Pharmacokinetics, absolute bioavailability and tolerability of ketamine after intranasal administration to dexmedetomidine sedated dogs

Lise Vlerick1*, Mathias Devreese2, Kathelijne Peremans3, Robrecht Dockx3,4, Siska Croubels2, Luc Duchateau5, Ingeborgh Polis1

1 Small Animal Department, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium, 2 Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium, 3 Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium, 4 Department of Psychiatry and Medical Psychology, Ghent Experimental Psychiatry (GHEP) lab, Ghent University, Ghent, Belgium, 5 Biometrics Research Centre, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

* lise.vlerick@ugent.be

Abstract

Intranasal ketamine has recently gained interest in human medicine, not only for its sedative, anaesthetic or analgesic properties, but also in the management of treatment resistant depression, where it has been shown to be an effective, fast acting alternative treatment. Since several similarities are reported between human psychiatric disorders and canine anxiety disorders, intranasal ketamine could serve as an alternative treatment for anxiety disordered dogs. However, to the authors knowledge, intranasal administration of ketamine and its pharmacokinetics have never been described in dogs. Therefore, this study aimed to examine the pharmacokinetics, absolute bioavailability and tolerability of intranasal ketamine administration compared with intravenous administration. Seven healthy, adult laboratory Beagle dogs were included in this randomized crossover study. The dogs received 2 mg/kg body weight ketamine intravenously (IV) or intranasally (IN), with a two-week washout period. Prior to ketamine administration, dogs were sedated intramuscularly with dexmedetomidine. Venous blood samples were collected at fixed times until 480 min post-administration. The dogs received 2 mg/kg body weight ketamine intravenously (IV) or intranasally (IN), with a two-week washout period. Prior to ketamine administration, dogs were sedated intramuscularly with dexmedetomidine. Venous blood samples were collected at fixed times until 480 min post-administration and ketamine plasma concentrations were determined by liquid chromatography-tandem mass spectrometry. Cardiovascular parameters and sedation scores were recorded at the same time points. Non-compartmental pharmacokinetic analysis revealed a rapid (Tmax = 0.25 ± 0.14 h) and complete IN bioavailability (F = 147.65 ± 49.97%). Elimination half-life was similar between both administration routes (T1/2el IV = 1.47 ± 0.24 h, T1/2el IN = 1.50 ± 0.97 h). Heart rate and sedation scores were significantly higher at 5 and 10 min following IV administration compared to IN administration, but not at the later time-points.
**Introduction**

Ketamine is a dissociative anesthetic commonly used in veterinary medicine, mainly for induction and maintenance of anesthesia, but also for pain management in the peri- and postoperative period [1,2]. Generally ketamine is administered intravenously, intramuscularly or subcutaneously. Recently, intranasal administration of ketamine has gained attention in human medicine. Intranasal drug administration delivers drugs directly to the central nervous system, bypassing the blood brain barrier and is associated with a fast onset of action [3,4]. In addition, intranasal drug delivery avoids painful parenteral administration. Intranasal ketamine has been successfully used for sedation and premedication of pediatric patients [5–7] and in pain management of both children and adults [8–13]. Another application lies in psychiatry, where intranasal ketamine has been shown to be safe and effective for the treatment of major depressive disorders [14–16]. Moreover, recently, the US Food and Drug Administration approved S-ketamine nasal spray as a new therapy for treatment-resistant depression. Since anxiety disorders in dogs show several similarities with human mood disorders [17–23], intranasal ketamine could also be a valuable alternative treatment for certain canine behavioral disorders.

