



## The role of amantadine as a premedication for induction of ketamine-balanced anesthesia in chick model

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### Abstract

The objective of this research was to investigate the pharmacological effects of amantadine in 7-14 day-old chicks and to determine its safety, as well as its role in inducing ketamine-balanced anesthesia, and to compare it with the traditional mixture (ketamine-xylazine) for future use in other animals. The analgesic median effective dose and the acute median lethal dose of amantadine were determined using the up-and-down method to be 15.72 and 930 mg/kg, orally (P.O.), respectively. These results showed that amantadine has a wide range of safety in the chick model by measuring the therapeutic index. Amantadine at multiple doses of 7.86, 15.72, and 31.44 mg/kg, P.O., caused analgesia in chicks at percentages of 33, 50, and 100%, respectively, in a dose-dependent fashion. Ketamine alone (25 mg/kg, IM) produces analgesia, while administration of xylazine (5 mg/kg, IM) or amantadine (31.44 mg/kg, P.O.) with ketamine significantly increases the pain relief. Amantadine with ketamine significantly reduced the hypnotic onset and recovery associated with ketamine or as a mixture with xylazine. When measuring the vital signs of chicks using a patient monitor when anesthetized with ketamine alone or with xylazine or amantadine, amantadine reduced the cardiopulmonary (heart rate, blood pressure, respiratory rate, and SPO<sub>2</sub>) suppression compared to xylazine. The results of this study specify that amantadine has analgesic and hypnotic properties and a wide margin of safety, in addition to the possibility of using it to induce ketamine-balanced anesthesia in chicks, which makes it useful for future use in veterinary medicine.

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### Introduction

Amantadine is an antiviral medication with activity against Parkinson's disease. Amantadine was served in the first 2000s to treat influenza (1). Amantadine has a mode of action comparable to ketamine, which is the antagonistic effect on the N-Methyl-D-Aspartate (NMDA) receptor in the central nervous system. This gives it analgesic and sedative effects by reducing the release of the excitatory neurotransmitter glutamate, which is responsible for causing pain (2). Amantadine is also used as an adjunct medication with central pain relievers such as morphine and peripheral

ones like the non-steroidal anti-inflammatory drug group to enhance their therapeutic efficacy against pain. It is also used to treat Parkinson's and Huntington's diseases, as it has been shown that there is a synergism paradigm when combined with levodopa, which that converted to dopamine by the dopaminergic neurons in the central nervous system (2-6). Studies have shown that amantadine affects dopamine-producing neurons as well as its pharmacological antagonism of the NMDA-receptor, leading to increased dopamine discharge. It also blocks the re-uptake of dopamine by the neuron. Although, amantadine not having cholinergic antagonistic effect, it may have anticholinergic

side-effects such as urinary retention, dry mouth, mydriasis, and constipation (7-9).

Ketamine is widely used for anesthesia purposes in veterinary medicine, producing its sedative and weak analgesia by its blocking action for the NMDA receptor at the level of the brain and spinal cord, which reduces the amount of calcium entering nerve cells, leading to anesthesia, due to its weak analgesic properties and lack of muscle relaxation in animals, it is necessary to administer pre-anesthetic medications such as xylazine to enhance its anesthetic effects and to produce balanced anesthesia characterized by efficient sleep, better pain relief, increased muscle relaxation, reduced body reflexes, and minimized adverse effects on the heart and lungs (10-13). As for the research hypothesis, it is attributed to the central analgesic effect of amantadine, which may be effective in alleviating pain in chicks and possibly in other animals. Through this central analgesic and sedative effect, it may enhance the anesthetic efficacy of ketamine, especially since both drugs share a common mechanism of action by inhibiting the NMDA receptor.

The purpose of this research was to reveal the pharmacological effects of amantadine in a model of 7-14-day old chicks and to demonstrate its safety, as well as its role in inducing ketamine balanced anesthesia and comparing it with the traditional mixture (ketamine-xylazine) for future use in other animals.

## **Materials and methods**

### **Ethical approval**

The research was permitted via the animal usage and care board at the Veterinary Medicine College / Mosul University as the approval number UM.VET.2024.089.

### **Animals**

Chicks for both sexes were used, which were brought from the Hamdaniya hatchery in Nineveh Governorate. The chicks were placed in the animal household in the College of Veterinary Medicine/Mosul University. The size of the breeding cages was 180×150×150 cm, containing bedding and concentrated feed. The chicks were placed in the cages at one day old, and suitable climatic conditions were provided for them, including ventilation and a temperature of (24-33 °C) with 23 hrs. of light and the darkness was 1 h. They were raised until the trials were performed at 7-14 days of their age.

