Iraqi Journal of Veterinary Sciences

www.vetmedmosul.com

Amantadine produces analgesia through a unique mechanism and pharmacokinetics in chickens

F.F. Idris[1] and Y.J. Mousa[2]

[1]Veterinarian, Private sector, [2]Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

Article information

Article history:
Received 19 January, 2025
Accepted 13 March, 2025
Published online 16 March, 2025

Keywords:
Amantadine
COX-2
Nociception
NMDA blockers
Pharmacodynamics

Correspondence:
Y.J. Mousa
yarub204@uomosul.edu.iq

Abstract

Nowadays, there is a requisite for worthy and effective analgesic drugs with the least side effects for proper use in veterinary medicine. The goal was to relate amantadine (AMN) pharmacodynamics (i.e., analgesia and COX-2 inhibition) with a preferential (nimesulide) COX-2 inhibitor besides detecting its pharmacokinetics in chickens. The methodology included assessing the analgesic median effective dose (ED_{50}), kidney and liver functions, Brain COX-2 activity, and AMN plasma concentration with its pharmacokinetics profile in the chickens. The analgesic ED_{50} of AMN was found to be 15.72 mg/kg, orally (P.O.). Oral administration of AMN (31.44 mg/kg) did not significantly alter the liver and kidney functions, as there were no significant changes in the aspartate transaminase (AST) and alanine transaminase (ALT), as well as uric acid and creatinine. AMN (31.44 mg/kg, P.O.) and nimesulide (20 mg/kg, intramuscularly) significantly inhibit COX-2 activity in the whole brain of chickens associated with the control animals by 26 and 14%, respectively. Plasma concentrations of AMN (31.44 mg/kg, P.O.) assessed at variant comparable times (0.25, 0.5, 1, 2, 4, and 8 hours) were 0.38, 0.42, 0.31, 0.30, 0.26 and 0.23 µg/ml. AMN pharmacokinetic variables were estimated to be $AUC_{0-\infty}$ 7.44, $AUMC_{0-\infty}$ 170.85, k_{el} 0.04, C_{max} 0.42, T_{max} 0.5, $t_{1/2\beta}$ 15.88, MRT 3.34, Vss 96.75, and Cl 4.22. The study concluded the safety of AMN (liver and kidney functions besides its pharmacokinetics) with its unique capability to modulate the activity of brain COX-2, which makes it a good analgesic and probably anti-inflammatory drug to be used in chickens.

DOI: 10.33899/ijvs.2025.156778.4093,

Introduction

The clinical importance of AMN is numerous in animals. Following the initial identification of AMN as an antiviral drug in chickens and other animals for treating viral invasion such as influenza A virus (AMN has no activity against influenza B or other upper respiratory viruses) by blocking the M_2 (a small viral membranous protein) (1). Later, it was found to play a vital role in managing Parkinson's illness and extrapyramidal reactions in humans (1). Parkinsonian movement disorders can be effectively treated with it, and its progression may be slowed. It helps people recover from traumatic brain injuries (2) and reduces chronic nociception (3). AMN's ability to inhibit ion channels seems to be the basis for its therapeutic benefits. Blocking the M_2 (a small viral membranous protein) is the cause of its antiviral effect (4). AMN was later discovered to block the channel related to N-methyl D-aspartate (NMDA) receptors like ketamine and subsequently modulation of glutamate release (the main neurotransmitter responsible for pain sensation) (5). Even though its pharmacological effectiveness in treating Parkinson's disease was first thought to be due to its effects on dopamine-releasing neurons in substantia nigra (6). There is growing evidence that AMN's ability to effectively treat

nervous system diseases is primarily thought from its suppression of NMDA receptors (2). The characteristics of NMDA receptor antagonists are varied. Because extracellular Mg^{+2} causes the strong voltage dependency of postsynaptic Ca^{+2} entrance at excitable synapses, channel obstruction by this substance has significant physiological implications (7). Unlike the clinically beneficial NMDA receptor antagonists like AMN and its main derived chemical compound (memantine), many famous antagonists like phencyclidine and ketamine are neurotoxic and cause schizophrenia-like neurobehavior in humans (8). A heme-containing enzyme called cyclooxygenase-2 (COX-2) adds molecular oxygen to free unesterified arachidonic acid to catalyze the rate-limiting step in prostaglandin (PG) production (9). PGs are necessary for some types of synaptic plasticity and activate G-protein-coupled receptors to engage bioactivity (10-14) and neurovascular coupling (15). However, it appears that COX-2's overproduction of PGs mediates aberrant plasticity, neuronal injury, inflammatory and immune responses in ischemia-reperfusion damage (16), neurodegenerations (17,18), and epilepsy (19,20). Considering that COX-2 has been connected to several brain traumas and that synaptic NMDA receptors promote neuro-protection, the finding synaptic NMDA receptors enhance COX-2 expression seems contradictory (19).