Brain imaging studies have reported similar abnormalities in regional cerebral blood flow of certain brain regions in dogs with pathological anxiety and in humans suffering from depression and anxiety disorders [17–23]. Furthermore, altered perfusion of these brain regions following intravenous subanesthetic ketamine administration has been demonstrated both in humans and dogs [24–30]. Additionally, functional imaging studies have demonstrated altered function of the serotonergic system in several cortical brain regions, both in humans and dogs suffering from mood and anxiety disorders [31–33]. Since the management of behavioral disorders in dogs is challenging and treatment outcome is often unsatisfactory, there is a need for faster and more effective treatment strategies [34–37]. Therefore, intranasal ketamine could be a promising adjunctive treatment in the management of canine anxiety disorders, complementary to standard behavioral therapy and pharmacotherapy. The intranasal route could also offer opportunities when ketamine is used for its anesthetic, sedative or analgesic properties in small animals. For example, when intravenous catheter placement is difficult due to medical or behavioral issues or for the ambulatory treatment of chronic pain. In cats, it has been demonstrated that intranasal administration of ketamine-midazolam is effective to induce sedation [38]. Moreover, compared with intramuscular administration of the same ketamine-midazolam combination, there were no differences in the measured parameters associated with sedation except for time to sternal recumbency, which was more rapid in the intranasal group. In rabbits, intranasal ketamine and S-ketamine was successfully used in combination with medetomidine to induce anesthesia [39]. Induction was more rapid compared to rabbits receiving medetomidine-ketamine intramuscularly or subcutaneously [40]. As rabbits are easily stressed, rapid onset of induction is desirable in this species. Intranasal ketamine has also been used in combination with dexmedetomidine and morphine to provide deep sedation sufficient for routine clinical examinations in rabbits [41]. However, to the authors knowledge, intranasal ketamine has never been used in dogs and its pharmacokinetics have never been described. Therefore, the primary objective of the present study was to determine and compare plasma concentrations of ketamine after intravenous and intranasal administration of 2 mg/kg body weight (BW) ketamine in healthy dogs. Secondly, the tolerability of a single intranasal ketamine administration was assessed.
1. Materials and methods

1.1. Animals

Seven neutered adult laboratory Beagles (5 females, 2 males; age 3.6 ± 1.7 years; weight 12.0 ± 2.6 kg) were included in a randomized crossover study. The animals were classified as healthy based on general clinical examination. Experiments were approved by the local Ethical Committee of the Faculty of Veterinary Medicine and of Bioscience Engineering, Ghent University (EC 2018_03) and all manipulations were performed according to good animal practice. Welfare of the animals was respected at each time and great care was taken to avoid stress and anxiety. No animals were sacrificed. The dogs were provided by the Small Animal Department of the Faculty of Veterinary Medicine and were purchased from Marshall BioResources (North Rose, New York, United States). The dogs were socially-housed in small groups (2 to 8 dogs), according to the European and Belgian legislation and received environmental enrichment (Directive 2010/63/EU, KB 29/05/2013). The bedding material in the inner part of the housing facility consisted of wood shavings. The dogs had permanent access to an outside area of 15 m² and twice a day, they were allowed to run and play outside in an enclosed play area, enriched with climbing platforms, hiding places and small bushes. In addition, the dogs were regularly walked by students of the Faculty of Veterinary Medicine. Food was withheld for at least 12 hours before the start of the experiments, but water was provided ad libitum.

1.2. Study design

The dogs were randomly allocated to a two-period crossover design by the principal investigator, using an online randomization program (www.randomizer.org). Two routes of administration of ketamine were examined: the intravenous (IV) and the intranasal route (IN). Following a two-week wash-out period, each dog underwent the same protocol but receiving ketamine through a different administration route. Prior to each ketamine administration, the dogs were sedated intramuscular with dexmedetomidine (375 μg/m² body surface, Dexdomitor®, Orion Corporation, Espoo, Finland). Following the placement of an IV 22G over-the-needle catheter (Optiva®, Jelco Smiths Medical International Ltd, Rossendale, UK) in one of the cephalic veins, the dogs were allowed to relax in a quiet room. The first blood sample (T0) was taken 20 minutes after dexmedetomidine injection and was followed by the administration of ketamine.

1.3. Drug administration and sample collection

A commercially available racemic ketamine preparation (Nimatek®, Eurovet Animal Health B.V., Bladel, the Netherlands) was used for IV injection. IV ketamine was administered at a dose of 2 mg/kg BW through the cephalic catheter, which was flushed with a standardized volume of saline prior to and following injection. For the nasal spray, an aqueous solution containing 2 mg/kg BW racemic ketamine (Nimatek®, Eurovet Animal Health B.V.) dissolved in 0.9% NaCl was administered to the mucous membranes of the nose using a mucosal atomization device (MAD Nasal™, Wolfe Tory Medical, South Salt Lake City, Utah, United States). The total volume was fixed at 0.5 mL and was divided over the two nostrils. The MAD converted the aqueous solution into a fine mist creating a film coating the nasal mucosa. During the nasal administration, dogs were held in sternal recumbency with the head and neck gently dorsoflexed and were kept in this position for approximately 1 min after nasal delivery. Blood samples (each 2 mL) were collected from the vena jugularis before ketamine administration (T0) and at 2, 5, 10, 20, 30, 60, 120, 240, 360 and 480 min after IV ketamine administration. Following IN administration of ketamine, blood samples were taken at 5, 10, 20, 30, 45, 60,
120, 240, 360 and 480 min after dosing. Blood samples were immediately transferred into tubes containing lithium heparin and separated by centrifugation within 2 h at 3,500 rpm for 10 min. The plasma was harvested and stored at -80°C until analysis.

