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Evaluation of the advantages of orphenadrine in anaesthesia caused by ketamine in mice

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Abstract

Mice are laboratory models used for evaluating anesthetic drugs; the combination of more than one drug to achieve general anesthesia was very common; orphenadrine considered as a special remedy because of its multiple pharmacodynamics properties in variant pathways and is use mainly as a muscle relaxant to treat muscle pain and muscle spasm. The purpose of our research was to appraise the effect of concomitant administration of orphenadrine and ketamine on the quality of general anesthesia in male albino mice. Male mice were used to assess the combination of orphenadrine and ketamine at the onset of anesthesia, duration, and recovery, as well as the presence or absence of notable reflex responses and the analgesic action of a mixture of ketamine and orphenadrine was evaluated by determining the median effective dose by using the up and down method in the tail immersion test. The combination of orphenadrine and ketamine formed a significant decrease in the onset of anesthesia compared with ketamine alone, a significant rise in the duration of anesthesia, and a significant decrease in the recovery time compared with ketamine alone; this mixture led to the disappearance of almost all reflex responses, which that presence in mice anesthetized, with ketamine alone. Our results showed a synergistic analgesic effect when orphenadrine and ketamine were administered together, depending on the calculated value of Y. We demonstrated the possibility of using orphenadrine as an alternative to xylazine when administered with ketamine to induce general anesthesia, and the analgesic action was synergistic when a combination of ketamine and orphenadrine was administered. Therefore, these results open new horizons for the use of orphenadrine in the field of anesthesia. Therefore, we recommended conducting more studies on this topic.

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Introduction

Anesthesia is a physiological condition that generates a regulated, temporary lack of sensation or consciousness for veterinary or medical applications (1,2). The ideal anesthesia depends on the concurrent treatment of diverse medications to achieve balanced anesthesia. The classic anesthetic state comprises essential drugs formed from hypnotics, painkillers, and muscle relaxants. It is mainly the analgesic support of this triad that has become increasingly reinforced by accessory medicines (3). Ketamine is an injectable anesthetic that is widely used in humans, especially in pediatric and veterinary surgery (4); it produces dissociative anesthesia and good analgesic, which has minimal respiratory depression and potent sympathetic effects on the cardiovascular system that are characterized by increases in inotropic and chronotropic and blood pressure (5,6), because of its psychotic side effects and inability to relax skeletal muscles (7,8) adequately, the limited use of ketamine can be treated by discover balanced ideal anesthesia to decrease the required doses needed for each drug while still producing the desired clinical effect (9). An anticholinergic drug called orphenadrine is primarily used to treat Parkinson's disease to reduce some of its bothersome symptoms, mainly resting

tremors (10,11). Orphenadrine is a medication that blocks muscarinic receptors (12), histaminic H1 receptors (13), N-methyl-D-aspartate (NMDA) receptors (13), voltage sodium channels, and potassium channels (14). Furthermore, it has an inhibitory effect on norepinephrine and dopamine reuptake (15). Orphenadrine applies unspecific antagonistic activity at the phencyclidine binding site of NMDA receptors, one of the subtypes of glutamate receptors (16). Orphenadrine has many therapeutic uses, such as muscle relaxant by central mechanism (17), pain killer mainly in combination with NSAIDs (18), and has activity in the treatment of Parkinson's disease (19). Our main aim of this study was to evaluate the possible effect of the coadministration of orphenadrine and ketamine on the quality of the anesthetic state. We put a hypothesis that the administration of orphenadrine might counteract muscle rigidity made by ketamine.

We assessed the effects of orphenadrine on onset, duration, and recovery in mice anesthetized with ketamine in addition to an evaluation of body reflexes and determined the type of interaction with ketamine at a level of analgesic activity.

Materials and methods

Ethical approval

Ethical approval for the study was obtained after the Institutional Animal Care Committee formed in the College of Veterinary Medicine at the University of Mosul, which is consistent with the principles of international ethics in dealing with animals, reviewed the application submitted to it by us on 15/3/2023 with the code UM.VET.2023.006.