To discover a new drug used as an analgesic as well as premedication in veterinary medicine, the goal of this research was to associate AMN pharmacodynamics (specified by analgesic efficacy and degree of COX-2 inhibition) with a standard COX-2 preferential inhibitor (nimesulide) besides detecting its pharmacokinetics profile in the chicken.

Materials and methods

Ethical approval

The animal usage and sponsorship committee at the Veterinary Medicine College, University of Mosul, agreed upon the research as the approval number UM.VET.2024.089 on August 20, 2024.

The experimental animals used

Broilers of both genders were used, which were brought from the Hamdaniya hatchery in Nineveh Governorate. The total number of chickens used in the experiments was fifty-five. The chickens were placed in the animal household at the Veterinary Medicine College, University of Mosul. The size of the breeding cages was 180×150×150 cm, containing bedding and concentrated feed. The chickens were placed in the cages at one day old. The appropriate climatic conditions for them were prepared, including ventilation and a temperature of 24-33 °C, with 23 hours of light and 1 hour of darkness. They were raised until the experiments were conducted on them at 7-14 days of age.

Preparation of medications and method of administration

The required doses of AMN (Amantadine hydrochloride powder, produced by Pharmaceutical Ingredients, API, CAS 768-94-5, China) and nimesulide (10%, Medivet, India) were obtained through dilution and preparation using physiological saline, with the oral administration of AMN or the intramuscular injection for nimesulide at 5 ml/kg.

Determination of the median efficacious dose (ED_{50}) of AMN for pain relief in chickens using the up-and-down method

In this experiment, 7- to 14-day-old chickens were used. The ED_{50} was determined using the up-and-down method, with 7 chickens weighing 150-250 grams. An initial dose of AMN of 25 mg/kg, b wt., was administered orally. The electrical stimulation device (Harvard Apparatus, USA) was used to evaluate the analgesic effect of AMN by measuring the device's voltage before administering AMN. After 30 minutes, the device's electrodes were connected under the wing to deliver the electric current. The area under the wing in contact with the electrodes was moistened with water. Then, the voltage was gradually increased until pain occurred, which was determined by the distress call and other signs of pain, such as wing flapping and calling. This was the first reading of the initial result before administration. Then, AMN was administered at 25 mg/kg, P.O. Based on previous experiments, the second reading was set at 30 minutes after administration. The device's electrodes were again connected under the wing, the area was moistened with water, and the voltage was increased until pain occurred. The final result, pain relief, was indicated by an increase in voltage after administering AMN compared to the current-voltage assessed before the drug administration (21-26). The occurrence of pain relief is indicated by the symbol X. 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 dose method is applied, with an elevation or reduction in the 5 mg/kg dose for pain relief or no antinociception in chickens. This process is repeated in ascending and descending doses for three chickens when a change occurs. Then, the analgesic ED_{50} is calculated (27-30).

The effect of administering AMN for several days on liver and kidney functions

In this experiment, 7-14 days-old chickens weighing 200-280 grams were used and divided into two groups of 6 chickens for each. The first one served as the control group. In contrast, the second one was administered AMN orally at 31.44 mg/kg for 7 consecutive days. On the seventh day, the blood samples were drawn through the two groups' jugular veins. The blood samples were collected in test tubes without anticoagulant to obtain serum by centrifuging (3000 rpm / 15 minutes). The samples then froze at -18ºC for 72 hours, after

which the required laboratory tests for liver functions, represented by ALT and AST, and kidney function (Creatinine and uric acid) were conducted (31,32).

Measuring the effect of AMN on the activity of cyclooxygenase-2 enzyme in the brain of chickens

In this experiment, 18 chickens aged 7-14 days, weighing between 150-250 grams, were used. They were separated into three clusters, with 6 chickens in every group. The first one served as the negative control (normal saline). The second one was injected with nimesulide at a dosage of 20 mg/kg intramuscularly (positive control). The last one was administered AMN at 31.44 mg/kg, P.O., using a gastric lavage tube. The treatment duration was 7 consecutive days. Brain samples were taken and frozen at -18 0C on the seventh day for 72 hours. The samples were then ground using an electrical homogenizer, and the brain fluid was separated using a micro-centrifuge (3000 rpm for 2 minutes). The required laboratory tests were then conducted (10,33). The percentage of COX-2 inhibition was calculated as follows: COX-2 inhibition (%)= COX-2 activity (negative control group) - COX-2 activity (treated group) / COX-2 activity (negative control group) × 100.