1.4. Tolerability assessment

Adverse reactions during and after intranasal drug administration were recorded to assess the tolerability (sneezing, coughing, head shaking, snorting and licking).

Sedation scores were determined at the same time points of blood collection. The degree of sedation was assessed with a modified numeric rating scale ranging from 0 (no sedation) to 15 (maximum sedation) [42] (Table 1).

Together with the scoring of sedation, the following physiological variables were monitored: heart rate, obtained by auscultation, respiratory rate, obtained by direct observation of thoracic excursions and systolic blood pressure, using an ultrasonic Doppler flow detector and an inflatable cuff.

1.5. Quantification of ketamine in plasma

Sample preparation was done as described by Devreese et al. (2015) [43]. The chromatographic system consisted of a Waters Alliance 2690 separation module and autosampler of the same type (Waters, Zellik, Belgium). Chromatographic separation was achieved on an Acquity UPLC® BEH C18 column (particle diameter: 1.7 μm) (Waters). The mobile phases were (A) 0.1% formic acid in UPLC water and (B) 0.1% formic acid in methanol. The following gradient elution program was run: 0–1.0 min (95% A, 5% B), 1.0–2.0 min (linear gradient to 5% A), 2.0–5.5 min (5% A, 95% B), 5.5–6.0 (linear gradient to 95% A), 6.0–10.0 min (95% A, 5% B). Flow rate was set at 300 μL/min.

Table 1. Numeric sedation rating scale, adapted from Gurney et al. (2009).

| Parameter                     | Behaviour of the dog         | Score |
|-------------------------------|------------------------------|-------|
| Spontaneous posture           | Standing                     | 0     |
|                               | Sternally recumbent          | 1     |
|                               | Laterally recumbent          | 2     |
| Palpebral reflex              | Brisk                        | 0     |
|                               | Slow                         | 1     |
|                               | Absent                       | 2     |
| Eye position                  | Forward (normal position)    | 0     |
|                               | Rotated ventrally            | 2     |
| Response to sound (handclap)  | Body movement                | 0     |
|                               | Head movement                | 1     |
|                               | Ear twitch                   | 2     |
|                               | No reaction                  | 3     |
| Resistance to lateral recumbency | Full (stands)               | 0     |
|                               | Moderate restraint required   | 1     |
|                               | Mild restraint required       | 2     |
|                               | No resistance                | 3     |
| Overall appearance            | No sedation apparent         | 0     |
|                               | Mild sedation                | 1     |
|                               | Moderate sedation            | 2     |
|                               | Well sedated                 | 3     |

https://doi.org/10.1371/journal.pone.0227762.t001
The LC column effluent was interfaced to a Waters Quattro Premier triple quadrupole mass spectrometer equipped with a heated electrospray ionization (h-ESI) probe operating in the positive ionization mode (Micromass Waters, UK). Acquisition was performed in the selected reaction monitoring (SRM) mode. The two most intense product ions of the precursor ion were monitored in the SRM mode for quantification and identification, respectively. For ketamine m/z 238.4 > 125.1/179.2 and for the internal standard (d3-ketamine) m/z 241.4 > 125.1/179.2. The method was validated according to a protocol previously described by [43]. The limit of quantification (LOQ) was 20 ng/mL and the linear range was 20–10,000 ng/mL.

1.6. Pharmacokinetic analysis

Plasma concentration-time profiles were modelled by non-compartmental analysis (NCA) using Phoenix 8.4 (Certara, NJ, USA). Plasma concentrations measured at 360 and 480 min after ketamine administration fell below the LOQ and were therefore not taken into account for pharmacokinetic analysis. The following major pharmacokinetic parameters were calculated: AUC$_{0-4h}$, area under the plasma concentration-time curve from 0 to 4 hours post-administration; AUC$_{0-\infty}$, area under the plasma concentration-time curve from 0 to infinity; C$_{max}$, maximal plasma concentration (IN); C$_0$, plasma concentration at time zero (IV); T$_{max}$, time to maximal plasma concentration (IN); Vd, volume of distribution; Cl, total body clearance; T$_{1/2,el}$, terminal elimination half-life; k$_{el}$, elimination rate constant. Vd and Cl values after IN administration were not corrected for IN bioavailability (F). The absolute IN F, expressed as percentage, was calculated according to the following formula:

$$ F = \frac{\text{AUC}_{0-\infty,\text{IN}}}{\text{AUC}_{0-\infty,\text{IV}}} \times 100. $$