Animals

Male albino mice weighing 35-40 grams were used in this study, and they were purchased and bred in the laboratory animal house in the College of Veterinary Medicine, University of Mosul. The mice were adapted in specially manufactured plastic cages for mice and allowed free access to water and food in a minimum pathogen-free laboratory animal room (12/12-h light/dark cycle, 24±2°C; relative humidity: 56%±2%). All experiments were performed between 8:00 a.m. and 2:00 p.m. to diminish the confounding effects of circadian timing on the experimental results. It is important to remember that the mice's cages have been washed once a week by changing the soiled bedding and cleaning down the remaining cages.

Drugs

Orphenadrine citrate injection 30mg/ml Teva®, and ketamine (10% INJ, Dutch Farm.) was further diluted in a saline solution to gain the recommended doses of the drugs. The administration volume of each drug was 10mg/ml body weight administered intraperitoneal.

Study design

Eighteen male albino mice were distributed into three equal groups: the first group was injected with ketamine 100mg/kg intraperitoneal (IP); the second group was administered with ketamine 100mg/kg and orphenadrine 10mg/kg IP simultaneously, the third group was administered with ketamine 100mg/kg and orphenadrine 20mg/kg simultaneously. The dose of ketamine and orphenadrine in our study was chosen based on previous studies (20,21). The intraperitoneal injection was accomplished adjacent to the midline near the umbilicus with a 25-gauge needle inserted at a 45° angle to the belly wall in the lower left guardant of the belly.

Anesthetic activity evaluation

After drug injection, the mouse was retained alone in a crate with a sawdust floor until loss of righting reflex (defined as incapability to revert to ventral recumbency) was achieved. This interval was known as the onset of anesthesia (Table 1). The pedal withdrawal reflex (assessed by pinching the tail and the metacarpal region of the hind foot between the finger and the thumb) was monitored every 5 minutes. The interval between the loss of the righting reflex and the return to the righting reflex is known as the duration of anesthesia, and the interval between the return to the righting reflex is known as recovery (Table 1) (22). Muscle tone was assessed by gently touching the caudal thigh, lumber, and temporal muscles for the presence or absence state with the tip of a finger (23). The corneal reflex was assessed by touching the cornea of a mouse with a cotton swab and noting if the mouse blinks or shakes its head (24).

Table 1: Anesthetic activity evaluation

Time	T0	Administration of drugs
	T1	Loss of righting reflex
	T2	Return of righting reflex
	T3	Return of normal movement
Interval	T1-T0	Onset of anesthesia
	T1-T2	Duration of anesthesia
	T2-T3	Recovery

Evaluation of analgesic activity

Using the tail immersion test (25), the median analgesic doses of orphenadrine and ketamine alone or in combination were calculated using the up-and-down method (26). The tail immersion test was carried out by holding the mouse and immersing its tail in a water bath at a temperature of 55-56°C; then, we calculated the time required to retract the tail in seconds with a stopwatch .The tail immersion test was conducted after 30 minutes of intraperitoneal injection of the drugs (27,28). The first dose of orphenadrine was 10mg/kg and ketamine 3mg/kg, whereas, in combination, the first doses of orphenadrine and ketamine were 7 and 1.5mg/kg, respectively (0.5:05 of their individual ED_{50} values). The

interaction index was determined using the following equation, were Y=(da/Da)/(db/Db). da: ED_{50} of orphenadrine in combination with ketamine. db: $ED_{50\ of}$ ketamine in combination with orphenadrine. Da: ED_{50} of orphenadrine alone. Db: ED_{50} of ketamine alone (29-31). The resulting number indicates the type of interaction between the two drugs. If the number is less than one, the interaction is considered synergistic. If the number is greater than one, the interaction is considered antagonistic. If the number is equal to one, the interaction is additive. The analgesic doses of our drugs were chosen from previous studies (30,32).