### **The drugs and chemicals used**

Amantadine Hydrochloride Powder, produced by Pharmaceutical Ingredients, API, (CAS 768-94-5, China). Ketamine (5%), produced by Alfasan, Netherlands. Xylazine (5%), produced by Nita, Russia.

## **Preparation of medications and methods of administration and injection**

The required doses of amantadine, ketamine, and xylazine were obtained by dilution and preparation using physiological saline, and the oral (P.O.) dose for amantadine or the intramuscular (IM) injection for ketamine or xylazine was 5 ml / kg of b. wt. of chicks.

## **Determination of the analgesic median effective dose (ED<sub>50</sub>) for amantadine in chicks via the up-and-down technique (14)**

In this first trial, 7-14-day old chicks were used. The ED<sub>50</sub> was determined using the up-and-down method, with 7 chicks weighing 150-250 grams. An initial dose of amantadine was given based on preliminary experiments at 25 mg/kg, P.O. using a gavage needle. The electrical stimulation device (Harvard Apparatus, USA) was used to evaluate the analgesic effect of amantadine by measuring the device's voltage before and 30 minutes after administering amantadine. The device's electrodes were attached under the wing, and to deliver the electric current, the area under the wing in contact with the electrodes was moistened with water. The voltage was then gradually increased until pain occurred (15-17) which is determined by the distress call, as well as observing other signs of pain such as wing flapping and calling. Here lies the first reading of the initial result before administration, then amantadine is dosed at 25 mg/kg, P.O. and based on previous experiments, the time for the second reading is set at 30 minutes after administration. The device's electrodes are also connected under the wing, and the area is moistened with water. The voltage increases until pain occurs, then the final result, which is the pain relief, is read as an elevation in voltage post administering amantadine compared to the voltage recorded before the drug administration (15-18). The occurrence of pain relief is indicated by the symbol X, and in the case of no pain relief or the voltage remaining the same, it is indicated by the symbol O. Then, the ascending and descending method of dosage is applied, with an elevation or reduction in dosage of 5 mg /kg in the case of pain relief or no pain relief in chicks. When a change occurs, this process is repeated, ascending and descending in dosage for three chicks, and then the analgesic ED<sub>50</sub> is calculated according to the following equation (14):

$$ED_{50} (\text{mg/kg}) = \text{final dose used in the trial} + (\text{value from the Dixon table}) \times (\text{amount of elevation or reduction in the dose})$$

## **Assessment the median lethal dose (LD<sub>50</sub>) of amantadine in chicks by the up-and-down technique (14)**

In this investigation, the acute LD<sub>50</sub> was determined using the up-and-down method. Seven chicks weighing 160-220 grams were used. A first dose of amantadine at 2500 mg /kg body weight was administered P.O. (based on

preliminary trials). The dose was increased or decreased by 500 mg/kg in case of death (designated as symbol X) or survival (designated as symbol O) of the chicks within 24 hours of oral administration. When a change occurred, the process was repeated up and down in dosage for three chicks, and then the acute LD<sub>50</sub> was calculated (19).

#### **Safety measurement of amantadine in the chicks**

This experiment was conducted on the basis of the outcomes of the previous two experiments using the following mathematical equation (20):

$$\text{Therapeutic index (T.I.)} = \text{LD}_{50} / \text{ED}_{50}$$

#### **The role of amantadine in inducing ketamine balanced anesthesia and its comparison with ketamine-xylazine combination**

This experiment involved the use of 18 chicks aged 7-14 days, weighing between 150-250 grams. These chicks were separated to three groups; six chicks per each. The amantadine dose was determined and used according to previous experiments, which was 31.44 mg/kg, P.O. The ketamine dose injected as 25 mg/kg, IM and for the xylazine was 5 mg /kg, IM based on previous studies (21-23) as follows: Group one (positive control): Ketamine was injected at a dosage of 25 mg/kg, IM into the chest muscle. Group two (Ketamine-Xylazine): Ketamine was injected with xylazine (25 and 5 mg/kg IM, respectively) and was injected simultaneously and separately. Group three (Ketamine-Amantadine): Ketamine was injected and amantadine was administered (25 and 31.44 mg/kg, respectively) at the same time and separately.

The analgesic efficacy of ketamine alone, ketamine with xylazine, and ketamine with amantadine was recorded using an electrical stimulator, and the voltage for each chick was measured before and after the injection of the used drugs at 30 minutes.