1.7. Statistical analysis

A Student t-test was used to compare both administration routes (IV and IN) for each pharmacokinetic parameter. The level of significance was set at 0.05. For the evaluation of heart rate, respiratory rate, systolic blood pressure and sedation scores, linear mixed models were fitted onto the data set using dog as a random effect and time, treatment and their interaction as fixed effects as the data could be assumed to be normally distributed according to the Shapiro-Wilks test. Next, the two administration routes were compared at seven different time points (5, 10, 20, 30, 60, 120 and 240 min after ketamine administration) and tested at the Bonferroni adjusted significance level of 0.05/7 = 0.0071. Measurements at 360 and 480 min were not included in the analysis since plasma concentrations at these time points were also not taken into account for pharmacokinetic analysis.

2. Results

Mean ketamine plasma concentration versus time curves for each administration route are displayed in Fig 1. Pharmacokinetic results are shown in Table 2. No significant differences in pharmacokinetic parameters were found between the two administration routes.

Concerning the heart rate, significant differences between the two administration routes were found at two time points: 5 (p < 0.001) and 10 min (p < 0.001) after ketamine administration, with a higher heart rate following IV administration. At the same time points, significant differences in sedation scores were also observed (p < 0.001) with higher sedation scores following IV administration compared to IN administration. No significant differences between the two administration routes were found for the respiratory rate and systolic blood pressure.
Dogs tolerated the IN administration relatively well. IN administration led to some degree of nasal irritation, reflected by sneezing, coughing and head shaking in almost all of the dogs (Table 3). However, these reactions were mild and only occurred immediately after nasal administration and disappeared fast.

3. Discussion

To our knowledge, this is the first study describing IN administration of ketamine in dogs and its pharmacokinetics and tolerance. Ketamine was rapidly absorbed after IN administration, with maximal plasma concentrations at 15 min and as early as 5 min in one subject. IN drug delivery is known to be associated with rapid drug absorption from the rich, IN vascular bed,

**Table 2. Pharmacokinetic parameters of ketamine in dogs administered a single dose of 2 mg/kg BW intravenously (IV) or intranasally (IN) (n = 7, mean ± SD).**

| Pharmacokinetic parameter | IV          | IN          |
|---------------------------|-------------|-------------|
| AUC₀-₄h (ng.h/mL)         | 1415.78 ± 338.40 | 1925.66 ± 789.83 |
| AUC₀-∞ (ng.h/mL)         | 1532.31 ± 397.01 | 2199.27 ± 773.23 |
| Cmax (ng/mL)             | /           | 1694.48 ± 876.67 |
| C₀ (ng/mL)               | 9725.69 ± 3121.04 | /           |
| Tₘₙₙₓ (h)                | /           | 0.25 ± 0.14  |
| Vd (mL/kg)               | 2869.08 ± 570.03 | 2342.36 ± 2086.60 |
| Cl (mL/h/kg)             | 1378.09 ± 340.02 | 1008.68 ± 333.27 |
| T½ₑₑₑₑ (h)              | 1.47 ± 0.24  | 1.50 ± 0.97  |
| kₑₑₑₑ (1/h)              | 0.48 ± 0.07  | 0.61 ± 0.29  |
| F (%)                    | 100         | 147.65 ± 49.97 |

AUC₀-₄h area under the plasma concentration-time curve from 0 to 4 hours post-administration; AUC₀-∞ area under the plasma concentration-time curve from 0 to infinity; Cmax maximal plasma concentration (IN); C₀ plasma concentration at time zero (IV); Tₘₙₙₙₓ time to maximal plasma concentration (IN); Vd volume of distribution; Cl total body clearance; T½ₑₑₑₑ terminal elimination half-life; kₑₑₑₑ elimination rate constant. Vd and Cl values after IN administration were not corrected for IN bioavailability (F).