Statistical analysis

The data obtained from the anesthesia experiment were analyzed using a statistical program (SPSS), where the results were analyzed using a one-way analysis of the variance test and least significant difference tests. The data are expressed as the mean ± standard error, and the values were considered statistically significant when the probability (P) was less than or equal to 0.05.

Results

Comparison of anesthetic effects

Mice in all groups lost their righting reflex in 55-109 seconds; there was a significant dose-dependent decline in the onset time in the group injected with orphenadrine 20 mg/kg plus ketamine compared to the group injected with orphenadrine 10 mg/kg and ketamine alone. There was a significant dose-dependent rise in the period of anesthetic time in the group injected with orphenadrine 20 mg/kg plus ketamine compared to the group injected with orphenadrine 10 mg/kg and ketamine alone. There was a significant decrease in recovery time among groups treated with orphenadrine in comparison with a group of ketamine alone. All mice recovered from anesthesia and were returned to the home cage following treatment (Table 2).

Administration of the anesthetic dose of ketamine alone caused death in 33% of mice, whereas this dose caused the presence of tail pinch, corneal, and toe pinch reflexes at 100%, and the muscle tone appeared at 100%. The depth of anesthesia appeared to be more typical in the groups treated with orphenadrine and ketamine (Table 3). Table 3 reveals that the analgesic ED_{50s} for orphenadrine and ketamine were 13.4 and 2.4mg/kg, respectively. However, the coadministration of orphenadrine and ketamine at a static ratio (50%:50%) of their separate ED_{50} value were 4.3 and 0.8mg/kg, respectively (Table 4). Calculation of the interaction index revealed that the coadministration of orphenadrine and ketamine had a synergistic index on initiating analgesia in our laboratory animals. The interaction index (Y) was 0.65 between both drugs (an index of < 1 indicated synergism).

Table 2: The anesthetic effect of coadministration of orphenadrine and ketamine

Groups	No. of death	Tail pinch reflex	Corneal Reflex	Muscle tone	Toe pinch reflex
Group 1	2/6 (33%)	6/6 (100%)	6/6 (100%)	6/6 (100%)	5/6 (83%)
Group 2	0/6 (0%)	1/6 (16%)	0/6 (0%)	1/6 (16%)	2/6 (33%)
Group 3	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (0%)	0/6 (%)

Table 3: The effect of coadministration of orphenadrine and ketamine on the depth of anesthesia

Groups	Onset of anesthesia in the second	Duration of anesthesia in minute	Recovery time in minute
Group 1	109±0.31	100±6.71	40±4.65
Group 2	70±0.16*	133±5.42*	27.6±2.05*
Group 3	55±0.10*a	192±5.43*a	27.7±2.50*

The value represented as (mean ± SD) for 6mice per groups. *Significantly (P< 0.05) different from corresponding values from group 1. a Significantly (P< 0.05) different from corresponding values from group 2.

Table 4: The interaction of analgesic effect of orphenadrine-ketamine coadministration

Variables	Orphenadrine	Ketamine	Orphenadrine and Ketamine	
			Orphenadrine	Ketamine
ED_{50} (mg/kg)	13.5	2.4	4.3	0.8
The average of the doses utilized (mg/kg)	14-10=4	3-2=1	7-4=3	1.5-0.75=0.75
first dose (mg/kg)	10	3	7	1.5
final dose (mg/kg)	12	2.5	5	1
Increment or decrement in the dose (mg/kg)	2	0.5	1	0.25
Number of mice involved	OOXOXO	XXOXOO	XXXOXOX	
The interaction index (Y)			0.65	

X= Death. O= alive.