The concentration of AMN in the plasma at different times in chickens

This experiment involved the use of 18 chickens aged 7-14 days, weighing between 150-200 grams, which were administered AMN at a dosage of 31.44 mg/kg, P.O. Blood was collected from them at six various assessed times (0.25, 0.5, 1, 2, 4, and 8 hours) after dosing, with three chickens per time assessed. The plasma concentration of AMN was measured at each of the times above using the spectrophotometric method (34).

AMN standards preparation

The AMN standards were fixed at various concentrations of 50,100, 200, 400, 800, and 1600 µg/ml by diluting in distilled water. Then, the optical density was determined by using a UV-visible spectrophotometric analysis (wavelength of 460 nanometers). The spectrophotometer was zeroed using distilled water as blank. Then, the plasma samples were taken with the addition of acetonitrile in a 1:1 ratio, and it was positioned at a centrifuge for two minutes at 3000 revolutions per minute. After that, the supernatant was taken and measured using the spectrophotometric method at a wavelength of 460 nanometers (34).

The simple linear regression curve of AMN standard solutions was cast off to estimate AMN concentration in plasma, with the coefficient of determination (R^2) being (0.987) (Figure 1). Then, AMN concentration in the plasma of the chicken groups was estimated according to the following simple linear equation of regression: y = bx – a. Since y: the absorbance of AMN in plasma samples at a wavelength of 460 nanometers; b: slope (0.0111), x: the unknown concentration of AMN (µg/ml) in a plasma sample and a: intercept (0.0012).

Measuring the pharmacokinetic parameters of AMN in chickens

The pharmacokinetics of AMN were estimated and measured after detecting the AMN plasma concentration from the previous experiment at various measurement times. The different pharmacokinetic variables of AMN were assessed manually and by using the PKSlover program integrated with Excel-add in (35). Pharmacokinetic parameters were calculated manually and compared with the program results using the following equations: k_{el} (rate constant for elimination) which is the proportion of the AMN elimination from the plasma for an hour since the k_{el} (h^{-1}) = slope of the regression line × 2.303; $t_{1/2\beta}$ (elimination half-life) signifies the time essential in hours for the drug concentration in the plasma to reduce by 50% ($t_{1/2\beta}$ = 0.693 / k_{el}); V_{ss} (volume of distribution of steady state) which is the apparent volume of fluids in the body serving in holding the drug [V_{ss} (L/ kg) = dose (mg) / concentration at time zero]; C_{max} (maximal concentration)(µg/ml) means the maximal concentration of AMN in plasma at a specific time; T_{max} (maximal time)(h) represents the time when the AMN concentration is at its highest level in the plasma; MRT (mean residency time) (hour) which is the predictable duration of the drug's stay in the plasma; Cl (total clearance) which is the ability of various body organs to excrete and clear the AMN [Cl (L/h/kg) = V_{ss} × k_{el}]; AUC (area under the curve) is the concentration of AMN present in the plasma at various periods [AUC (µg/h/ml) = dose (mg) / Cl] and finally AUMC (area under the moment curve) represents the AMN concentration present in the plasma at the moment of estimation [AUMC (µg × h^2/ml) = V_{ss} × (AUC)^2 / dose (mg)].

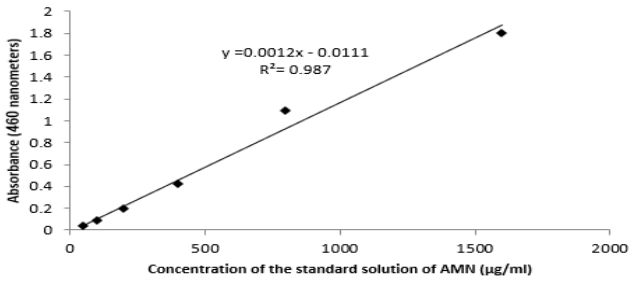

Figure 1: Concentration of different AMN standards in µg/ml.

Statistics

One-way analysis was the statistical examination of parametric data, which was achieved by comparing multiple means. The T-test was applied to analyze the average of the two clusters of chickens (36). The significance level for all experiments was at the probability P<0.05.

Results

Determining the analgesic ED_{50} of AMN

The effective dose (ED_{50}) of AMN for pain relief was assessed to be 15.72 mg/kg b. wt. When administered orally, the dose required to relieve pain in 50% of the chickens after 30 minutes of AMN dosing (Table 1).