https://doi.org/10.1371/journal.pone.0227762.t002
leading to rapidly attained peak blood levels, as observed in this study [3]. Ketamine was completely bioavailable following IN administration. This is much higher than the reported IN bioavailability of 45 and 50% in human studies [44,45]. This can be partially explained by differences in anatomy of the nasal cavity between humans and dogs. Following intranasal administration, ketamine can be delivered directly to the central nervous system, where it can exert its actions [3,4,46]. This direct nose to brain delivery, bypassing the blood brain barrier, occurs mainly through the olfactory epithelium, which comprises 77% of the nasal cavity in dogs [46]. The human olfactory epithelium, on the contrary, is restricted to a small area in the roof of the nasal cavity and only covers less than 10% of the nasal cavity. The complete IN bioavailability can further be explained by the fact that the dogs were sedated, which facilitated nasal drug delivery and is associated with less risk of spilling and swallowing. Moreover, using a spray device instead of droplet administration of the drug into the nose and dividing the dose over the two nostrils would also enhance nasal absorption and bioavailability, since this increases the area over which the drug is spread [7,46].

Total body clearance (Cl) of ketamine was lower compared to other veterinary studies examining the pharmacokinetics of ketamine in dogs [47–49]. In the study of Pypendop and Ilkiw (2005), mean Cl after IV administration of ketamine was 3492 ± 1038 mL/h/kg, while volume of distribution at steady state (Vss) was 4060.3 ± 2405.7 mL/kg. Romagnoli et al. (2017) reported separate Cl values for S- (4309.2 ± 768 mL/h/kg) and R-ketamine (4048.8 ± 640.8 mL/h/kg) following IV racemic ketamine administration, with a volume of distribution for the central compartment of 750 ± 370 mL/kg. The study of Sandbaumhütter et al. consisted of two groups of dogs receiving ketamine, with one group anesthetized with sevoflurane and one group sedated with medetomidine. In the sevoflurane group, Cl was 3341.4 ± 664.2 mL/h/kg for R-ketamine and 3490.2 ± 642 mL/h/kg for S-ketamine with Vss of 1630 ± 1170 mL/kg and 1620 ± 1230 mL/kg respectively. In the medetomidine group Cl was 2844.6 ± 474 mL/h/kg for R-ketamine and 2745.6 ± 996.6 mL/h/kg for S-ketamine, with Vss of 3370 ± 660 mL/kg and 3130 ± 660 mL/kg respectively. Elimination half-life was comparable with that reported in the study of Pypendop and Ilkiw (2005) (1.57 ± 0.61 h), but was longer than documented by Romagnoli et al. (2017) (0.26 ± 0.12 h for S-ketamine and 0.26 ± 0.09 h for R-ketamine) and Sandbaumhütter et al. (2016) (0.50 ± 0.04 h for R-ketamine and 0.48 ± 0.42 h for S-ketamine in the sevoflurane group; 1.14 ± 0.17 h for R-ketamine and 1.11 ± 0.21 h for S-ketamine in the medetomidine group). The longer half-life of ketamine in the medetomidine group compared with the sevoflurane group in the study of Sandbaumhütter et al. (2017) indicates a slower elimination in the latter group. The lower clearance and subsequent longer half-life in the current study compared to the literature is in agreement with this and could be explained by the fact that the dogs were sedated with dexmedetomidine. Dexmedetomidine and medetomidine are strong inhibitors of the N-demethylation of ketamine to norketamine by competition for the binding site on cytochrome P450 enzymes [48]. Since the formation of norketamine is a

| Dog  | Sneezing | Coughing | Head shaking | Snorting | Licking | Duration |
|------|----------|----------|--------------|----------|---------|----------|
| Dog 1| -        | +        | -            | -        | -       | < 10 sec |
| Dog 2| +        | -        | +            | +        | -       | < 1 min  |
| Dog 3| +        | +        | -            | +        | +       | < 1 min  |
| Dog 4| -        | +        | -            | -        | -       | < 1 min  |
| Dog 5| +        | -        | -            | +        | -       | < 10 sec |
| Dog 6| +        | -        | -            | +        | -       | < 10 sec |
| Dog 7| -        | -        | -            | -        | -       | -        |

https://doi.org/10.1371/journal.pone.0227762.t003
major pathway in the biotransformation and hence elimination of ketamine, inhibition of nor-ke
Please avoid any sensitive topics.
A limitation of this study is the fact that the dogs were sedated with dexmedetomidine prior to the ketamine administration. Dexmedetomidine was administered to avoid behavioural and cardiovascular adverse effects due to the ketamine administration. Dexmedetomidine-ketamine is a frequently used combination in veterinary medicine as the two drugs are complementary to each other and side effects of both drugs are minimized when used together. Dexmedetomidine may attenuate or prevent tachycardia, hypertension, delirium, excitement and hallucinations caused by ketamine [51,60]. On the other hand, ketamine may reduce the bradycardia and hypotension associated with dexmedetomidine administration [61]. However, the use of co-medication can have an influence on drug disposition and pharmacokinetics.

