects, evaluate long-term safety in diverse populations, and confirm these findings in clinical environments. Such investigations will be essential to properly ascertain the therapeutic potential of ALA as an adjuvant in anaesthesia practice, assuring improved patient outcomes and safety.

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Conflict of interest

I declare that I have no competing interests.

References

[1] Zonooz SR, Hasani M, Morvaridzadeh M, Pizarro AB, Heydari H, Yosaee S, et al.(2021) Effect of alpha-lipoic acid on oxidative stress parameters: A systematic review and meta-analysis. J Funct Foods.;87:104774.
[2] El-Senousey H, Chen B, Wang J, Atta A, Mohamed F& Nie Q. (2018)Effects of dietary

vitamin C, vitamin E, and alpha-lipoic acid supplementation on the antioxidant defense system and immune-related gene expression in broilers exposed to oxidative stress by dexamethasone. Poultry science.;97(1):30-8.

[3] Maha R. Abd El-Fadile & Hussine A.H.M.(2016) Role of lipoic acid in improving vitality of defferent tissue culture cells. J of Applied Veterinary Sciences;1(1):43-47.

[4] Wu Y, Liao W, Dawuda MM, Hu L& Yu J. (2019)5-Aminolevulinic acid (ALA) biosynthetic and metabolic pathways and its role in higher plants: a review. Plant Growth Regulation.;87:357-74.

[5] Bratovcic A(2020). Antioxidant enzymes and their role in preventing cell damage. Acta Sci Nutr Health. 2020;4(3):01-7.

[6] Reifen R, Karlinsky A, Stark AH, Berkovich Z & Nyska A.(2015) α-Linolenic acid (ALA) is an anti-inflammatory agent in inflammatory bowel disease. The J Nutr Biochem.;26(12):1632-40.

[7] Reifen R, Karlinsky A, Stark AH, Berkovich Z & Nyska A.(2015) α-Linolenic acid (ALA) is an anti-inflammatory agent in inflammatory bowel disease. The J Nutr Biochem.;26(12):1632-40.

[8] Serhiyenko VA, Serhiyenko LM, Sehin VB & Serhiyenko AA.(2021) Effect of alpha-lipoic acid on arterial stiffness parameters in type 2 diabetes mellitus patients with cardiac autonomic neuropathy. Endocr Regul.;55(4):224-33.

[9] Hu Q-F& Sun A-J.(2020) Cardioprotective effect of alpha-lipoic acid and its mechanisms. Cardiology Plus.;5(3):109-17.

[10] Shanaida M, Lysiuk R, Mykhailenko O, Hudz N, Abdulsalam A, Gontova T& et al.(2025) Alpha-lipoic acid: An antioxidant with anti-aging properties for disease therapy. Current Medicinal Chemistry.;32(1):23-54.

[11] Hosseinpour-Arjmand S, Amirkhizi F & Ebrahimi-Mameghani M.(2019) The effect of alpha-lipoic acid on inflammatory markers and body composition in obese patients with non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther;44(2):258-67.

[12] Dragomanova S, Miteva S, Nicoletti F, Mangano K, Fagone P, Pricoco S &, et al. (2021)Therapeutic potential of alpha-lipoic acid in viral infections, including COVID-19. Antioxidants.;10(8):1294.

[13] Mirtaheri E, Pourghassem Gargari B, Kolahi S, Dehghan P, Asghari-Jafarabadi M, Hajalilou M, &et al. (2015) Effects of alpha-lipoic acid supplementation on inflammatory biomarkers and matrix metalloproteinase-3 in rheumatoid arthritis patients. J Am Nutr Assoc.;34(4):310-7

[14] 14-Al-Zubaidi, M.N., (2022). Study of the effect of fluoxetine on the process of implantation of the blastocyst and some biochemical parameters in the blood serum of pregnant white rats. M.Sc. thesis, Karbala University, Iraq :pp98.

[15] Li Y, Yu Z, Liu Y, Wang T, Liu Y, Bai Z, & et al.(2022) Dietary α-linolenic acid-rich flaxseed oil ameliorates high-fat diet-induced atherosclerosis via gut microbiota-inflammation-artery axis in ApoE−/− mice. Frontiers in Cardiovascular Medicine.;9:830781.

[16] Attia M, Essa EA, Zaki RM & Elkordy AA.(2020;) An overview of the antioxidant effects of ascorbic acid and alpha lipoic acid (in liposomal forms) as adjuvant in cancer treatment. Antioxidants. 9(5):359.

[17] Dos Santos SM, Romeiro CFR, Rodrigues CA, Cerqueira ARL & Monteiro MC.(2019) Mitochondrial Dysfunction and Alpha-Lipoic Acid: Beneficial or Harmful in Alzheimer's Disease? Oxidative medicine and cellular longevity.;2019(1):8409329.

[18] Khan H, Singh TG, Dahiya RS & Abdel-Daim MM.(2022) α-Lipoic acid, an organosulfur biomolecule a novel therapeutic agent for neurodegenerative disorders: an mechanistic perspective. Neurochemical research.;47(7):1853-64.