The beginning time of hypnosis (onset) was documented (duration from ketamine injection till the loss of the righting reflex) for every chick individually. The duration of hypnosis was also calculated, which is the time from the absence of the RR to their recurrence to natural body posture. Additionally, the total recovery time was also noted, that is the time from the onset of hypnosis pending the chicks returned the mobility to the normal (21,23-25).

At the same time, the vital signs were measured using a portable patient monitor (Yonker company, China), which included heart rate, respiratory rate, blood pressure, body temperature, and oxygen saturation of the anesthetized experimental animals in the above groups. This was done by attaching the device's electrodes to the chicks' bodies, connecting the device's sensors to the toe and inside the chicks' rectum, as well as placing a cuff around the thigh and

recording the aforementioned readings displayed on the device's screen.

#### **Statistical analysis**

The parametric data were statistically analyzed (more than three groups) using one-way ANOVA, and then the outcomes were analyzed by the least significant difference (LSD) test. Meanwhile, the two parametric groups (paired and unpaired) were statistically examined by the Student's paired and unpaired T-test, with the significant set at  $P < 0.05$  (26-27).

#### **Results**

##### **Determination the amantadine analgesic ED<sub>50</sub> in the chicks**

The ED<sub>50</sub> of amantadine for pain relief was determined to be 15.72 mg/kg body weight when administered P.O., which is the dose required to relieve pain in 50% of chicks 30 minutes after amantadine injection (Table 1).

Table 1: Determination of the analgesic ED<sub>50</sub> for amantadine in chicks

| Measurements                                   | The result        |
|------------------------------------------------|-------------------|
| Analgesic ED <sub>50</sub> for amantadine      | 15.72 mg/kg, P.O. |
| Dosage range                                   | 25-10= 15 mg/kg   |
| Initial dose                                   | 25 mg/kg          |
| Final dose                                     | 15 mg/kg          |
| Amount of elevation or reduction in the dosage | 5 mg/kg           |
| Number of chicks                               | 7 (XXXOOXO)       |

Amantadine was administered 30 minutes before the assessment of pain relief using the electrical stimulator device. X: Pain relief occurs 30 minutes after administering amantadine. O: Pain relief does not occur 30 minutes after administering amantadine.

##### **Acute LD<sub>50</sub> for amantadine in the chicks**

The acute LD<sub>50</sub> of amantadine was 930 mg /kg body weight when administered P.O., with the observation of chick deaths within 24 hours after amantadine administration. Signs of poisoning before death included lethargy, drooping wings, loss of balance, respiratory distress, lethargy, and muscle tremors, followed by death. Table 2 presents the details and number of doses and animals used in the experiment.

##### **Examination of the safety level of amantadine in chicks**

Based on the first experiment (ED<sub>50</sub>) and the second experiment (LD<sub>50</sub>) for amantadine, where ED<sub>50</sub> equals 15.72 mg/kg and LD<sub>50</sub> equals 930 mg/kg, the equation was then applied mathematically, and the result was as follows:

Therapeutic index (T.I.) =  $LD_{50} / ED_{50} = 930 \text{ mg/kg} / 15.72 \text{ mg/kg} = 59$  (i.e., multiplication of the  $ED_{50}$  for amantadine fifty-nine times to kill 50% of the chicks).

### **The role of amantadine for inducing ketamine balanced anesthesia and its comparison with ketamine-xylazine combination**

#### **A- Pain relief**

The administration of ketamine alone had a significant analgesic effect (3.50 volt), while the addition of xylazine or amantadine (7.66 and 5.33 volts, respectively) increased the analgesic efficacy of ketamine significantly, with the increase being greater when xylazine was given with ketamine, as shown in Table 3.

Table 2: Determination of the analgesic  $ED_{50}$  for amantadine in chicks

| Measurements                                   | The result                     |
|------------------------------------------------|--------------------------------|
| Acute $LD_{50}$ for amantadine                 | 930 mg/kg of body weight, P.O. |
| Dose range                                     | 2500- 500= 2000 mg/kg          |
| The first dosage                               | 2500 mg/kg                     |
| The final dosage                               | 500 mg/kg                      |
| Amount of elevation or reduction in the dosage | 500 mg/kg                      |
| Number of chicks                               | 7 (XXXOXXO)                    |

X: The occurrence of death in chicks. O: The absence of death in chicks.