**Conclusion**

IN administration of 2 mg/kg BW ketamine to healthy dogs, sedated with dexmedetomidine, was well tolerated by all of the dogs. Rapid systemic absorption and complete bioavailability of IN ketamine were demonstrated. These findings encourage the use of IN ketamine in veterinary medicine, not only as anesthetic, sedative or analgesic but potentially also in the treatment of dogs with anxiety disorders. Further studies are necessary to assess the clinical effects of IN ketamine in anxiety-disordered dogs.

**Supporting information**

S1 Table. Heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP) and sedation score following intravenous (IV) and intranasal (IN) administration of 2 mg/kg BW racemic ketamine. (n = 7, mean ± SD). The degree of sedation was assessed with a modified numeric rating scale ranging from 0 (no sedation) to 15 (maximum sedation), adapted from Gurney et al. (2009).

S2 Table. Heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP) and sedation score (SS) at different time points (T) in the individual dogs following intravenous administration of 2 mg/kg BW racemic ketamine. T: min; HR: beats/min; RR: breaths/min; SAP: mm Hg; NA: not available. The degree of sedation was assessed with a modified numeric rating scale ranging from 0 (no sedation) to 15 (maximum sedation), adapted from Gurney et al. (2009).

S3 Table. Heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP) and sedation score (SS) at different time points (T) in the individual dogs following intranasal administration of 2 mg/kg BW racemic ketamine. T: min; HR: beats/min; RR: breaths/min; SAP: mm Hg; NA: not available. The degree of sedation was assessed with a modified numeric rating scale ranging from 0 (no sedation) to 15 (maximum sedation), adapted from Gurney et al. (2009).

**Acknowledgments**

The authors would like to thank the dedicated animal caretaker Bieke Weyn for her help during experiments and for her daily care for the animals.
Author Contributions

Conceptualization: Lise Vlerick, Kathelijne Peremans, Ingeborgh Polis.

Formal analysis: Lise Vlerick, Mathias Devreese, Robrecht Dockx, Luc Duchateau.

Funding acquisition: Lise Vlerick.

Investigation: Lise Vlerick.

Methodology: Lise Vlerick, Kathelijne Peremans, Ingeborgh Polis.

Project administration: Lise Vlerick.

Resources: Mathias Devreese, Siska Croubels, Ingeborgh Polis.

Supervision: Ingeborgh Polis.

Writing – original draft: Lise Vlerick.

Writing – review & editing: Lise Vlerick, Mathias Devreese, Kathelijne Peremans, Robrecht Dockx, Siska Croubels, Luc Duchateau, Ingeborgh Polis.

References

1. Sarrau S, Jourdan J, Dupuis-Soyris F, Verwaerde P. Effects of postoperative ketamine infusion on pain control and feeding behaviour in bitches undergoing mastectomy. J Small Anim Pract. 2007; 48(12):670–6. https://doi.org/10.1111/j.1748-5827.2007.00362.x PMID: 17725589

2. Wagner AE, Walton Ja, Hellery PW, Gaynor JS, Maha KR. Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. J Am Vet Med Assoc. 2002; 221(1):72–5. https://doi.org/10.2460/javma.2002.221.72 PMID: 12420827

3. Andrade C. Intranasal drug delivery in neuropsychiatry: focus on intranasal ketamine for refractory depression. J Clin Psychiatry [Internet]. 2015; 76(5):e628–31. Available from: http://www.psychiatrist.com/jcp/article/Pages/2015/v76n05/v76n0514.aspx https://doi.org/10.4088/JCP.15f10026 PMID: 26035196

4. Illum L. Nasal drug delivery—Possibilities, problems and solutions. J Control Release. 2003; 87(1–3):187–98. https://doi.org/10.1016/s0168-3659(02)00363-2 PMID: 12618035

