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Detection of potential effects of orphenadrine upon anesthesia with propofol and/or thiopental in mice

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Abstract

Orphenadrine is an anticholinergic drug used in clinics as a muscle relaxant. It acts on several receptors, including muscarinic, histaminic, and NMDA. This study aimed to evaluate the effect of pretreatment with orphenadrine on the anesthesia indices of two essential parenteral anesthetic drugs in mice. Three experiments were performed with 15 mice per experiment. All experiments used orphenadrine at 10 mg and 20 mg/kg/IP b.wt as a pretreatment drug. Propofol (100 mg/kg/IP), thiopental (50 mg/kg/IP), and their combinations were used in the first, second, and third experiments, respectively. The indices of anesthesia, represented by the latency to onset of anesthesia, duration of anesthesia, and recovery from anesthesia, were recorded. Orphenadrine at doses of 10 mg and 20 mg/kg/IP as a pretreatment drug showed a dose-dependent decrease in the latency to the onset of anesthesia and an increase in the duration of anesthesia compared to the control groups of all three experiments (propofol 100 mg/kg, thiopental 50 mg/kg, and combinations of propofol and thiopental) respectively. We conclude that orphenadrine affects anesthesia indices, which are recorded for the first time, laying the foundation for further studies and the possibility of using it as an anesthesia co-treatment.

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Introduction

With the advancement of technology, intravenous anesthesia is progressively being introduced into clinical practice, and it is distinguished by faster effects and fewer adverse effects when compared to inhalation anesthetics (1). The specific mechanism of anesthetic achievement is not entirely known; the anesthetic deed can be caused via increasing inhibitory neurotransmitters, decreasing excitatory neurotransmitters, or both (2). Currently, available intravenous anesthetics do not meet the criteria for ideal anesthetic agents because they do not produce all five wanted properties: unconsciousness, amnesia, analgesia, autonomic reflex inhibition, and skeletal muscle relaxation (3). In order to reduce side effects, balanced anesthesia typically uses a combination of medicines, including inhaled anesthetics, sedatives, hypnotics, opioids, and neuromuscular blocking agents (4). Propofol is a frequently used intravenous anesthetic in the clinical setting. Propofol is a short-acting anesthetic that allows quick and painless recovery (5). Propofol is used for procedures that require quick recovery to preoperative mental capacity (6). Owing to its widespread use, it is now preferred over thiopental for the induction of general anesthesia and sedation (7). Thiopental induces anesthesia; it is given intravenously. Thiopental has a very rapid beginning of action and a high level of lipid solubility (8). The reason for its brief duration of action is that it is also rapidly transferred from the brain to other tissues (muscle and fat). It is utilized for quick surgical procedures and anesthetic induction (9). Orphenadrine is an anticholinergic drug used in Parkinson's disease treatment to decrease some of the most bothersome symptoms, particularly involuntary resting tremors (10). It is used in clinics as a muscle relaxant (11). Orphenadrine acts on several receptors, including

muscarinic, histamine, and NMDA (12). It is also used as an analgesic, even though its particular mode of action is unknown (13).

This study aimed to evaluate the effects of two doses of orphenadrine on propofol and thiopental anesthesia indices. We anticipated that these combinations would lead to secure anesthetic protocols with prompt induction of anesthesia.

Materials and methods

Ethical approval

The animals handling ethics protocol of the College of Veterinary Medicine, University of Mosul, was followed. The Scientific Board of Physiology, Biochemistry, and Pharmacology department approved this study (Ref: UM.VET. 2023. 007, date: 25/3/2023).

Animals

Adult male albino mice (10-12 weeks old, 20-30 g) were used in the study. Five mice were housed per cage in a room kept at 25±1°C with a relative humidity of 55±5% and an alternate 12-hour light and dark sequence, with free access to food and water. The animals were used only once in all experiments. The animals were separated and housed in different cages after the IP injection. The experimenters observed the reactions of the mice during the experiments that had been followed from 8 a.m. to 2 p.m.