Table 1: Results of the AMN analgesic ED_{50} in the chickens

Parameters	AMN
ED_{50}	15.72 mg/kg, P.O.
Doses range	25-10= 15 mg/kg
First dosage	25 mg/kg
Final dosage	15 mg/kg
±Doses	5 mg/kg
Number of chickens	(XXXOOXO) 7

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

Measuring the effect of AMN over several days of administration on liver and kidney functions

Kidney and liver functions (creatinine/uric acid and ALT/AST) were assessed specifically, and we observed no significant difference in the numerical readings after seven consecutive days of administration. This indicates that using AMN for several consecutive days does not affect liver and kidney functions (Table 2).

Table 2: Measuring the effect of AMN on liver and kidney functions of chickens

Groups	ALT (U/L)	AST (U/L)	Creatinine (mg/dl)	Uric acid (mg/dl)
Control	8.16±0.76	195.08±9.72	0.22±0.01	8.01±1.24
AMN	9.08±0.80	202.51±13.46	0.23±0.02	9.80±0.81

Numbers are the average ± STD error (six chickens in the group) AMN was dosed orally at 31.44 mg/kg for 7 consecutive days.

Measuring the effect of AMN on the activity of COX-2 enzyme in the brain of chickens

Three different groups were used to compare the inhibition rate of COX-2. The first one was negative (control) group administered saline solution, the second one was injected with nimesulide at a dosage of 20 mg/kg intramuscularly (positive control group), which is selective for COX-2, and the third group was administered AMN at a dosage 31.44 mg/kg, P.O. We observed a significantly dissimilar in inhibition rates in COX-2 compared to the control group for both groups treated with nimesulide and AMN 26 and 14%, respectively. This leads us to conclude that AMN has an inhibitory effect on COX-2, so we can also consider it an analgesic and an anti-inflammatory drug (Table 3).

Table 3: The effect of AMN on the activity of COX-2 enzyme in the brain of chickens

Groups	COX2 activity (ng/L)	Inhibition (%)
Normal saline	16.69±1.15	0
Nimesulide	12.31±0.25 *	26
AMN	14.39±0.50 *	14

Numbers are the mean ± STD error (six chickens in the group) AMN was administered at 31.44 mg/kg, P.O. while nimesulide was injected at a dosage of 20 mg/kg, intramuscularly, for seven successive days. * Differs significantly compared to the negative control group injected with physiological saline at $P<0.05$ COX-2 inhibition percentage (%) = Control (negative) group - Treated group / Control (negative) group×100.

The concentration of AMN in the plasma at different times in the chickens

In this experiment, the plasma concentration of AMN (31.44 mg/kg, P.O.) was assessed at various times (0.25, 0.5, 1, 2, 4, and 8 hours) after dosing and was 0.38, 0.42, 0.31, 0.30, 0.26 and 0.23 µg/ml., respectively. A significant change was noted in the AMN plasma concentration, which decreased at 4 and 8 hours compared to 0.25 and 0.5 hours. This means that AMN reaches its peak concentration at 30 minutes (Table 4 and Figure 2).

Table 4: Concentration of AMN in the plasma at different times in chickens

Time (hour)	AMN concentration (µg/ml)
0.25	0.38±0.02
0.5	0.42±0.04
1	0.31±0.04
2	0.30±0.05
4	0.26±0.05#
8	0.23±0.02*#

Values are the mean±the STD error (3 chickens/time measured) AMN was administered at a dosage of 31.44 mg/kg, P.O. * differs significantly from the time after 0.25 h of AMN dosing at $P<0.05$. # Significantly differs from the time after 0.5 h of AMN dosing at $P<0.05$.

Pharmacokinetic parameters of AMN in chickens

The pharmacokinetics of AMN were determined after detecting the AMN concentration in the plasma from the preceding trial at different measured times. The

pharmacokinetic variables of AMN were determined using the PKSlover program integrated with Excel to be as $AUC_{0-\infty}$ 7.44, $AUMC_{0-\infty}$ 170.85, k_{el} 0.04, C_{max} 0.42, T_{max} 0.5, $t_{1/2\beta}$ 15.88, MRT 3.34, V_{ss} 96.75, and Cl 4.22 (Table 5).

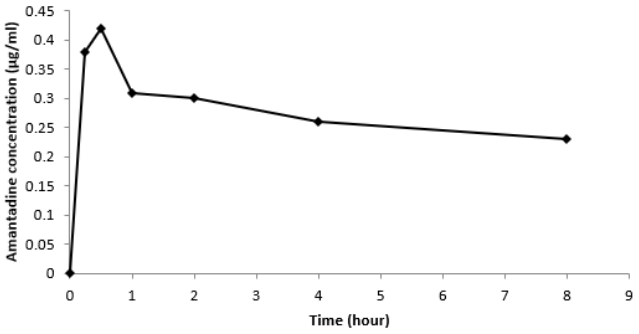

Figure 2: Concentration of AMN in plasma at different times after oral administration in chickens.