5. Roelofse J a, Shipton E a, de la Harpe CJ, Blignaut RJ, Med D, Harpe CJ De, et al. Intranasal sufentanil/midazolam versus ketamine/midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: a prospective, double-blind, randomized comparison. Anesth Prog [Internet]. 2004; 51(4):114–21. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2007493&tool=pmcentrez&rendertype=abstract PMID: 15675259

6. Weber F, Wulf H, el Saedi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. Can J Anesth [Internet]. 2003; 50(5):470–5. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=2003281847 https://doi.org/10.1007/BF03021058 PMID: 12734155

7. Pandey R, Bahetwar S, Sakseza A, Chandra G. A Comparative Evaluation of Drops versus Atomized Administration of Intranasal Ketamine for the Procedural Sedation of Young Uncooperative Pediatric Dental Patients: A Prospective Crossover Trial. J Clin Pediatr Dent. 2015; 36(1):79–84.

8. Yeaman F, Meek R, Egerton-Warburton D, Rosengarten P, Graudins A. Sub-dissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients. EMA—Emerg Med Australas. 2014; 26(3):237–42.

9. Shimonovich S, Gigi R, Shapira A, Sarig-Meth T, Nadav D, Rozenek M, et al. Intranasal ketamine for acute traumatic pain in the Emergency Department: a prospective, randomized clinical trial of efficacy and safety. BMC Emerg Med [Internet]. 2016; 16(1):43. Available from: http://bmcemergmed.biomedcentral.com/articles/10.1186/s12909-016-0107-0 PMID: 27829367

10. Afridi SK, Giffin NJ, Kaube H, Goadsby PJ. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. Neurology. 2013; 80(7):642–7. https://doi.org/10.1212/WNL.0b013e3182624e66 PMID: 23365053

11. Hugue V, Lauchart M, Magerl W, Schelling G, Beyer A, Thieme D, et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. Eur J Pain [Internet]. 2010; 14(4):387–94. Available from: http://dx.doi.org/10.1016/j.ejpain.2009.08.002 PMID: 19733106
12. Riediger C, Haschke M, Bitter C, Fabbro T, Schaeren S, Unwyler A, et al. The analgesic effect of combined treatment with intranasal S-ketamine and intranasal midazolam compared with morphine patient-controlled analgesia in spinal surgery patients: a pilot study. J Pain Res. 2015; 8:87–94. https://doi.org/10.2147/JPR.S75928 PMID: 25709497

13. Graudins A, Meek R, Egerton-Warburton D, Oakley E, Seith R. The PICHFORK (Pain in Children Fentanyl or Ketamine) Trial: A randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. Ann Emerg Med [Internet]. 2015; 65 (3):248–254.e1. Available from: http://dx.doi.org/10.1016/j.annemergmed.2014.09.024 PMID: 25447557

14. Lapidus KAB, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry [Internet]. 2014; 76 (12):970–6. Available from: https://doi.org/10.1016/j.biopsych.2014.03.026 PMID: 24821196

15. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression. JAMA Psychiatry. 2017; 75(2):139–48.

16. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry. 2018; 175(7):620–30. https://doi.org/10.1176/appi.ajp.2018.17060720 PMID: 29666663

17. Vermeire S, Audenaert K, Dobbeleir A, de Meester R, Vandermeulen E, Waelbers T, et al. Regional cerebral blood flow changes in dogs with anxiety disorders, measured with SPECT. Brain Imaging Behav. 2009; 3(4):342–9.

18. Deckersbach T, Dougherty DD, Rauch SL. Functional Imaging of Mood and Anxiety Disorders. J Neuroimaging [Internet]. 2006; 16(1):1–10. Available from: https://doi.org/10.1177/1051228405001474 PMID: 16483270

19. Eren I, Tükel R, Polat A, Karaman R, Ünal S. Evaluation of regional cerebral blood flow changes in panic disorder with Tc99m-HMPAO SPECT. Psychiatry Res Neuroimaging. 2003; 123:135–43.

20. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007; 164(10):1476–88. https://doi.org/10.1176/appi.ajp.2007.07030504 PMID: 17898336

21. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A Meta-Analytic Study of Changes in Brain Activation and Metabolite Levels in Major Depressive Disorder. JAMA Psychiatry. 2017; 75(2):139–48. https://doi.org/10.1001/jamapsychiatry.2016.2765 PMID: 28936024

22. Järvum H, Simon F, Steffensen EG, Fründ E. Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. Acta Psychiatr Scand. 2011; 124:435–46. https://doi.org/10.1111/j.1600-0447.2011.01776.x PMID: 21923809

23. Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, et al. Executive and prefrontal dysfunction in unipolar depression: A review of neuropsychological and imaging evidence. Neurosci Res. 2004; 50(1):1–11. https://doi.org/10.1016/j.neures.2004.05.003 PMID: 15288493

24. Rowland LM, Beason-held L, Tamminga CA, Holcomb HH. The interactive effects of ketamine and nicotine on human cerebral blood flow. Psychopharmacology (Berl). 2010; 208:575–84.

