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ORIGINAL CONTRIBUTION

Lurasidone in the management of Ketamine overdose

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ABSTRACT

Background: Ketamine is an anesthetic compound that has recreational use and can cause heart-related toxicity, different psychiatric disorder, and even death. Nevertheless, the management of ketamine overdose is not yet perfect. Hence, the discovery or identification of compounds that can manage ketamine overdose is essential. Ketamine can induce schizophrenia and lurasidone can treat schizophrenia, on its basis, the present study was aimed to determine if lurasidone can alter ketamine-induced death and/or reduce recovery time from ketamine-induced anesthesia.

Methods: Mice were initially injected with 50 mg/kg, 100mg/kg, 150mg/kg, and 200mg/kg i.p. ketamine for toxicity test, and any death was recorded. Based on the toxicity study, the lethal dose was determined (150mg/kg b.w.) and further administered intra-peritoneally to fresh mice groups followed by treatment with 0.5mg/kg, 1mg/kg, 2mg/kg lurasidone. Afterward, survival rate and recovery time were recorded.

Results: Control (only ketamine) treated mice group showed only 20% survival, whereas all three doses of lurasidone were able to keep all of the mice alive. However, no significant difference was found between the applied doses of lurasidone. In addition, all three doses of lurasidone minimized recovery time compared to control in a dose-dependent manner. The fastest recovery time recorded was 54 minutes by 2 mg/kg of lurasidone-pretreated mice.

Conclusion: Although lurasidone was able to reduce ketamine-induced mortality rate and recovery time, the mechanism of lurasidone by which it exhibits recovery against ketamine is yet to be explored.

Keywords

Ketamine,
Lurasidone,
Recovery Time,
Survival Rate

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***Significance Statement*:** *The study obtained three new findings; first, the lethal dose of ketamine is 150mg/kg for mice; second, lurasidone 0.5/1/2 mg/kg can prevent the lethality of ketamine; third, the recovery time of ketamine-induced anesthesia is associated with the dose of lurasidone. Hence, the study shall be further useful in designing the safe dose line for ketamine-based investigations and in its management at overdose.*

INTRODUCTION

In 1964, ketamine was introduced as an anesthetic medicine [1]. It was heavily used for war injuries [2]. Still, ketamine is a preferred choice of drug for anesthetic medication. However, recent studies suggest its potential for being an antidepressant medicine [3]. Ketamine exerts its anti-depressive activity through an increase in glutamate level in synaptic cleft [4]. Furthermore, ketamine is used in mice models to induce schizophrenia [5]. Nevertheless, ketamine also increases dopamine level in brain which makes it a recreational drug that can cause addiction and is prone to be abused [6]. Ketamine toxicity includes effects like hypertension, tachycardia, hallucination in lower doses and in higher doses it can induce respiratory depression, hypotension, coma or even death [7]. In 2016 around 30 people died in UK alone by ketamine overdose/recreational use and the number of death per annum is raising every year in UK [8]. In addition, China, New York, Australia had reported death by ketamine abuse in different years [9]. Nonetheless, currently, FDA guideline does not have any approved medicine for the management of ketamine overdose, yet charcoal for oral overdose and some sedatives such as lorazepam and butyrophenones like haloperidol are given to reduce agitation, hypertension, etc [10].

Lurasidone is an antipsychotic drug that is used to treat depression in bipolar disorder and schizophrenia [11]. The mechanism of action of lurasidone is not fully established but it is assumed that lurasidone blocks the binding of dopamine in D2 receptor and serotonin in 5-HT2A and 5-HT7 receptors [12].

Till date, the effect of lurasidone on ketamine is not much studied, few studies are done regarding their co-use such as effect of lurasidone to improve depression of ketamine is studied [13]. Yet, no study is conducted to evaluate lurasidone's effect on reducing ketamine high dose-induced death or toxicity. Thus, this study aims to evaluate lurasidone's ability to alter morbidity and mortality due to ketamine i.p higher dose and its ability to minimize the recovery time from the induced-immobility.

