Journal of Veterinary Science and Public Health
Revista de Ciência Veterinária e Saúde Pública
ISSN online 2358-46-10
Volume 12, número 1, 2025

Pharmacodynamic effects of intranasal ketamine in cats

Efeitos farmacodinâmicos da cetamina intranasal em gatos

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DOI: 10.4025/revcivet.v12i1.70705

ABSTRACT

Ketamine is a versatile drug that is widely used in various clinical contexts. It is commonly administered intravenously, but several studies have shown that it can be used by alternative routes, such as intranasal. The aim of this study was to evaluate the cardiovascular, respiratory and sedative effects of ketamine after intranasal administration in cats. The experiment was conducted with six cats (n = 6) subdivided equally into two groups: intravenous (IV) and intranasal (IN), which received ketamine at doses of 2 mg/kg and 5 mg/kg, respectively. The physiological parameters and degree of sedation of the animals were assessed before and after administration of the drug. The data was submitted to statistical analysis using the Shapiro-Wilk test and the Kruskal-Wallis test, as well as a descriptive evaluation. The results showed similar effects between the two treatments ($p > 0.05$), with the sedation score being significantly different for the IV group up to 20 minutes after ketamine administration. The main adverse effect observed immediately after intranasal administration of ketamine was salivation, while with intravenous administration it was mydriasis and muscle rigidity. The physiological and sedative effects of ketamine were similar between the intranasal and intravenous groups, and there were no relevant changes compared to baseline values.

KEYWORDS: *Felis catus*, Drug Administration Routes, N-methyl D-aspartate, sedation

INTRODUCTION

Ketamine is a derivative of phencyclidine and exists as two enantiomers: (S)- (+) and (R)- (–). For veterinary use, it is commonly available as a racemic mixture of both (NOWACKA and BORCZYK, 2019; JELEN et al., 2021). Its mechanism of action is primarily due to its antagonistic effect on *N*-methyl-*D*-aspartate (NMDA) receptors, which grants the drug anesthetic, analgesic, and antihyperalgesic properties (CONWAY et al., 2020). Increased heart rate and blood pressure are expected with ketamine use. Among the factors that favor its application, its ability to induce anesthesia and analgesia while preserving respiratory function and cardiac output is particularly relevant when choosing this anesthetic (MILLER et al., 2011; BROWN and TUCKER, 2020).

Ketamine is considered a versatile drug, offering various clinical benefits depending on the administered dose, and it can be delivered via multiple routes (LI and VLISIDES, 2016; MCINTYRE et al., 2021). The use of ketamine through alternative routes, such as intranasal administration, has already been approved for humans (TRAYNOR, 2019; MCINTYRE et al., 2021; XIONG et al., 2021). In veterinary medicine, its use has been explored in diverse clinical contexts, particularly for promoting sedation (MARJANI et al., 2014; VLERICK et al., 2020).

This study aimed to compare the cardiovascular, respiratory, and sedative effects of ketamine after intranasal and intravenous administration in cats, as well as to describe potential adverse effects.

MATERIAL AND METHODS

This study was approved by the Ethics Committee for the Use of Animals in Research of the State University of Maringá (CEUA/UEM) under the protocol 3292020621. The participating animals were included only after their guardians had agreed to participate voluntarily, by signing an Informed Consent Form which was strictly worded to contain all the objectives and proposals of the experiment.

The study was conducted at the Veterinary Hospital of the State University of Maringá, Umuarama, Paraná, and involved the participation of six (n = 6) cats, five males and one female, considered healthy based on physical assessment and laboratory tests. The animals were standardized according to age, weight and were at least one and no more than ten years old (2.5± 0.32), with a minimum live weight of 4 kg (4.65± 0.26).

The animals were divided into the Intranasal Group (IN) and the Control Group (IV), in which they received ketamine 100 mg/mL (vetanarcol®, Konig) intranasally (5 mg/kg)

Journal of Veterinary Science and Public Health
Revista de Ciência Veterinária e Saúde Pública
ISSN online 2358-46-10
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and intravenously (2 mg/kg). Intranasal administration was carried out using a laryngotracheal atomizer (MADgic®, Teleflex), with the volume of the drug divided equally between the nostrils. To administer the drug, the animals were held with their heads suspended in a dorsal direction by the assistant, who placed both hands on the area of the animal's mandible. After administering the drug, the animals were kept with their heads in an upward position for approximately sixty seconds. The final volume of ketamine corresponded to the animal's weight and the drug was administered undiluted. One hour before the intranasal administration of ketamine, the nostrils were cleaned with 0.25 mL of saline solution in each nostril using a 1 mL luer slip syringe (BD®). Participants underwent both groups at least seven days apart.