Discussion

Mice and rats are widespread laboratory animals and are often available to veterinarians for assessment and medical management (33). Anesthesia in pet animals is essential for many surgical and diagnostic procedures, and it is related to advanced perioperative hazards in rodents and rabbits compared to canine and feline (33-35). There are many advantages to injectable anesthesia, such as needing no more instruments, administration, and dosing are very easily educated and calculated (23). The mixture of ketamine and xylazine is one of the most commonly used anesthetic regimens in rats and mice (8,36,37). Bradycardia and hypotension are the main side effects of xylazine/ketamine in mice (36), cows (38), sheep, and goats (39). The primary objective of our study was to evaluate a new mixture of anesthetics, orphenadrine, and ketamine to reduce the side effects of ketamine/xylazine. The main side effects of using ketamine alone were muscle stiffness, the presence of body reflexes during anesthesia, and the adverse effects of xylazine on laboratory animals and ruminants.

One of the most essential clinical uses of orphenadrine is muscle relaxation, owing to the multiple mechanisms through which it works on the body. Therefore, this pharmacological action affects the quality of anesthesia when used with ketamine, which lacks the most important element of ideal anesthesia: the relaxation of skeletal muscles. Muscle relaxation is necessary when performing surgical operations, as the surgical incision of the skin and muscles during the operation is easier with relaxed muscles through a small incision and then pulling the skin and muscles with special tools, furthermore, it's very important. It is a fundamental process during abdominal closure (40). Thus, wound healing was faster. One of the critical things we noticed in mice anesthetized with a combination of orphenadrine and ketamine is the disappearance of body reflexes, which may constitute an obstacle to the surgeon when choosing ketamine alone. Anesthesia mixtures of xylazine and ketamine are common in veterinary medicine, especially in small animals such as dogs and cats, and laboratory animals such as rodents (41), hamsters (42), guinea pigs (43), and rabbits (44); however, ruminants are very sensitive to xylazine, and their doses must be calculated carefully because of their side effects (45). Therefore, our study aimed to evaluate the efficacy of orphenadrine as a substitute for xylazine in combination with ketamine. To the best of our knowledge, no study has evaluated the combination of anesthesia orphenadrine with ketamine in humans or animals. Our findings indicated that the administration of orphenadrine decreased the onset of anesthesia and increased the duration of anesthesia with ketamine in mice; the expected hypothesis for these effects may be that the two drugs have similar mechanisms of action on NMDA receptors. The NMDA receptor is an ionotropic receptor that permits electrical impulses to be transferred between neurons in the brain and the spinal cord neurons. The NMDA receptor must be open for electrical signals to pass; glycine and glutamate have an agonist activity on the NMDA receptor to maintain keep it open. Ketamine and orphenadrine are non-competitive antagonists of NMDA receptors (16). The anesthetic effect of ketamine was not attributed to antagonistic activity on NMDA receptors only, but it acts on muscarinic receptors, opioid receptors, monoaminergic receptors, and voltage-sensitive calcium ion channels. Ketamine, unlike other general anesthetic agents, does not affect GABA receptors (46). After evaluating the anesthetic action of the mixture of orphenadrine and ketamine, we decided to evaluate the analgesic action of this mixture, as pain relief is one of the aspects of ideal anesthesia. The mechanism of action of these two drugs is via the same NMDA receptor. Orphenadrine is used as a painkiller alone or in combination with paracetamol (47) and diclofenac (18). A molecular study refers to a new mechanism action of the analgesic effect of orphenadrine that inhibits diverse subtypes of voltage-gated sodium channels at recommended doses, including the Nav1.7, Nav1.8, and Nav1.9 channel subtypes that are primarily involved in pain (13). Pain, inflammation, and some toxicological and behavioral studies on laboratory animals are trustworthy and their scientific findings can be relied upon (48-51). Further studies should be conducted in dogs and cats.

Conclusions

In conclusion, administering orphenadrine with ketamine has many advantages; it produces safe, smooth, and surgical anesthesia, and the unwanted effects of ketamine can disappear with orphenadrine. Orphenadrine and ketamine has a synergistic analgesic effect.

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Competing interests

The authors declare no competing interests.