METHODS

Drugs and Chemicals

Ketamine was obtained from Popular Pharmaceuticals Ltd. (Bangladesh) in injection form at the concentration of 50mg/ml. On the other hand, lurasidone was obtained from Square Pharmaceuticals Ltd. (Bangladesh) in tablet form where the dose was 20mg per tablet. 0.9% NaCl solution was obtained from Opsonin Pharmaceuticals Ltd. (Bangladesh).

Experimental Animal

Swiss albino mice of 45 days of age and 25-30g of body weight were selected for the experiments. The animals were exposed to 12h light/dark cycle and proper air ventilation along with ambient temperature. The animals were provided with sufficient water and *ad libitum* food and kept at animal house of Institute for Pharmaceutical Skill Development and Research, Bangladesh.

Experimental Design

For initial toxicity study we divided mice into four groups, each containing 15 mice. The groups included blank (0.9% saline water) and ketamine 50, 100, 150 and 200 mg/kg of body weight, received through i.p route.

Fresh sets of mice were again tested with Lurasidone-pre-treatment against ketamine and observed for both survival and recovery. The test mice were divided into 5 groups, each containing 10 mice. Lurasidone was given orally at 0.5/1/2mg/kg concentration and after 30 minutes ketamine was administered intraperitoneally at 100mg/kg concentration except for the Blank group. The groups followed following treatment regimens:

Group 1: Blank (Only i.p saline water), Group 2: Control (ketamine 150mg/kg i.p.), Group 3: lurasidone (0.5mg/kg p.o.) + ketamine (150mg/kg i.p.), Group 4: lurasidone (1 mg/kg p.o.) + ketamine (150mg/kg i.p.), Group 5: lurasidone (2 mg/kg p.o.) + ketamine (150mg/kg i.p.).

Observational Parameters

Upon intraperitoneal administration of ketamine, mice were kept under continuous observation to monitor any death. In addition, their recovery time from immobile to mobile state was also observed and recorded. Here, the recovery time has been defined as the duration from full loss of consciousness and activity (immobility) to the time point of regaining it (mobility). A duration of 120 min was considered as a cut-off observation period for recovery.

Statistical Analysis

Two-way ANOVA was done for statistical analysis of recovery time experiment and Dunnett's multiple comparison test was performed in GraphPad Prism 8. The results of recovery time were compared with the control group to check statistical significance. P values <0.05, 0.01 and 0.001 were considered as statistically significant denoted by *, ** and *** respectively.

RESULTS

Acute Toxicity Test

Acute toxicity test was performed to determine the lethal dose of ketamine. The data of survival rate for different doses of ketamine is illustrated in Figure 1 where it can be noted that mice from the group of blank, 50 mg/kg and 100mg/kg showed no death. Nevertheless, mice treated with ketamine (150mg/kg) showed only 20% survival rate. Hence, 150 mg/kg was considered as the lethal dose of ketamine for mice and the same dose was selected further for the studies of survival and recovery time.

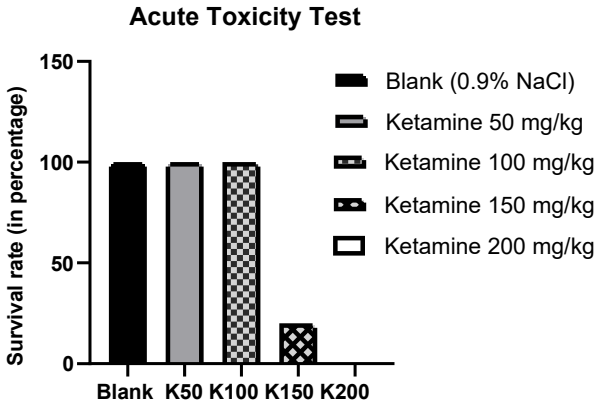

Figure 1. Survival rate of mice after injecting ketamine at toxic doses.

Data presented as the percentage based on the counts of survived mice among 15 population in each group after injecting ketamine in various doses.

Survival Rate

The data of survival rate is illustrated in Figure 2 where it was noted that blank group of mice caused no death due to the treatment of normal saline. However, when mice were treated with ketamine (150mg/kg), only 20% mice survived. On the contrary, the pretreatment of lurasidone at 0.5/1/2mg/kg, retained the survival rate to 100%.