Table 5: The pharmacokinetic profile of AMN in the chickens

Parameters	Units	Value
k_{el}	h^{-1}	0.04
$t_{1/2\beta}$	h	15.88
MRT	h	3.34
V_{ss}	L/kg	96.75
C_{max}	µg/ml	0.42
T_{max}	h	0.5
Cl	L/h/kg	4.22
$AUC_{0-\infty}$	µg × h / ml	7.44
$AUMC_{0-\infty}$	µg × h^2 / ml	170.85

AMN was injected at 31.44 mg/kg, P.O. PKSolver program was used for the assessment of pharmacokinetic variables of a non-compartmental model of pharmacokinetics.

Discussion

The aim was to compare AMN pharmacodynamics (an analgesic effect besides the degree of COX-2 inhibition) with a standard COX-2 inhibitor (nimesulide), besides detecting its pharmacokinetics in chickens. The 50% of the effective dose (ED_{50}) of AMN for pain relief was assessed to be 15.72 mg/kg b. wt. When administered orally, the dose required to relieve pain in 50% of the chickens 30 minutes after AMN dosing is close to the previous study in dogs (37).

Liver (AST and ALT) and kidney (creatinine and uric acid) functions were analyzed for seven consecutive days after AMN dosing. They revealed the safety of AMN, which is a controversial problem and maybe because AMN has minimal hepatic metabolism and is excreted largely unchanged in the urine. These factors perhaps explain the absence of significant hepatic and renal toxicity, as described by a previous study (38).

In this research, we focus on the COX-2 inhibitory action of AMN and its comparison to the effectiveness of nimesulide (a preferential COX-2 inhibitor). The result revealed that both AMN and nimesulide inhibit the activity of COX-2 to a varying degree with nimesulide superiority, as expected. Nimesulide is considered an NSAID drugs that have numerous therapeutic effects in human and veterinary fields because of its different medical effects as an antipyretic, anti-inflammatory, and analgesic drug (3,39). The effects occur due to a reduction of the COX-2 enzyme, resulting from the reduction of prostaglandin E_2 biosynthesis (9,11,40). The analgesic effect of nimesulide was studied in previous research in humans (8,41), mice (39,42), and dogs (37,43). As for AMN, a few studies suggest it may have a modulatory effect on COX-2 overexpression (11,44). We, in turn, conducted this experiment to investigate its efficacy on cyclooxygenase. It turned out that it does affect cyclooxygenase, producing its analgesic efficacy due to its capability of lowering the COX-2 level significantly, besides its recorded ability to block the NMDA receptors (as ketamine) and subsequently modulation of glutamate release (the main neurotransmitter responsible for pain sensation) (5).

At the level of AMN concentration in the plasma, which was determined at various times, the plasma concentration of AMN was measured at different times (0.25, 0.5, 1, 2, 4, and 8 hours) with the highest concentration at time 30 min after AMN dosing. We noted a significant modification in the plasma concentration of AMN, where the concentration decreased at 4 and 8 hours compared to the other times. This means that AMN reaches its peak concentration at 30 minutes, according to previous research (45).

Conclusions

The study concluded the safety of AMN (liver and kidney functions besides its pharmacokinetics) with its unique capability to modulate the activity of COX-2 in the brain, making it a good analgesic and probably anti-inflammatory drug to be used in chickens.

Acknowledgments

This research was sponsored by the University of Mosul, College of Veterinary Medicine.

Conflict of interest

The authors declared there is no conflict of interest.

References

1. Prud'homme IT, Zoueva O, Weber JM. Amantadine susceptibility in influenza A virus isolates: Determination methods and lack of resistance in a Canadian sample, 1991-94. Clin Diagn Virol. 1997;8(1):41-51. DOI: 10.1016/s0928-0197(97)00011-1