Table 3: The analgesic efficacy of amantadine when given with ketamine and compared to ketamine-xylazine

| Groups              | Voltage before (volt) | Voltage after (volt) | The change in voltage (volt) |
|---------------------|-----------------------|----------------------|------------------------------|
| Ketamine            | 8.50±0.42             | 12.00±0.32 #         | 3.50±0.76                    |
| Ketamine-xylazine   | 8.83±0.30             | 16.50±0.76 * #       | 7.66±0.91 *                  |
| Ketamine-Amantadine | 8.00±0.36             | 13.33±0.33 #         | 5.33±0.33*                   |

The values are the mean ± standard error of six chicks in the group. Ketamine and xylazine were injected intramuscularly at doses of 5 and 25 mg/kg, respectively, while amantadine was administered P.O. at a dose of 31.44 mg/kg. \* It is significantly different from the ketamine group at a significance level of  $P < 0.05$  # It differs significantly from the voltage before administration in the same group at a significance level of  $P < 0.05$ .

#### **B- The hypnotic effect**

Sleep onset in chicks occurred three minutes after ketamine injection at 25 mg/kg IM, with the duration of sleep lasting 67 minutes and the total recovery time from sleep being 87 minutes. The addition of xylazine significantly increased both the sleep (206 min) and recovery (393 min) durations. In contrast, the administration of amantadine with ketamine significantly reduced the sleep (32 min) and recovery (69 min) durations compared to ketamine alone or when xylazine was given with it, as shown in Table 4.

#### **C- Vital biomarkers (Cardiopulmonary biomarkers)**

Administering ketamine alone significantly reduced the temperature after anesthesia by 15 minutes compared to the temperature measured before anesthesia. Additionally, administering xylazine or amantadine with it also significantly reduced the temperature after anesthesia, with a greater effect when xylazine was given with ketamine.

Furthermore, injecting ketamine alone significantly affected the respiratory rate after anesthesia by 15 minutes compared to the respiratory rate measured before anesthesia. In contrast, administering xylazine or amantadine with it significantly reduced the respiratory rate after anesthesia, with a more pronounced effect when xylazine was given with ketamine. As for oxygen saturation, the value slightly increased when ketamine was administered alone or with xylazine or amantadine in chicks (Table 5).

Administering ketamine alone reduced the heart rate after anesthesia by 15 minutes compared to the heart rate measured before anesthesia. Additionally, the administration of xylazine with it caused a significant reduction in the heart rate after anesthesia, while amantadine reduced it slightly compared to the ketamine-xylazine mixture. Furthermore, administering ketamine alone or with xylazine or amantadine generally reduced blood pressure (both systolic and diastolic) after anesthesia in chicks, as shown in Table (6).

Table 4: The hypnotic efficacy of amantadine when given with ketamine and compared to ketamine-xylazine

| Groups              | Onset     | Duration                | Recovery                |
|---------------------|-----------|-------------------------|-------------------------|
| Ketamine            | 3.66±0.40 | 67.33±7.00              | 87.66±8.81              |
| Ketamine-xylazine   | 3.00±0.25 | 206.00±16.00 *          | 393.33±8.52 *           |
| Ketamine-Amantadine | 3.50±0.61 | 32.33±2.70 <sup>a</sup> | 69.33±1.05 <sup>a</sup> |

Numbers were as mean ± std. error (six chicks per the group). Ketamine and xylazine were administered IM (25 and 5 mg/kg, respectively), while amantadine was dosed at 31.44 mg/kg, P.O. \* significantly dissimilar to ketamine group,  $P < 0.05$ .

<sup>a</sup> significantly dissimilar to ketamine-xylazine group,  $P < 0.05$ .

Table 5: Vital biomarkers (temperature, respiratory rate, and oxygen saturation) during anesthesia with ketamine alone or with xylazine and amantadine

| Groups              | Biomarkers       |                                   |                      |                               |                                   |                      |
|---------------------|------------------|-----------------------------------|----------------------|-------------------------------|-----------------------------------|----------------------|
|                     | Pre-anesthesia   |                                   |                      | Post-anesthesia in 15 minutes |                                   |                      |
|                     | Temperature (°C) | Respiratory rate (breaths/minute) | SPO <sub>2</sub> (%) | Temperature (°C)              | Respiratory rate (breaths/minute) | SPO <sub>2</sub> (%) |
| Ketamine            | 40.70±0.63       | 22.83±2.76                        | 96.50±0.92           | 39.85±0.18 <sup>+</sup>       | 13.83±1.10 <sup>+</sup>           | 86.33±2.95           |
| Ketamine-xylazine   | 40.81±0.14       | 32.66±3.74                        | 75.33±6.70           | 38.80±0.32 <sup>*+</sup>      | 12.16±3.27 <sup>+</sup>           | 79.66±4.15           |
| Ketamine-Amantadine | 40.40±0.10       | 31.16±6.42                        | 77.83±4.92           | 39.44±0.18 <sup>#</sup>       | 18.66±2.66 <sup>+</sup>           | 82.66±4.12           |