Recovery Time

The data in Figure 3 demonstrates that lurasidone holds a dose dependent relationship with recovery time from ketamine induced anesthesia. Among the survived population (20%), it took around 119.4 minutes to recover from immobility. However, lurasidone-pretreated mice were found with reduced recovery time in a linear ratio. At 0.5 mg/kg, lurasidone treated mice recovered within 66.6 minutes and at 1 mg/kg, lurasidone-treated mice took 60.2 minutes to recover. In addition, 2 mg/kg lurasidone-treated mice recovered within 54 minutes.

DISCUSSION

Ketamine, chemically known as 2-(2-chlorophenyl)-2-(methylamino) cyclohexanone is often denoted as K or special K. Ketamine non-selectively blocks a glutamate receptor N-methyl-D-aspartate (NMDA) to produce anesthesia and analgesic effect. Additionally, it can weakly stimulate opioid receptors and calcium channels, increases neurotransmitters like dopamine, serotonin etc., antagonizes muscarinic, nicotinic acetylcholine receptors, GABA (gamma aminobutyric acid) receptors and sodium and potassium channels [14-18]. Ketamine high dose can be lethal which was also found in this study. Ketamine 150mg/kg concentration proved to be lethal for 80% of control group whereas all mice of blank group survived. However, pretreating mice with lurasidone (0.5/1/2 mg/kg) inhibited the death. The cause of death could be sudden cardiac arrest or respiratory depression or coma [7]. The causes are yet unknown however, many reported hypertension as an attributor [19]. Nevertheless, anti-hypertensive drug, anti-arrhythmic and bronchodilator need to be given in different groups without giving lurasidone in further study to assess the actual cause of death in mice.

Lurasidone usually antagonizes serotonin and dopamine receptor whereas ketamine increases their function indirectly [20]. However, lurasidone was found to reduce hypotension and sedation which could have attributed to the survival if the cause of death is hypotension or coma [12]. Another hypothesis from the finding could be drawn that if the cause of death was hypertension/ tachycardia then lurasidone might have interacted with calcium channel and or sodium and or potassium channel. Thus, further studies are recommended to explore the mechanism behind lurasidone's potential on survival as well as how ketamine overdose induces death. However, the present finding that lurasidone can protect against death caused by ketamine, can be useful upon further

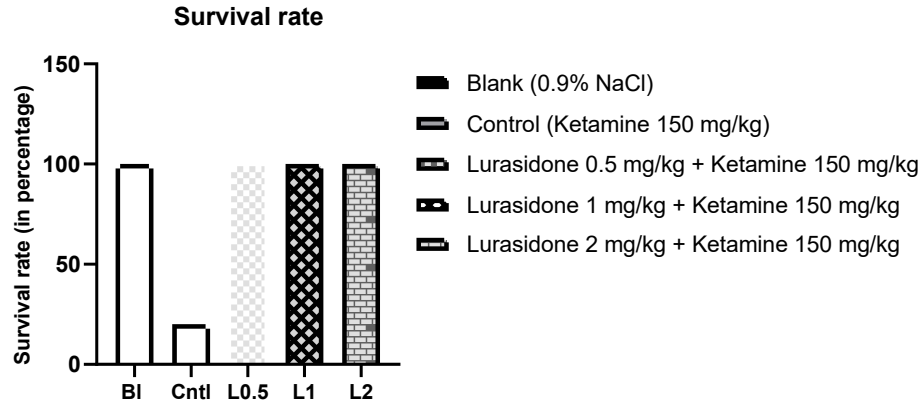

Figure 2: Survival rate of lurasidone-treated mice after injecting lethal dose of ketamine.
Data presented as the percentage based on the counts of survived mice among 10 population in each group after injecting ketamine in various doses.