Impact of orphenadrine on the anesthesia induced by propofol in mice

Fifteen mice were randomized into three equal groups. Group 1 mice were pretreated with normal saline, after 15 min with propofol 100 mg/kg IP (14). Group 2 mice were pretreated with orphenadrine 10 mg/kg /IP (15), after 15 min with propofol 100 mg/kg /IP. The mice of the third group were previously administered by orphenadrine at 20mg/kg intraperitoneal, followed by fifteen minutes administered by propofol at 100mg/kg intraperitoneal.

Impact of orphenadrine on the anesthesia generated by thiopental in mice

Fifteen mice were allocation for three groups. First group were administered by normal saline intraperitoneal, followed by fifteen minutes administered by thiopental at 50mg/kg, intraperitoneal (16). The second group were administered by orphenadrine at 10mg/kg, intraperitoneal, followed by fifteen minutes administered by thiopental at 50mg/kg, intraperitoneal. The third group were administered by orphenadrine at 20mg/kg, intraperitoneal, followed by fifteen minutes administered by thiopental at 50mg/kg, intraperitoneal.

Impact of orphenadrine on anesthesia generated by propofol and thiopental in mice

Fifteen mice were allocation for three groups. Group 1 mice were pretreated with normal saline, after 15 min with propofol 100 mg/kg/IP and thiopental 50 mg/kg/IP. Group 2 mice were pretreated with orphenadrine 10 mg/kg /IP, after 15 min with propofol 100 mg/kg/IP and thiopental 50 mg/kg/IP. Group 3 mice were pretreated with orphenadrine 20 mg/kg /IP, after 15 min with propofol 100 mg/kg /IP and thiopental 50 mg/kg/IP.

Drugs

Orphenadrine citrate injection 30 mg/ml Teva® (USA), propofol 100 mg/10 ml DIPRIVAN® (U.K), thiopental sodium injection 1 g powder THOWELL®(INDIA). The volume of administration was 10 ml/kg/IP of body weight (3). All drugs were injected after preparing the doses in different syringes, and then the latency to onset of anesthesia was noted, which is the interval between the injection and the loss of the righting reflex of mice. The duration of anesthesia was noted, which is the interval between the loss of the righting reflex and the time it took for the mice to correct their posture, and the recovery from anesthesia, which is the interval between the time the mouse had returned to normal position and the time to resumed movement (17).

Statistical analysis

One-way analysis of variance (ANOVA) followed by the Least Significant Difference test was used to assess the results statistically. Data are expressed as mean±standard error. $P \leq 0.05$ was chosen as the minimal degree of significance. The analysis was conducted with the statistical software SPSS 17.

Results

Effect of orphenadrine on the anesthesia induced by propofol in mice

As shown in table 1, the latency to onset of propofol anesthesia within approximately four minutes, the duration of anesthesia continued for half an hour through the mice return to normal position, and the recovery period was approximately twenty-five minutes, which the mice represented a return to its normal movement and behavior. When treated with orphenadrine, there was a dose-dependent decrease in latency to the onset of anesthesia and an increase in the duration of anesthesia compared with the propofol group. It was noted that the orphenadrine prolonged the anesthesia duration time. In addition, there was an increase in the recovery period in the group treated with orphenadrine 20 mg/kg compared to the propofol group.

Table 1: Impact of orphenadrine on anesthesia induced by propofol

Groups	Latency to onset (min)	Duration (min)	Recovery time (min)
Group 1	4.16±0.22[a]	37.33±1.94[c]	25.44±1.14[b]
Group 2	3.59±0.18[a]	61.49±1.43[b]	19.95±0.68[c]
Group 3	2.39±0.25[b]	92.27±2.55[a]	35.55±1.00[a]

At the 5% significance level, differences between values in each column denoted by various superscript letters are significant. Values are Mean±SE.