Numbers were as mean ± std. error (six chicks per the group). Ketamine and xylazine were administered IM (25 and 5 mg/kg, respectively), while amantadine was dosed at 31.44 mg/kg, P.O. \* significantly dissimilar to ketamine group, P<0.05. # significantly dissimilar to ketamine-xylazine group, P<0.05 + significantly dissimilar compared to the value before anesthesia within the same group, P<0.05.

Table 6: Vital signs (heart rate and blood pressure) during anesthesia with ketamine alone or with xylazine and amantadine

| The groups          | Biomarkers            |                                              |                               |                                              |
|---------------------|-----------------------|----------------------------------------------|-------------------------------|----------------------------------------------|
|                     | Pre-anesthesia        |                                              | Post-anesthesia in 15 minutes |                                              |
|                     | Heart rate (Beat/min) | Blood pressure (mmHg) (Systolic / Diastolic) | Heart rate (Beat/min)         | Blood pressure (mmHg) (Systolic / Diastolic) |
| Ketamine            | 69.50±2.32            | 186.00±9.13/149.16±15.40                     | 59.66±5.23                    | 157.00±14.90/129.66±16.40                    |
| Ketamine-xylazine   | 59.16±4.42            | 120.00±30.90/93.16±11.30                     | 46.33±7.06 <sup>+</sup>       | 115.90±15.90/85.16±14.65 <sup>*</sup>        |
| Ketamine-Amantadine | 71.16±7.70            | 102.00±8.16/72.50±18.10                      | 66.50±7.43 <sup>#</sup>       | 118.00±13.90/88.16±12.06 <sup>*</sup>        |

Numbers were as mean ± std. error (six chicks per the group). Ketamine and xylazine were administered IM (25 and 5 mg/kg, respectively), while amantadine was dosed at 31.44 mg/kg, P.O. \* significantly dissimilar to ketamine group, P<0.05. # significantly dissimilar to ketamine-xylazine group, P<0.05, + significantly dissimilar compared to the value before anesthesia within the same group, P<0.05.

## Discussion

The purpose of this research was to reveal the pharmacological effects of amantadine in a model of 7-14 day old chicks and to demonstrate its safety level, as well as its role in inducing balanced anesthesia with ketamine and comparing it with the traditional mixture (ketamine-xylazine) for future use in other animals.

Amantadine has a mode of action like that of ketamine, which is the antagonistic effect on the NMDA receptor in the central nervous system. This gives it analgesic and sedative effects by reducing the release of the excitatory neurotransmitter glutamate, which is responsible for causing pain, as well as inhibiting the reuptake of dopamine (2). Amantadine is also used as an adjunct medication with central pain-relieving drugs such as morphine and peripheral non-steroidal anti-inflammatory drugs to enhance their analgesic therapeutic efficacy (2,3,28).

In this study, an electric stimulation was used to induce pain and examine and measure pain relief in chick models. This device was applied to measure pain relief, and the ED<sub>50</sub> for amantadine was determined, which was similar to a previous study in dogs (3).

The acute LD<sub>50</sub> of amantadine was measured within 24 hours after administration, and pre-mortem signs of toxicity were recorded, which included recumbency, drooping wings, loss of balance, respiratory distress, lethargy, and muscle tremors, followed by death. The measured LD<sub>50</sub> was comparable to a previous study in different animals. This similar result may be due to the fact that the mode of amantadine action is the same in different animals, which is its inhibition of the NMDA receptor (29).

The outcomes indicate that amantadine has a wide margin of safety by measuring its therapeutic index for short term use in chicks, as a previous study showed that amantadine has this feature with minimal side effects in small animals (30) although the study is limited discussion of the potential side effects for long-term consequences of using amantadine in veterinary practice.

In this study, a pain-relieving dose of amantadine was administered, and it was observed that administering amantadine at 31.44 mg/kg, P.O. increased the pain relief resulting from ketamine injection in a chick model. This effect may be due to amantadine having a mode of action comparable to ketamine, which is the antagonistic effect on NMDA receptors in the brain and spinal cord. This mechanism gives it a pain-relieving effect by reducing the

release of the excitatory neurotransmitter glutamate, which is responsible for causing pain, as well as inhibiting dopamine reuptake (2,3,28).