References

1. Velonis D, EmmanouiAl D, Mason KP. Pharmacologic behavior management (sedation-general anesthesia). In: Kotsanos N, Sarnat H, Park K, editors. Pediatric dentistry. USA: Springer; 2022. 131-53 p. DOI: 10.1007/978-3-030-78003-6_8
2. Taylor S, St Denis K, Collins S, Dowgray N, Ellis SL, Heath S, Rodan I, Ryan L. 2022 ISFM/AAFP cat-friendly veterinary environment

guidelines. J Feline Med Surg. 2022;24(11):1133-63. DOI: 10.1177/1098612X221128763
3. Coppens M, Steenhout A, De Baerdemaeker L. Adjuvants for balanced anesthesia in ambulatory surgery. Best Pract Res Clin Anaesthesiol. 2023. DOI: 10.1016/j.bpa.2022.12.003
4. Alatrushi AN, Naser AS. The safety profile of the anesthetic effect of alfaxalone and its interaction with xylazine and ketamine in chick's model. Maced Vet Rev. 2021;44(2):203-209. DOI: 10.2478/macvetrev-2021-0025
5. Fernandez-Parra R, Adami C, Dresco T, Donnelly TM, Zilberstein L. Dexmedetomidine-methadone-ketamine versus dexmedetomidine-methadone-alfaxalone for cats undergoing ovariectomy. Vet Anaesth Analg. 2017;44(6):1332-40. DOI: 10.1016/j.vaa.2017.03.010
6. Craven R. Ketamine. Anaesthesia. 2007;62(1):48-53. DOI: 10.1111/j.1365-2044.2007.05298.x
7. Morgan CA, Mofeez A, Brandner B, Bromley L, Curran HV. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacol. 2004;29(1):208-18. DOI: 10.1038/sj.npp.1300342
8. Buitrago S, Martin TE, Tetens-Woodring J, Belicha-Villanueva A, Wilding GE. Safety and efficacy of various combinations of injectable anesthetics in BALB/c mice. J Am Assoc Lab Anim Sci. 2008;47(1):11-7. [available at]
9. Li C, Peng J, Hu R, Yan J, Sun Y, Zhang L, Liu W, Jiang H. Safety and efficacy of ketamine versus ketamine-fentanyl-dexmedetomidine combination for anesthesia and analgesia in rats. Dose-Response. 2019;17(1):1559325819825902. DOI: 10.1177/1559325819825902
10. Lees A. Alternatives to levodopa in the initial treatment of early Parkinson's disease. Drugs Aging. 2005;22:731-40. DOI: 10.2165/00002512-200522090-00002
11. Foffani G, Priori A, Egidi M, Rampini P, Tamma F, Caputo E, Moxon KA, Cerutti S, Barbieri S. 300-Hz subthalamic oscillations in Parkinson's disease. Brain. 2003;126(10):2153-63. DOI: 10.1093/brain/awg229
12. Maltese M, Martella G, Madeo G, Fagiolo I, Tassone A, Ponterio G, Sciamanna G, Burbaud P, Conn PJ, Bonsi P, Pisani A. Anticholinergic drugs rescue synaptic plasticity in DYT1 dystonia: Role of M1 muscarinic receptors. Mov Disord. 2014;29(13):1655-65. DOI: 10.1002/mds.26009
13. Desaphy JF, Dipalma A, De Bellis M, Costanza T, Gaudioso C, Delmas P, George Jr AL, Camerino DC. Involvement of voltage-gated sodium channels blockade in the analgesic effects of orphenadrine. Pain. 2009;142(3):225-35. DOI: 10.1016/j.pain.2009.01.010
14. Chen YW, Tzeng JI, Chen YC, Hung CH, Wang JJ. Intrathecal orphenadrine elicits spinal block in the rat. Eur J Pharmacol. 2014;742:125-30. DOI: 10.1016/j.ejphar.2014.08.035
15. Scholz EP, Konrad FM, Weiss DL, Zitron E, Kiesecker C, Bloehs R, Kulzer M, Thomas D, Kathöfer S, Bauer A, Maurer MH. Anticholinergic antiparkinson drug orphenadrine inhibits HERG channels: Block attenuation by mutations of the pore residues Y652 or F656. Naunyn Schmiedebergs Arch Pharmacol. 2007;376:275-84. DOI: 10.1007/s00210-007-0202-6
16. Kornhuber J, Parsons CG, Hartmann S, Retz W, Kamolz S, Thome J. Orphenadrine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist: Binding and patch clamp studies. J Neural Transm Sect JNT. 1995;102:237-46. DOI: 10.1007/BF01281158
17. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Muscle relaxants for nonspecific low back pain: A systematic review within the framework of the cochrane collaboration. Spine. 2003;28(17):1978-92. DOI: 10.1097/01.BRS.0000090503.38830.AD
18. Schaffler K, Reitmeir P, Gschanes A, Eggenreich U. Comparison of the analgesic effects of a fixed-dose combination of orphenadrine and diclofenac (Neodolpasse®) with its single active ingredients diclofenac and orphenadrine: A Placebo-controlled study using laser-induced somatosensory-evoked potentials from capsaicin-induced hyperalgesic human skin. Drugs RD. 2005;6:189-99. DOI: 10.2165/00126839-200506040-00001