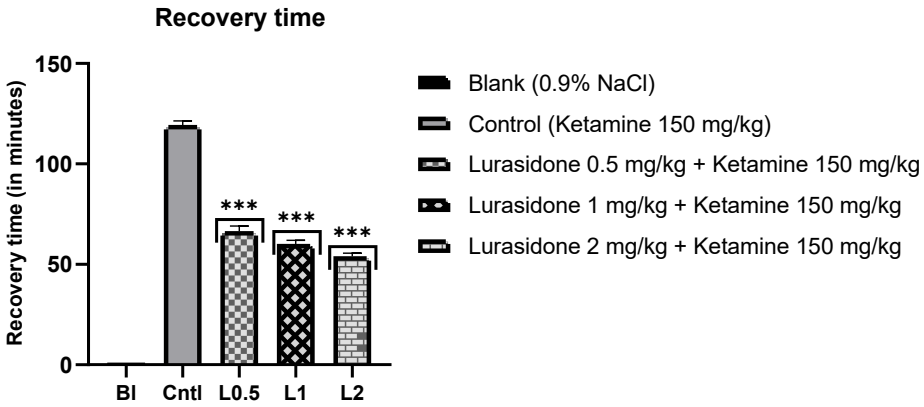

Figure 3: Recovery time of lurasidone-treated mice after injecting lethal dose of ketamine.
Data illustrated as mean ± SEM, (n=10); *** = p <0.001; Dunnett's multiple comparison test was performed, where only ketamine treated mice group served as control and all other groups were compared against the control.

investigation to treat emergency patient of ketamine abuse or overdose to reduce mortality rate.

Furthermore, it can be concluded that lurasidone reduced ketamine intoxication time in a dose dependent manner. Therefore, lurasidone can be used as an antitoxin in case of accidental overdose in anesthesia or in any other relevant purpose which can be confirmed upon further studies.

CONCLUSION

Although ketamine and lurasidone do not share pathways or same receptor target in terms of their mechanism of action according to current available information. The present study was able to indicate their possible pharmacotherapeutic relationship. The results suggested that lurasidone gives protection against death caused by ketamine overdose and decreases the intoxication time in a dose dependant manner. Nevertheless, further studies are needed to discover how lurasidone blocks or reverses activities of ketamine.

Abbreviations

NMDA: N-methyl-D-aspartate; GABA: Gamma Amino-Butyric Acid; FDA: Food and Drug Administration; D2: Dopamine D2 Receptor: 5-HT; Serotonin Receptors.

Authors' Contributions

This work was a collaborative effort between all authors. The project was conceived, coordinated, and supervised by MNI and SMRQN. SMRQN and KN conducted the experiments and created graphical displays. KN and SMRQN took part in the writing of the manuscript. MNI and SMRQN contributed to the interpretation of data in order to obtain a scientific conclusion. The final manuscript was read and approved by the authors.

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Availability of Data and Materials

The datasets used and/or analysed during this research are available upon reasonable request from the corresponding authors.

Ethics Approval and Consent to Participate

All animal studies were conducted in compliance with the Guide for the Care and Use of Laboratory Animals, 8th edition; The National Academies Collection, as accepted by the institutional guideline for animal care (Ref. no. IPSDRLAB/AHCP/01/18).

Institutional Ethical Committee Clearance (Ref. No. IPSDRLAB/IECC/07/22) from the Institute of Pharmaceutical Skill Development and Research, Bangladesh (project approved on 07/01/2022) authorized the experimental design.

Consent for Publication

Not applicable.

Competing Interests

Before submitting the article, all authors were in accord and there were no conflicts of interest.