The animals underwent a sedation assessment based on eyelid reflexes and spontaneous posture (Table 1), followed by a physical assessment at T0, which corresponded to the moment before ketamine was administered, and 5, 10, 20, 30, 60, 120, 240, 360 and 480 minutes after the drug was administered. The physical examination included evaluations of heart rate (HR), performed by auscultating the heart with a stethoscope for 15 seconds, respiratory rate (RR), based on visual evaluation of abdominal respiratory movements per minute, capillary refill time (CRT), which was based on the time needed for the oral mucosa to return to its initial color after digitally compressing it for approximately five seconds, as well as evaluation of mucosal coloration (MM). Finally, systolic blood pressure (SBP) was measured using a non-invasive vascular Doppler method. In addition, the other behavioral changes observed in the animals after treatment were described according to how they occurred and how long they lasted.

Table 1. Composite Evaluation System used to evaluate the sedative effects of cats administered ketamine intravenously (2 mg/kg) and intranasally (5 mg/kg).

Spontaneous posture	Score
Standing	0
Tired, but in season	1
Lying down, able to get up	2
Lying down, difficulty getting up	3
Unable to get up	4
Eyelid reflex	**Score**
Quickly	0
Slow, eyes open	1
Slow, eyes partially open	2
Absent	3

Source: WAGNER *et al.* (2017).

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The data collected was described in spreadsheets and subjected to statistical analysis using the Shapiro-Wilk test to assess the distribution of the data. Data with a normal distribution was evaluated using the ANOVA test for comparison. For behavior scores and data without normal distribution, the Kruskal-Wallis test was used, with Dunn's post-test. In addition to the descriptive analysis for physiological parameters. A p-value ≤ 0.05 was used as the limit of statistical significance.

RESULTS

The physiological parameters related to HR, RR and SBP were similar between the two treatments ($p > 0.05$) (Table 2). The eyelid reflex and spontaneous posture did not differ statistically between the groups. The spontaneous posture score was significantly different for group IV up to 20 minutes after ketamine administration, compared to T0, characterized by increased difficulty in locomotion.

Table 2. Results referring to the means ± standard deviation obtained in relation to the physiological parameters of HR, RR and SBP and the median (maximum-minimum value) of sedation (spontaneous posture and eyelid reflex) at each time point (T0 to T480) among all the animals administered ketamine intravenously - IV (2 mg/kg) and intranasally - IN (5 mg/kg) (n = 6).

Group	Parameter	Moment										p
		T0	T5	T10	T20	T30	T60	T120	T240	T360	T480	
IV	FC	186± 44,4	218± 26,2	210± 29,2	192± 28,6	204± 31,6	188± 34,2	158± 41,1	172± 36,1	186± 44,6	192± 41,6	0.32
IN	FC	167± 23.4	186± 30,5	190± 39,4	200± 29	191± 15,8	181± 18	163± 17,9	171± 19,5	150± 21,5	166± 29,5	
IV	FR	80± 26,6	84± 52,4	68± 38,5	104± 37,4	84± 33,9	72± 31	72± 24,8	76± 19,4	64± 20,7	64± 15,6	0.69
IN	FR	66± 24,2	67± 18,6	69± 65,3	64± 32	74± 22	76± 37,4	54± 17,2	62± 25,1	68± 25,6	40± 32,2	
IV	PAS	150± 23	180± 20,5	168± 7,5	160± 13,7	180± 16,2	140± 21,6	160± 15,5	180± 22	170± 13,3	160± 25,4	0.54
IN	PAS	155± 20,8	142± 16,7	160± 63,7	172± 65,2	164± 61,8	150± 18,1	183± 43	156± 59,6	160± 48,8	176± 27,1	
IV	PE	0a (0-2)	3b (3-3)	3b (3-3)	3b (2-3)	2a (0-3)	2a (0-2)	0a (0-2)	0a (0-2)	2a (0-2)	2a (0-2)	<0.05
IN	PE	0 (0-0)	2 (0-3)	2 (0-3)	2 (0-3)	2 (0-3)	2 (0-2)	2 (0-2)	2 (0-2)	1 (0-2)	0 (0-2)	
IV	PR	0 (0-0)	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.99
IN	PR	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	

Abbreviations: T: time in minutes; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure. SP, spontaneous posture. PR, palpebral reflex. Different lowercase letters on the line indicate a difference between the moments.