The study revealed the ability of amantadine to reduce the durations of sleep and wakefulness when administered with ketamine. This is attributed to the ability of amantadine (similar to ketamine) to antagonize the NMDA receptor in the central nervous system (2,3,28) which may lead to antagonistic interference at the target receptor level, and subsequently, competition for binding sites, displacing one another, thereby reducing the anesthetic efficacy of ketamine.

The values of the natural vital indicators (pre-anesthesia) were like a preceding study in chicks (31). It is clear that administering ketamine alone caused harmful inhibition at the level of the heart and lungs during anesthesia (32), in addition to the increased inhibition when xylazine was given with it due to the increased inhibition in the brain and spinal cord, especially in the medulla oblongata, which controls the functions of the heart and lungs. Meanwhile, amantadine worked to reduce this inhibition caused by ketamine on the central nervous system. This effect may be attributed to amantadine's ability (similar to ketamine) to antagonize the NMDA receptor in the neurons (2,3,28), which may lead to competitive interference at the target receptor and reduce its binding, thereby decreasing its inhibitory effects.

## Conclusions

The outcomes of the research specify that amantadine has analgesic and hypnotic properties and a wide range of safety, in addition to the possibility of using it to induce ketamine-balanced anesthesia in chicks, which make it useful for future use in veterinary medicine; another studies in different animal models or clinical settings are recommended to verify its pharmacological benefits.

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## Conflict of interest

The authors declared there is no conflict of interest.

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## دور الأمانتادين كدواء ما قبل التخدير في أحداث التخدير الموزون للكيثامين في نموذج افراخ الدجاج

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### الخلاصة

كان الهدف من هذه الدراسة هو الكشف عن التأثيرات الدوائية للأمانتادين في نموذج افراخ الدجاج بعمر ٧-١٤ يوماً وبيان درجة أمانه فضلاً عن بيان دوره في أحداث التخدير الموزون للكيثامين ومقارنته مع المزيج التقليدي (الكيثامين-الزايلازين) لاستخدامه مستقبلاً في الحيوانات الأخرى. تم تحديد الجرعة الفعالة الوسطية (الجف ٥٠) المسكنة للألم والجرعة المميتة الوسطية الحادة (الجم ٥٠) للأمانتادين باستخدام طريقة الصعود والنزول وكانت ١٥,٧٢ و ٩٣٠ ملغم/كغم، عن طريق الفم، على التوالي. وبيّنت هذه النتائج امتلاك الأمانتادين مدى أمان واسع في نموذج افراخ الدجاج من خلال قياس المعيار العلاجي Therapeutic index. وسبب تجريع الأمانتادين بجرع متعددة وهي ٧,٨٦، ١٥,٧٢ و ٣١,٤٤ ملغم/كغم، عن طريق الفم حدوث تسكين للألم في افراخ الدجاج ونسبة ٣٣، ٥٠ و ١٠٠ % على التوالي وبصورة معتمدة على الجرعة. وعمل اعطاء الكيثامين لوحده (٢٥ ملغم/كغم، في العضل) على تسكين الألم بينما سبب اعطاء الزايلازين (٥ ملغم/كغم، في العضل) او الأمانتادين (٣١,٤٤ ملغم/كغم، عن طريق الفم) معه على الزيادة منها وبصورة معنوية. وسبب اعطاء الأمانتادين مع الكيثامين تقليلاً معنوياً في مدتي النوم والافاقة مقارنة بالكيثامين لوحده او عند اعطاء الزايلازين معه. وعند قياس المؤشرات الحيوية لأفراخ الدجاج بجهاز مراقبة المريض Patient monitor عند التخدير بالكيثامين لوحده او مع الزايلازين او الأمانتادين تبين تقليل الأمانتادين من التأثيرات المثبطة الحاصلة على القلب والرئتين (تردد القلب، ضغط الدم، تردد التنفس وتسبع الاوكسجين) مقارنة بالزايلازين. تشير نتائج هذه الدراسة الى امتلاك الأمانتادين قابلية للتسكين من الألم والتنويم مع مدى واسع من الامان فضلاً عن امكانية استخدامه مع الكيثامين لإحداث التخدير الموزون في افراخ الدجاج مما قد يجعله مفيداً للاستخدام المستقبلي في مجال الطب البيطري.