2. Blanchet PJ, Metman LV, Chase TN. Renaissance of amantadine in the treatment of Parkinson's disease. Adv Neurol. 2003;91:251-257. [available at]
3. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage. 2000;20(5):358-373. DOI: 10.1016/s0885-3924(00)00213-x
4. Hay AJ. The action of adamantanamines against influenza A viruses: Inhibition of the M2 ion channel protein. Semin Virol. 1992;3:21-30. [available at]
5. Lupp A, Lücking CH, Koch R, Jackisch R, Feuerstein TJ. Inhibitory effects of the antiparkinsonian drugs memantine and amantadine on N-methyl-D-aspartate-evoked acetylcholine release in the rabbit caudate nucleus in vitro. J Pharmacol Exp Ther. 1992;263(2):717-724. [available at]
6. Danysz W, Parsons CG, Kornhuber J, Schmidt WJ, Quack G. Aminoadamantanes as NMDA receptor antagonists and antiparkinsonian agents--preclinical studies. Neurosci Biobehav Rev. 1997;21(4):455-468. DOI: 10.1016/s0149-7634(96)00037-1
7. Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. Pharmacol Rev. 1999;51(1):7-61. [available at]
8. Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine: From NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacol. 1999;20(3):201-225. DOI: 10.1016/S0893-133X(98)00060-8
9. Smith WL, Dewitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annu Rev Biochem. 2000;69:145-182. DOI: 10.1146/annurev.biochem.69.1.145
10. Kaufmann WE, Worley PF, Pegg J, Bremer M, Isakson P. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc Natl Acad Sci U S A. 1996;93(6):2317-2321. DOI: 10.1073/pnas.93.6.2317
11. Chen C, Magee JC, Bazan NG. Cyclooxygenase-2 regulates prostaglandin E2 signaling in hippocampal long-term synaptic plasticity. J Neurophysiol. 2002;87(6):2851-2857. DOI: 10.1152/jn.2002.87.6.2851
12. Chen C, Bazan NG. Endogenous PGE2 regulates membrane excitability and synaptic transmission in hippocampal CA1 pyramidal neurons. J Neurophysiol. 2005;93(2):929-941. DOI: 10.1152/jn.00696.2004
13. Sang N, Zhang J, Marcheselli V, Bazan NG, Chen C. Postsynaptically synthesized prostaglandin E2 (PGE2) modulates hippocampal synaptic transmission via a presynaptic PGE2 EP2 receptor. J Neurosci. 2005;25(43):9858-9870. DOI: 10.1523/JNEUROSCI.2392-05.2005
14. Akaneya Y, Tsumoto T. Bidirectional trafficking of prostaglandin E2 receptors involved in long-term potentiation in visual cortex. J Neurosci. 2006;26:10209-10221. DOI: 10.1523/JNEUROSCI.3028-06.2006
15. Niwa K, Araki E, Morham SG, Ross ME, Iadecola C. Cyclooxygenase-2 contributes to functional hyperemia in whisker-barrel cortex. J Neurosci. 2000;20(2):763-770. DOI: 10.1523/JNEUROSCI.20-02-00763.2000
16. Nogawa S, Zhang F, Ross ME, Iadecola C. Cyclo-oxygenase-2 gene expression in neurons contributes to ischemic brain damage. J Neurosci. 1997;17(8):2746-2755. DOI: 10.1523/JNEUROSCI.17-08-02746.1997
17. Hunot S, Vila M, Teismann P, Davis RJ, Hirsch EC, Przedborski S, Rakic P, Flavell RA. JNK-mediated induction of cyclooxygenase 2 is required for neurodegeneration in a mouse model of Parkinson's disease. Proc Natl Acad Sci U S A. 2004;101(2):665-670. DOI: 10.1073/pnas.0307453101
18. Liang X, Wang Q, Hand T, Wu L, Breyer RM, Montine TJ, Andreasson K. Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. J Neurosci. 2005;25(44):10180-10187. DOI: 10.1523/JNEUROSCI.3591-05.2005
19. Yamagata K, Andreasson KI, Kaufmann WE, Barnes CA, Worley PF. Expression of a mitogen-inducible cyclooxygenase in brain neurons: Regulation by synaptic activity and glucocorticoids. Neuron. 1993;11(2):371-386. DOI: 10.1016/0896-6273(93)90192-t