19. Bersani G, Grispini A, Marini S, Pasini A, Valducci M, Ciani N. 5-HT2 antagonist ritanserin in neuroleptic-induced parkinsonism: a double-blind comparison with orphenadrine and placebo. Clin Neuropharmacol. 1990;13(6):500-6. DOI: 10.1097/00002826-199012000-00003
20. Xu Q, Ming Z, Dart AM, Du X. Optimizing dosage of ketamine and xylazine in murine echocardiography. Clin Exp Pharmacol Physiol. 2007;34(5-6):499-507. DOI: 10.1111/j.1440-1681.2007.04601.x
21. Hunskaar S, Rosland JH, Hole K. Mechanisms of orhenadrine-induced antinociception in mice: A role for serotonergic pathways. Eur J Pharmacol. 1989;160(1):83-91. DOI: 10.1016/0014-2999(89)90656-0
22. Alves HC, da Silva AM, Olsson IS, Orden JG, Antunes LM. Anesthesia with intraperitoneal propofol, medetomidine, and fentanyl in rats. J Am Assoc Lab Anim Sci. 2010;49(4):454-9. [available at]
23. Siriarchavatana P, Ayers JD, Kendall L V. Anesthetic activity of alfaxalone compared with ketamine in mice. J Am Assoc Lab Anim Sci. 2016;55(4):426-30. [available at]
24. Zhang H, Xu J, Wu Q, Fang H, Shao X, Ouyang X, He Z, Deng Y, Chen C. Gut microbiota mediates the susceptibility of mice to sepsis-associated encephalopathy by butyric acid. J Inflamm Res. 2022;2103-19. DOI: 10.2147/JIR.S350566
25. Ramabadran K, Bansinath M, Turndorf H, Puig MM. Tail immersion test for the evaluation of a nociceptive reaction in mice: Methodological considerations. J Pharmacol Methods. 1989;21(1):21-31. DOI: 10.1016/0160-5402(89)90019-3
26. Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20(1):441-62. DOI: 10.1146/annurev.pa.20.040180.002301
27. Abdul-gani MR, Naser AS. Assessment of the analgesic effect of Alpha-lipoic acid by three acute pain models. Iraqi J Vet Sci. 2022;36(3):803-7. DOI: 10.33899/IJVS.2022.132184.2062
28. Alberifki NM, Naser AS. Flurbiprofen: Determination of safety profile, analgesic effect, and interaction with lipoic acid in murine. Iraqi J Vet Sci. 2023;37(2):447-52. DOI: 10.33899/IJVS.2023.136615.2599
29. Tallarida RJ. Statistical analysis of drug combinations for synergism. Pain. 1992;49(1):93-7. DOI: 10.1016/0304-3959(92)90193-F
30. Naser AS, Albadrany Y, Shaaban KA. Isobolographic analysis of analgesic interactions of silymarin with ketamine in mice. J Hell Vet Med Soc. 2020;71(2):2171-8. DOI: 10.12681/jhvms.23653
31. Naser AS, Mohammad FK. Central depressant effects and toxicity of propofol in chicks. Toxicol Rep. 2014;1:562-8. DOI: 10.1016/j.toxrep.2014.08.003
32. Köse Ç, Shahzadi A, Akkan AG, Özyazgan S. The effect of orphenadrine on rewarding property of morphine-induced conditioned place preference. Cerrahpaşa Med J. 2020;44(2):80-5. [available at]
33. Wenger S. Anesthesia and analgesia in rabbits and rodents. J Exot Pet Med. 2012;21(1):7-16. DOI: 10.1053/j.jepm.2011.11.010
34. Divers SJ. Exotic mammal diagnostic endoscopy and endosurgery. Vet Clin Exot Anim Pract. 2010;13(2):255-72. DOI: 10.1016/j.cvex.2010.01.006
35. Szabo Z, Bradley K, Cahalane AK. Rabbit soft tissue surgery. Vet Clin Exot Anim Pract. 2016;19(1):159-88. DOI: 10.1016/j.cvex.2015.08.007
36. Arras M, Autenried P, Rettich A, Spaeni D, Rülicke T. Optimization of intraperitoneal injection anesthesia in mice: Drugs, dosages, adverse effects, and anesthesia depth. Comp Med. 2001;51(5):443-56. [available at]
37. Gargiulo S, Greco A, Gramanzini M, Esposito S, Affuso A, Brunetti A, Vesce G. Mice anesthesia, analgesia, and care, Part II: Anesthetic considerations in preclinical imaging studies. Inst Lab Anim Res J. 2012;53(1):E70-81 .DOI: 10.1093/ilar.53.1.70
38. Guerri G, Cerasoli I, Straticò P, De Amicis I, Giangaspero B, Varasano V, Petrizzi L. The clinical effect of xylazine premedication in water buffalo calves (*Bubalus bubalis*) undergoing castration under general anaesthesia. Anim. 2021;11(12):3433. DOI: 10.3390/ani11123433
39. Ismail ZB, Jawasreh K, Al-Majali A. Effect of xylazine-ketamine-diazepam anesthesia on certain clinical and arterial blood gas parameters in sheep and goats. Comp Clin Path. 2010;19:11-4. DOI: 10.1007/s00580-009-0896-6