One of the animals didn't take part in the IV treatment because it wouldn't be handled on the day of the experiment (n = 5). Mucosal coloration (MM) remained within the normal range in all participants in both groups, with the exception of one animal in the IN group, which had hypocolored mucosa for up to 30 minutes after ketamine administration. Despite this, there was no increase in CPT, which remained within the physiological limit (1 to 2 seconds) in all participants in both groups.

The main adverse effect observed immediately after intranasal administration of ketamine was salivation (4/6), which occurred within 10 seconds of the drug being administered and lasted an average of one minute. Next, mydriasis (5/6), lateral decubitus (1/6) and facilitated handling (5/6) were observed 5 minutes after administration, which lasted an average of 30 (4/6) to 60 minutes (2/6) and showed that the animals were mentally alert but easy to manage.

The main immediate adverse effects of intravenous ketamine administration were mydriasis and muscle rigidity (4/5), which ceased around 5 minutes after the drug was administered. Other signs observed were difficulty in locomotion (5/5), ventral relaxation of the head (1/5) and stereotyped movements with the head (1/5). The animals remained more submissive to manipulation within 20 minutes of the drug being administered (4/5), with one of them having difficulty moving for up to 60 minutes.

DISCUSSION

Intranasal administration of ketamine has been effective in promoting sedation in dogs and humans (POONAI *et al.*, 2017; VLERICK *et al.*, 2020; RACHED-D'ASTOUS *et al.*, 2023). The use of the intranasal route enables the delivery of molecules directly to the CNS, through absorption by the trigeminal and olfactory pathways present in the nasal cavity. This condition favors the PK/PD (pharmacokinetic/pharmacodynamic) profile of drugs acting on the CNS, and by avoiding first-pass metabolism it is possible to reduce the doses administered, as well as adverse events (ERDO *et al.*, 2018; LOCHHEAD and DAVIS, 2019). Even so, it is necessary to overcome the absorption barrier, and part of the drug may have been directed to the systemic circulation and be subject to hepatic metabolism. In addition, the main adverse event observed after the administration of ketamine via the IN route in cats was salivation, which may have contributed to the reduction in the drug used by the body.

In addition to the possibility of direct absorption between the nasal mucosa and the CNS, the use of the intranasal route acts as a non-traumatic alternative for drug administration, which reduces stress and anxiety that are already frequent in the hospital

environment (RACHED-D'ASTOUS *et al.*, 2023). In addition, the nasal mucosa has benefits related to the quality of drug absorption with a short latency period, provided by the highly vascularized epithelium (LUNGARE *et al.*, 2016; ERDO *et al.*, 2018). However, the sedative effects did not occur as expected, given the mechanism of action described. Ketamine administered by the IV route had a greater degree of sedation, despite the lower dose used. The use of intravenous ketamine has already been described as effective for promoting sedation and analgesia (MILLER *et al.*, 2011; MOHRIEN *et al.*, 2011; BROWN and TUCKER, 2020) and is widely used in this context. Although no significant changes in physiological parameters were visualized, the peripheral effect of muscle stiffness was frequent. The expression of NMDA receptors extends beyond the CNS to the peripheral nervous system and thus modulates the release of neurotransmitters in the peripheral endings (SAWYNOK, 2014; BOUVIER *et al.*, 2015; DENG *et al.*, 2019), and results in visible effects on the somatic nervous system.

Previous studies have shown effective sedative effects when ketamine was used at doses between 2 and 10 mg/kg intranasally in humans (POONAI *et al.*, 2017; GUTHRIE *et al.*, 2019; RACHED-D'ASTOUS *et al.*, 2023). In dogs, the sedative effects were satisfactory when ketamine was used at a dose of 2 mg/kg (VLERICK *et al.*, 2020), which showed changes in behavior, such as spontaneous posture, eyelid reflex and general appearance. As for the use of the intranasal route in cats, one study describes the use of ketamine at a dose of 10 mg/kg, combined with midazolam, compared to intramuscular administration. In this case, no differences were observed in the sedation variables between the two groups (MARJANI *et al.*, 2015), with both being satisfactory. Ketamine is a drug with a wide therapeutic window and the visualization of its effects varies according to the dose used (BURNETT *et al.*, 2015; RADVANSKY *et al.*, 2015). In this study, ketamine was administered at a dose of 5 mg/kg intranasally and there were no significant changes in cardiovascular and sedation parameters.

CONCLUSION

Ketamine in the doses and routes used proved to be safe. The dose used intranasally was not enough to promote sedation, but it was enough to facilitate handling the animals for up to 60 minutes. The main adverse effects were salivation after the intranasal route administration and muscle rigidity after the intravenous route. The physiological and sedative effects of ketamine were similar between the intranasal and intravenous groups, and there were no relevant changes compared to baseline values.

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