20. Tu B, Bazan NG. Hippocampal kindling epileptogenesis upregulates neuronal cyclooxygenase-2 expression in neocortex. Exp Neurol. 2003;179(2):167-175. DOI: 10.1016/s0014-4886(02)00019-5
21. Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20:441-462. DOI: 10.1146/annurev.pa.20.040180.002301
22. Mousa YJ. Effect of chlorpheniramine on acute dichlorvos poisoning in chicks. Iraqi J Vet Sci. 2009;23(2):35-43. DOI: 10.33899/ijvs.2009.5738
23. Mousa Y. Etomidate anesthesia in chicks: Effect of xylazine. J Hell Vet Med Soc. 2020;71(4):2463-2470. DOI: 10.12681/jhvms.25921
24. Mousa YJ. Effect of nefopam in normal chickens and its relationship to hydrogen peroxide-induced oxidative stress. Iraqi J Vet Sci. 2021;35(I):7-12. DOI: 10.33899/ijvs.2021.127013.1433
25. Mousa YJ, Mahmood MB, Mohammad MS. Administration of ketamine with the central and peripheral analgesics for induction of balanced anesthesia in the chicks. IOP Conf Ser Earth Environ Sci. 2019;388:012021. DOI: 10.1088/1755-1315/388/1/012021
26. Jassim OY, Mousa YJ. Nefopam and ketorolac: Isobolographic analysis of analgesic effect and pharmacokinetic profile in chicks. Iraqi J Vet Sci. 2022;36(1):145-150. DOI: 10.33899/ijvs.2021.129540.1660
27. Mousa YJ, Mahmood MB. Effect of meloxicam coadministration on the anaesthetic potency of thiopental sodium in a chick model. Vet Stanica. 2022;53(2):155-163. DOI: 10.46419/vs.53.2.5
28. Mousa YJ, Mohammad FK. Effects of hydrogen peroxide on diazepam and xylazine sedation in chicks. Interdisip Toxicol. 2012;5(4):179-183. DOI: 10.2478/v10102-012-0030-5
29. Mousa YJ. Anaesthetic properties of ketamine in chicks stressed with hydrogen peroxide. Vet Med. 2014;59(8):369-375. DOI: 10.17221/7656-VETMED
30. Yahya TA, Mousa YJ. Molecular effects of nimesulide and aspirin on caspase-3, PPAR-α, and COX-2 gene expression in mice. Iraqi J Vet Sci. 2024;38(4):801-807. DOI: 10.33899/ijvs.2024.149230.3638
31. Reitman S, Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am J Clin Pathol. 1957;28(1):56-63. DOI: 10.1093/ajcp/28.1.56
32. Plummer DT. An introduction to practical Biochemistry. 3rd ed. USA: McGrew-Hill Co. Inc.; 1987. 182-188 pp. [available at]
33. Lee B, Dziema H, Lee KH, Choi YS, Obrietan K. CRE-mediated transcription and COX-2 expression in the pilocarpine model of status epilepticus. Neurobiol Dis. 2007;25(1):80-91. DOI: 10.1016/j.nbd.2006.08.015
34. Mahmoud AM, Khalil NY, Darwish IA, Aboul-Fadl T. Selective Spectrophotometric and Spectrofluorometric Methods for the Determination of Amantadine Hydrochloride in Capsules and Plasma via Derivatization with 1,2-Naphthoquinone-4-sulphonate. Int J Anal Chem. 2009;2009:810104. DOI: 10.1155/2009/810104
35. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed. 2010;99(3):306-314. DOI: 10.1016/j.cmpb.2010.01.007
36. Berke O. Statistics for Veterinary and Animal Science, 2nd ed. Can Vet J. 2007;48(8):867. [available at]
37. Lascelles BD, Gaynor JS, Smith ES, Roe SC, Marcellin-Little DJ, Davidson G, Boland E, Carr J. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. J Vet Intern Med. 2008;22(1):53-59. DOI: 10.1111/j.1939-1676.2007.0014.x
38. Rees WA, Harkins JD, Woods WE, Blouin RA, Lu M, Fenger C, Holland RE, Chambers TM, Tobin T. Amantadine and equine influenza: Pharmacology, pharmacokinetics and neurological effects in the horse. Equine Vet J. 1997;29(2):104-110. DOI: 10.1111/j.2042-3306.1997.tb01650.x
39. Balaji T, Subramanian M, Gnanasundaram V, Rajendran SS, Rajendran HS. Nimesulide induced histopathological changes in the vas deferens of mice. J Clin Diagn Res. 2013;7(10):2116-2118. DOI: 10.7860/JCDR/2013/6693.3446