Effect of orphenadrine on the anesthesia induced by thiopental in mice

As shown in table 2, latency to onset of thiopental anesthesia within approximately ten minutes, the duration of anesthesia continued for a third of an hour through the mice return to normal position, and the recovery period was approximately ten minutes, which the mice represented a return to its normal movement and behavior. When treated with orphenadrine, there was a dose-dependent decrease in latency to the onset of anesthesia and an increase in the duration of anesthesia compared with the thiopental group. It was noted that the orphenadrine prolonged the anesthesia duration time. In addition, there was an increase in the recovery period in the orphenadrine group compared to that in the propofol group.

Table 2: Impact of orphenadrine on anesthesia induced by thiopental

Groups	Latency to onset (min)	Duration (min)	Recovery time (min)
Group 1	9.87±0.52[a]	21.03±0.73[c]	10.18±0.36[c]
Group 2	4.74±0.17[b]	40.58±1.01[b]	20.31±0.65[b]
Group 3	2.55±0.19[c]	84.41±1.34[a]	40.03±1.69[a]

At the 5% significance level, differences between values in each column denoted by various superscript letters are significant. Values are Mean±SE.

Effect of orphenadrine on the anesthesia induced by propofol and thiopental combination in mice

As shown in table 3, concomitant treatment with propofol and thiopental resulted in the latency to onset of anesthesia within approximately one minute, the duration of anesthesia continued for almost two hours through the mice returned to the normal position, and the recovery period was approximately half an hour, which the mice represented a return to its normal movement and behavior. When treated with orphenadrine, there was a dose-dependent decrease in the latency to the onset of anesthesia and an increase in the duration of anesthesia compared to the propofol and thiopental group. It was noted that the orphenadrine prolonged the anesthesia duration time. In addition, there was an increase in the recovery period in the orphenadrine group compared to the propofol and thiopental group.

Table 3: Impact of orphenadrine on anesthesia induced by propofol and thiopental

Groups	Latency to onset (min)	Duration (min)	Recovery time (min)
Group 1	1.26±0.12[a]	86.88±0.88[c]	26.01±0.75[c]
Group 2	0.93±0.06[b]	127.55±1.91[b]	39.28±1.88[b]
Group 3	0.73±0.05[b]	177.43±5.92[a]	72.37±2.63[a]

At the 5% significance level, differences between values in each column denoted by various superscript letters are significant. Values are Mean±SE.

Discussion

A logical method for multimodal general anesthesia should include the following steps: administration of combinations of antinociceptive drugs, each targeting a distinct circuit in the nociceptive system; continuous monitoring of levels of antinociception and unconsciousness; expressly using the sedative effects of antinociceptive medicines to minimize the doses of hypnotic medications and inhaled anesthetics used to maintain unconsciousness; and maintaining multimodal pain control during the in-hospital postoperative period and after discharge (18,19). No anesthetic medication can supply all the constituents of general anesthesia without interfering with essential organ roles. As a result, a multi-drug method (balanced anesthesia) is used to decrease sensory, motor, sympathetic, and parasympathetic response actions, as well as distinct constituents of the anesthetic state (20-22). Therefore, this study aimed to estimate a new combination of anesthetic drugs with orphenadrine, a muscle-relaxant drug, and its effect on anesthesia indices.

Among the significant results noted in our research is that the administration of orphenadrine in doses 10 and 20 mg/kg reduced the period of onset of anesthesia and increased the induction period of anesthesia (period of surgical operation). This effect is recorded for the first time and needs further study and research to reveal the mechanism of this synergistic effect at the level of anesthesia. GABA is the core inhibitory neurotransmitter in the mammalian central nervous system (23,24). Glutamate is the primary excitatory amino acid neurotransmitter acting on NMDA and non-NMDA receptors, which play a main part in physiological processes such as memory and learning (and thus consciousness under anesthesia) and principal pain transduction mechanisms (25-27).