REFERENCES

1. Morgan CJA, Curran HV. Ketamine use: A review. Addiction. 2012;107(1):27-38. doi:10.1111/j.1360-0443.2011.03576.x
2. Feifel D. Breaking Sad: Unleashing the Breakthrough Potential of Ketamine's Rapid Antidepressant Effects. Drug Dev Res. 2016;77(8):489-494. doi:10.1002/ddr.21347
3. Ignácio ZM, Réus GZ, Arent CO, Abelaira HM, Pitcher MR, Quevedo J. New perspectives on the involvement of mTOR in depression as well as in the action of antidepressant drugs. Br J Clin Pharmacol. Published online 2016:1280-1290. doi:10.1111/bcp.12845
4. Sleigh J, Harvey M, Voss L, Denny B. Ketamine - more mechanisms of action than just NMDA blockade. Trends Anaesth Crit Care. 2014;4(2-3):76-81. doi:10.1016/j.tacc.2014.03.002
5. Monte AS, De Souza GC, McIntyre RS, et al. Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: Possible involvement of antioxidant and nitrergic pathways. J Psychopharmacol. 2013;27(11):1032-1043. doi:10.1177/0269881113503506
6. Rabiner EA. Imaging of striatal dopamine release elicited with NMDA antagonists: Is there anything there to be seen? J Psychopharmacol. 2007;21(3):253-258. doi:10.1177/0269881107077767
7. Sarton E, Teppema LJ, Olievier C, et al. The involvement of the μ-opioid receptor in ketamine-induced respiratory depression and antinociception. Anesth Analg. 2001;93(6):1495-1500. doi:10.1097/00000539-200112000-00031
8. Corkery JM, Hung WC, Claridge H, Goodair C, Copeland CS, Schifano F. Recreational ketamine-related deaths notified to the National Programme on Substance Abuse Deaths, England, 1997–2019. J Psychopharmacol. 2021;35(11):1324-1348. doi:10.1177/02698811211021588
9. Li F, Liu J, Yip PSF, Lu X, Liu S. Mortalities of methamphetamine, opioid, and ketamine abusers in Shanghai and Wuhan, China. Forensic Sci Int. 2020;306:110093. doi:10.1016/j.forsciint.2019.110093
10. Bokor G, Anderson PD. Ketamine: An update on its abuse. J Pharm Pract. 2014;27(6):582-586. doi:10.1177/0897190014525754
11. Fornaro M, De Berardis D, Perna G, et al. Lurasidone in the Treatment of Bipolar Depression: Systematic Review of Systematic Reviews. Biomed Res Int. 2017;2017. doi:10.1155/2017/3084859
12. Ishibashi T, Horisawa T, Tokuda K, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther. 2010;334(1):171-181. doi:10.1124/jpet.110.167346
13. Kalsi SS, Wood DM, Dargan PI. The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. Emerg Health Threats J. 2011;4(1). doi:10.3402/ehtj.v4i0.7107
14. Pham TH, Gardier AM. Fast-acting antidepressant activity of ketamine: highlights on brain serotonin, glutamate, and GABA neurotransmission in preclinical studies. Pharmacol Ther. 2019;199:58-90. doi:10.1016/j.pharmthera.2019.02.017
15. Burgdorf J, Zhang XL, Nicholson KL, et al. GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without

ketamine-like side effects. Neuropsychopharmacology. 2013;38(5):729-742. doi:10.1038/npp.2012.246

16. Can A, Zanos P, Moaddel R, et al. Effects of ketamine and ketamine metabolites on evoked striatal dopamine release, dopamine receptors, and monoamine transporters. J Pharmacol Exp Ther. 2016;359(1):159-170. doi:10.1124/jpet.116.235838
17. Celada P, Puig MV, Casanovas JM, Guillazo G, Artigas F. Control of Dorsal Raphe Serotonergic Neurons by the Medial Prefrontal Cortex: Involvement of Serotonin-1A, GABAA, and Glutamate Receptors.J Neurosci.2001;21(24):1-13. papers2://publication/uuid/E203997B-C1AB-4AB4-BEA2-8C4125966118
18. Dinis-Oliveira RJ. Metabolism and metabolomics of ketamine: a toxicological approach. Forensic Sci Res.2017;2(1):2-10. doi:10.1080/20961790.2017.1285219
19. Liebe T, Li S, Lord A, et al. Factors influencing the cardiovascular response to subanesthetic ketamine: A randomized, placebo-controlled trial. Int J Neuropsychopharmacol. 2017;20(11):909-918. doi: 10.1093/ijnp/pyx055
20. Lindefors N, Barati S, O'Connor WT. Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res. 1997;759(2):205-212. doi:10.1016/S0006-8993(97)00255-2.