الأمانتادين ينتج تسكين للألم من خلال آلية عمل وحركية دوائية فريدة في الدجاج

فيصل فارس إدريس[١] و يعرب جعفر موسى[٢]

[١]طبيب بيطري، قطاع خاص، [٢]فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

في الوقت الحاضر، هناك حاجة إلى أدوية مسكنة للألم ذات فعالية وآثار جانبية أقل للاستخدام في الطب البيطري. كان الهدف هو مقارنة الديناميكية الدوائية للأمانتادين (أي تسكين الألم وتثبيط إنزيم الأكسدة الحلقية-٢) مع المثبط الانتقائي القياسي (النيميسولايد) بالإضافة إلى اكتشاف حركيته الدوائية في الدجاج. تم تقييم الجرعة الفعالة الوسطية المسكنة للألم (الجف٥٠)، ووظائف الكلى والكبد، ونشاط إنزيم الأكسدة الحلقية-٢ في الدماغ، وتركيز الأمانتادين في البلازما مع ملف حركيته الدوائية في الدجاج. وجد أن الجف٥٠ المسكنة للألم للأمانتادين هو ١٥,٧٢ ملغم/كغم، عن طريق الفم. لم يؤثر إعطاء الأمانتادين (٣١,٤٤ ملغم/كغم، عن طريق الفم) بشكل ملحوظ ومعنوي على وظائف الكبد والكلى، حيث لم تحدث تغييرات كبيرة في إنزيم ناقلة أمين الأسبارتيت وإنزيم ناقلة أمين الألنين، وكذلك الكرياتينين وحامض البوليك. كما ثبط (٣١,٤٤ ملغم/كغم، عن طريق الفم) والنيميسولايد (٢٠ ملغم/كغم، في العضل) من نشاط إنزيم الأكسدة الحلقية-٢ في الدماغ بشكل معنوي للدجاج مقارنة بمجموعة السيطرة وبنسبة ١٤ و٢٦% على التوالي. وكان تركيز الأمانتادين في البلازما (٣١,٤٤ ملغم/كغم، عن طريق الفم) المقاسة في أوقات مختلفة وهي ٠,٢٥ ، ٠,٥ ، ١ ، ٢ ، ٤ و٨ ساعات هي ٠,٣٨ ، ٠,٤٢ ، ٠,٣١ ، ٠,٣٠ ، ٠,٢٦ و٠,٢٣ ميكروغرام/مل. تم تقدير متغيرات الحركية الدوائية للأمانتادين المنطقة تحت المنحنى ٧، ٤٤، المنطقة تحت المنحنى الأني ١٧٠,٨٥ ، ثابت معدل الطرح ٠,٠٤ ، التركيز الأعلى ٠,٠٤ ، الوقت الأعلى ٠,٥ ، عمر النصف ١٥,٨٨ ، معدل وقت البقاء ٣,٣٤ ، حجم الانتشار ٩٦,٧٥ والتصفية الكلية ٤,٢٢. خلصت الدراسة إلى أمان الأمانتادين (وظائف الكبد والكلى بالإضافة إلى حركيته الدوائية) وبقدرته الفريدة على تعديل نشاط إنزيم الأكسدة الحلقية-٢ في الدماغ مما يجعله دواء مسكن للألم بشكل جيد وربما كدواء مضاد للالتهاب مفيد للاستخدام البيطري في الدجاج.

40. Hemmateenejad B, Javidnia K, Saeidi-Boroujeni M. Spectrophotometric monitoring of nimesulide photodegradation by a combined hard-soft multivariate curve resolution-alternative least square method. J Pharm Biomed Anal. 2008;47(3):625-630. DOI: 10.1016/j.jpba.2008.01.040
41. Pong SF, Demuth SM, Kinney CM, Deegan P. Prediction of human analgesic dosages of nonsteroidal anti-inflammatory drugs (NSAIDs) from analgesic ED50 values in mice. Arch Int Pharmacodyn Ther. 1985;273(2):212-220. [available at]
42. Gupta SK, Bansal P, Bhardwaj RK, Velpandian T. Comparative anti-nociceptive, anti-inflammatory and toxicity profile of nimesulide vs nimesulide and piperine combination. Pharmacol Res. 2000;41(6):657-662. DOI: 10.1006/phrs.1999.0640
43. Guillé PG, Guillé PE, Espinosa RL, Juárez-Olguín H, Álvarez GR, Brisuela ON, Portugal CM, Garcidueñas CL, Rosales SE, Luna JA, Medina AR, Pacheco CL. Pharmacokinetic variations of nimesulide in mongrel dogs according to age. Pharmazie. 2019;74(12):728-731. DOI: 10.1691/ph.2019.9121
44. Ivanova E, Kaptisa I, Valdman E, Voronina T. Comparison of the Analgesic Activity of Antiparkinsonian Aminoadamantane Derivatives Amantadine and Hemantane. Adv Parkinson's Dis. 2016;5:50-60. DOI: 10.4236/apd.2016.53007
45. Nishikawa N, Nagai M, Moritoyo T, Yabe H, Nomoto M. Plasma amantadine concentrations in patients with Parkinson's disease. Parkinsonism Relat Disord. 2009;15(5):351-353. DOI: 10.1016/j.parkreldis.2008.08.005