Propofol inhibits postsynaptic neurons by preventing GABA from dissociating from its receptors. This increases chloride entry via channels, leading to hyperpolarization of postsynaptic cell membranes and inhibition of postsynaptic neurons (28,29). Propofol also inhibits the NMDA subtype

of the glutamate receptor, probably by modulation in the channel gating (30). Propofol inhibits voltage-gated sodium currents and controls calcium influx via slow calcium channels (31,32).

Thiopental works in a manner analogous to barbiturate drugs. It acts as an agonist of (the $GABA_A$) receptor, increasing inhibitory neurotransmission. It increases GABA binding to its receptor (an inhibitory neurotransmitter) and then increases transmembrane chloride entrances, causing hyperpolarization of the postsynaptic cell and inhibition of the postsynaptic neurons (33,34). Thiopental inhibitory activity on NMDA receptors may not be mediated via the secondary effects of the $GABA_A$ receptor agonist. These findings suggest that NMDA receptors play a role in mice's thiopental-induced anesthesia (35).

Notably, orphenadrine has no anesthetic effects; however, studies have indicated its effects on different receptors (36). Orphenadrine is a diphenylmethane analog of diphenhydramine with antimuscarinic, NMDA antagonistic, and antihistaminic characteristics to a lesser extent (37). The synergistic action of orphenadrine on propofol and thiopental anesthesia indices can be explained by its action on different receptors. Nevertheless, the hypothesis closest to explaining this synergistic effect may be through NMDA antagonism, as N-methyl-D-aspartate (NMDA) receptors are essential in the nervous system's excitatory neurotransmission. Some general anesthetics preferentially block them, so they have been implicated in mediating their effects (38). Hypnotic effects of ketamine occur by blocking NMDA receptors in nervous tissue (39). Blocking NMDA receptors is related to the immobilization effect of inhalational anesthetics (40,41).

Conclusion

It could be concluded that pretreatment with orphenadrine affects anesthesia indices for both propofol and thiopental alone or together. These results provide a foundation for further research and investigation. Orphenadrine can be used in clinical studies on different animals to investigate its safety and its possible use in various surgical procedures.

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Conflict of interest

No conflict of interest.

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الكشف عن التأثيرات المحتملة للاورفينادرين على التخدير بالبروبوفول و/أو الثايوبنتال في الفئران

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الخلاصة

الاورفينادرين هو دواء مضاد للكولين يستخدم سريريا كمرخي للعضلات. ويعمل على العديد من المستقبلات بما في ذلك مستقبلات المسكارين والهستامين ومستقبلات NMDA.هدفت هذه الدراسة إلى تقييم تأثير المعاملة المسبقة بألورفينادرين على مؤشرات التخدير لعقارين مهمين للتخدير بالحقن في الفئران. أجريت ثلاث تجارب مع ١٥ فأر لكل تجربة. في جميع التجارب تم استخدام الاورفينادرين بالجرع (١٠ و ٢٠ ملغم/كغم/في الخلب) كدواء معاملة مسبق. تم استخدام البروبوفول (١٠٠ ملغم/كغم/في الخلب)، والثايوبنتال (٥٠ ملغم/كغم/في الخلب)، وكلا الدوائيين سويا في التجارب الأولى والثانية والثالثة على التوالي. تم تسجيل مؤشرات التخدير، المتمثلة في بداية التخدير، ومدة التخدير، والتعافي من التخدير. أظهرت النتائج الرئيسية للاستخدام الاورفينادرين كعلاج مسبق انخفاضًا يعتمد على الجرعة في بداية التخدير وزيادة في مدة التخدير مقارنة بمجموعات السيطرة في كل التجارب. نستنتج أن للأورفينادرين تأثير على مؤشرات التخدير، والتي تم تسجيلها لأول مرة، مما يضع الأساس لمزيد من الدراسات وإمكانية استخدامه كعلاج مرافق في التخدير.