تقييم فوائد الاورفينادرين في التخدير المحدث بالكتامين في الفئران

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فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

تستخدم الفئران كحيوانات مختبرية لتقييم الأدوية المخدرة، كان الجمع بين أكثر من دواء لتحقيق التخدير العام شائعًا جداً، ويعتبر الاورفينادرين عقارًا مميزا نظرًا لآليات عمله المتعددة في مسارات مختلفة ويستخدم بشكل أساسي كمرخي للعضلات ولعلاج آلام العضلات وتشنج العضلات. كان الهدف من دراستنا هو تقييم تأثير الإعطاء المتزامن للاورفينادرين والكيتامين على جودة التخدير العام في ذكور الفئران البيضاء. تم استخدام ذكور الفئران لتقييم توليفة الأورفينادرين والكيتامين في بدء التخدير ومدته والإفاقة، بالإضافة إلى اختفاء أو وجود استجابات للمنعكسات، وتم تقييم التأثير المسكن لمزيج من الكيتامين والأورفينادرين عن طريق تحديد متوسط الجرعة الفعالة باستخدام طريقة الصعود النزول في اختبار غمر الذيل. أدى الجمع بين الأورفينادرين والكيتامين إلى انخفاض معنوي في بدء التخدير مقارنة بالكيتامين وحده، وزيادة معنوية في مدة التخدير وانخفاض كبير في وقت الإفاقة مقارنة بالكيتامين وحده، وهذا الخليط أدى إلى اختفاء جميع الاستجابات الانعكاسية للفئران بالمقارنة مع الفئران المخدرة بالكتامين لوحده. أظهرت نتائجنا تأثيرًا مسكنًا تآزريًا عند تناول الأورفينادرين والكيتامين معًا اعتمادًا على القيمة المحسوبة لـ واي. لقد أظهرنا إمكانية استخدام الأورفينادرين كبديل للزيلازين عند إعطائه مع الكيتامين للحث على التخدير العام، وكان التأثير المسكن متآزراً عند تناول مزيج من الكيتامين والأورفينادرين. تفتح هذه النتائج آفاقًا جديدة لاستخدام الأورفينادرين في مجال التخدير، لذلك أوصينا بإجراء المزيد من الدراسات حول هذا الموضوع.