[19] Li G, Fu J, Zhao Y, Ji K, Luan T, Zang B.2015))Alpha-lipoic acid exerts anti-inflammatory effects on lipopolysaccharide-stimulated rat mesangial cells via inhibition of nuclear factor kappa B (NF-κB) signaling pathway. Inflammation. 2015;38:510-9.

[20] Esposito C, Garzarella EU, Santarcangelo C, Di Minno A, Dacrema M, Sacchi R & et al.(2021) Safety and efficacy of alpha-lipoic acid oral supplementation in the reduction of pain with unknown etiology: A monocentric, randomized, double-blind, placebo-controlled clinical trial. Biomedicine & Pharmacotherapy.;144:112308.

[21] Abubaker SA, Alonazy AM, Abdulrahman A, Abubaker S, Alonazy A & Albasseet A.(2022) Effect of alpha-lipoic acid in the treatment of diabetic neuropathy: A systematic review. Cureus.;14(6)

[22] Dixon W.I.J.(1980) efficient analysis of experimental observation , Annual review of Pharmacology and Toxicology 20(1):441-462 .

[23] Danielle SM. Camila DM, Rafaela CC, Francisca CS, Júnia VS, Thomás AM, Thomas NH, Roger S M, João Q and , André F C (2012). Effects of alpha-lipoic acid in an animal model of mania induced by D-amphetamine . international journal of psychiatry and neuroscience;14(7):707-18.

[24] Yılmaz B.(2018.) 3rd International Congress of the Turkish Neuroendocrinology Society. 1–40.

[25] Losada-Barreiro S, Sezgin-Bayindir Z, Paiva-Martins F & Bravo-Díaz C.(2022) Biochemistry of antioxidants: Mechanisms and pharmaceutical applications. Biomedicines.;10(12):3051.

[26] Woodward T.J., Tesic V., Stamenic T.T., Jevtovic-Todorovic v & Todorovic S.m. (2019) Pharmacological Antagonism of T-Type Calcium Channels Constrains Rebound Burst Firing in Two Distinct Subpopulations of GABA Neurons in the Rat Ventral Tegmental Area: Implications for α-Lipoic Acid. Front Pharmacol. 26;10:1402.

[27] Sun y., Yang P., Song P, Feng Y., Hu D., Hu J, Xu G & Zhang H.(2017) α-lipoic acid suppresses neuronal excitability and attenuates colonic hypersensitivity to colorectal distention in diabetic rats. J Pain Res . 14;10:1645–1655.

[28] Wang X, Zhao B & Li X.(2015) Dexmedetomidine attenuates isoflurane-induced cognitive impairment through antioxidant, anti-inflammatory and anti-apoptosis in aging rat. Int J Clin Exp Med.;8(10):17281.

[29] Gao K, Wu Y, Zhang Y, Dang P, Xue H, Li T & et al. (2025)Alpha-lipoic acid alleviates oxidative stress and brain damage in patients with sevoflurane anesthesia. Frontiers in Pharmacology.;16:1572156.

[30] Bosnjak ZJ, Logan S, Liu Y& Bai X. (2016;)Recent insights into molecular mechanisms of propofol-induced developmental neurotoxicity: implications for the protective strategies. Anesthesia & Analgesia. 123(5):1286-96.

[31] Superti F& Russo R.(2024) Alpha-Lipoic Acid: Biological Mechanisms and Health Benefits. Antioxidants.;13(10):1228.

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التحدي الدوائي لحامض الالفا ليبوك وتداخله مع التخدير العام المحدث بواسطة البروبوفول في نموذج الجرذان

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الملخص

يعتبر حمض ألفا- ليبويك مضاد أكسدة طبيعي يلعب دورًا في استقلاب الطاقة الميتوكوندرية، حيث يعمل كعامل مساعد للتفاعلات الإنزيمية.و يتمتع بقدرات قوية على التقاط الجذور الحرة التي تقلل من الإجهاد التأكسدي الناتج من التفاعلات الايضية للخلية. حيث هدفت هذه الدراسة إلى تقييم تأثير حمض ألفا-ليبويك (ALA) وتداخله مع التخدير العام الناجم عن البروبوفول في ذكور الجرذان.كانت الجرعة الحاده الفعالة المتوسطة (ED50) لحمض ألفا-ليبويك 45.43 ملغم/كغم بعد الحقن داخل الصفاق. بالإضافة إلى ذلك، بحثت الدراسة تأثير ثلاث جرعات مختلفة من حمض ألفا-ليبويك (30 و60 و120 ملغم/كغم) على بداية ومدة وفترة التعافي من التخدير الناتج عن البروبوفول.أظهرت النتائج أن حمض ألفا-ليبويك قلل بشكل ملحوظ وقت البدء وفتره التعافي من المخدر، بينما أطال مدة التخدير بطريقة تعتمد على الجرعة. تشير هذه البيانات إلى أن ALA يعزز فعالية البروبوفول وقد يكون له أهمية سريرية في تحسين جودة التخدير ونتائج التعافي في العمليات الجراحية .

الكلمات المفتاحية: حامض الالفا ليبوك، الجرعه الفعالة الوسطية، التخدير العام، بروبوفول.