40. Amaki Y, Haziri H, Sugimoto N, Shudo Y, Kobayashi K. The degree of muscle relaxation requested by the surgeons during upper abdominal surgery. J Anesth. 1990;4:249-52. DOI: 10.1007/s0054000040249
41. Levin-Arama M, Abraham L, Waner T, Harmelin A, Steinberg DM, Lahav T, Harlev M. Subcutaneous compared with intraperitoneal ketamine-xylazine for anesthesia of mice. J Am Assoc Lab Anim Sci. 2016;55(6):794-800. [available at]
42. Rajaei SM, Mood MA, Paryani MR, Williams DL. Effects of diurnal variation and anesthetic agents on intraocular pressure in Syrian hamsters (*Mesocricetus auratus*). Am J Vet Res. 2017;78(1):85-9. DOI: 10.2460/ajvr.78.1.85
43. Sloan RC, Rosenbaum M, O'Rourke D, Oppelt K, Frasier CR, Waston CA, Allan AG, Brown DA. High doses of ketamine-xylazine anesthesia reduce cardiac ischemia-reperfusion injury in guinea pigs. J Am Assoc Lab Anim Sci. 2011;50(3):349-54. [available at]
44. Lipman NS, Marini RP, Erdman SE. A comparison of ketamine/xylazine and ketamine/xylazine/acepromazine anesthesia in the rabbit. Lab Anim Sci. 1990;40(4):395-8. [available at]
45. Riebold TW. Ruminants. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, editors. Veterinary anesthesia and analgesia: The fifth edition of Lumb and Jones. USA: Wiley; 2015. 912-27 p. DOI: 10.1002/9781119421375.ch49
46. Xu J, Lei H. Ketamine-an update on its clinical uses and abuses. CNS Neurosci Ther. 2014;20(12):1015-2. DOI: 10.1111/cns.12363
47. Hunskaar S, Donnell D. Clinical and pharmacological review of the efficacy of orphenadrine and its combination with paracetamol in painful conditions. J Int Med Res. 1991;19(2):71-87. DOI: 10.1177/030006059101900201
48. Mohammed QM, Albadrany YM. Pregabalin potentiates the analgesic effect of tramadol, diclofenac and paracetamol in chicks: Isobolographic analysis. Iraqi J Vet Sci. 2022;36(4):931-937. DOI: 10.33899/ijvs.2022.132586.2108
49. Abdul-Ghani MR, Naser AS. The protective impacts of lipoic acid on diclofenac-induced hepatorenal toxicity in broiler chicks. Iraqi J Vet Sci. 2022;36(4):1023-1027. DOI: 10.33899/ijvs.2022.132915.2148
50. Fadel MA, Mustafa KA. The anti-inflammatory effect of allopurinol and diclofenac in chicks' model. Iraqi J Vet Sci. 2023;37(3):٥٤٧-٥٥٣. DOI: 10.33899/ijvs.2023.138108.2769
51. Naser AS, Albadrany YM. The neurobehavioral effects of flumazenil in chicks. Iraqi J Vet Sci. 2021;35(4):783-788. DOI: 10.33899/ijvs.2020.128443.1577