25. Holcomb HH, Lahti AC, Medoff DR, Weiler M, Tamminga CA. Sequential Regional Cerebral Blood Flow Brain Scans Using PET with Tc99m O Ketamine Actions in CNS Dynamically. Neuropsychopharmacology. 2001; 25(2):165–72. https://doi.org/10.1016/S0893-133X(01)00229-9 PMID: 11425500

26. Holcomb HH, Lahti AC, Medoff DR, Cullen T, Tamminga CA. Effects of Noncompetitive NMDA Receptor Blockade on Anterior Cingulate Cerebral Blood Flow in Volunteers with Schizophrenia. Neuropsychopharmacology. 2005; 30:2275–82. https://doi.org/10.1038/sj.npp.1300824 PMID: 16034443

27. Pollak TA, De Simoni S, Barimani B, Zelaya FO, Stone JM, Mehta MA. Phenomenologically distinct psychotomimetic effects of ketamine are associated with cerebrovascular flow changes in functionally relevant cerebral foci: A continuous arterial spin labelling study. Psychopharmacology (Berl). 2015; 232 (4):4515–24.

28. Waelbers T, Polis I, Vermeire S, Dobbeleir A, Eersels J, De Spiegeleer B, et al. Effect of ketamine on the regional cerebral blood flow and binding index of the 5-HT2A receptor radioligand 123I–R91150 in the canine brain. J Vet Behav Clin Appl Res [Internet]. 2015; 10(4):332–7. Available from: http://dx.doi.org/10.1016/j.jveb.2015.03.009

29. Vierick L, Peremans K, Dockx R, Audenaert K, Baeken C, De Spiegeleer B, et al. The influence of subanaesthetic ketamine on regional cerebral blood flow in healthy dogs measured with 99mTc-HMPAO SPECT. PLoS One [Internet]. 2018;1–15. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0209316
30. Vlerick L, Perenaerts K, Dockx R, Audenaert K, Baeken C, Saunders JH, et al. The long-term effects of single and repeated subanaesthetic ketamine administration on regional cerebral blood flow in healthy dogs measured with 99mTc-HMPAO SPECT. Psychiatry Res—Neuroimaging [Internet]. 2019; 285 (January):18–24. Available from: https://doi.org/10.1016/j.psychresns.2019.01.005

31. Vermeire S, Audenaert K, Dobbeleir A, De Meester R, De Vos F, Perenaerts K. Evaluation of the brain 5-HT2A receptor binding index in dogs with anxiety disorders, measured with 123I-F18R91150 and SPECT. J Nucl Med [Internet]. 2009; 50(2):284–9. Available from: http://jnm.snmjournals.org/content/50/2/284.full.pdf https://doi.org/10.2967/jnumed.108.055731 PMID: 19164223

32. Mintun MA, Sheline YI, Morrel LM, Vlassenko AG, Huang Y, Snyder AZ. Decreased hippocampal 5-HT2A receptor binding in major depressive disorder: In vivo measurement with [18F]altanserin positron emission tomography. Biol Psychiatry. 2004; 55(3):217–24. https://doi.org/10.1016/j.biopsych.2003.08.015 PMID: 14744461

33. Yatham LN, Liddle PF, Shah I-S, Scarrow G, Lam RW, Adam MJ, et al. Brain Serotonin 2 Receptors in Major Depression. Arch Gen Psychiatry. 2000; 57:850–8. https://doi.org/10.1001/archpsyc.57.9.850 PMID: 10986548

34. Beata C, Beaumont-Graff E, Diaz C, Marion M, Massal N, Marlois N, et al. Effects of alpha-casozone (Zylkene) versus selegiline hydrochloride (Selgian, Anipryl) on anxiety disorders in dogs. J Vet Behav Clin Appl Res. 2007; 2(5):175–83.

35. Takeuchi Y, Houpit KA, Scarlett JM. Evaluation of treatments for separation anxiety in dogs. J Am Vet Med Assoc. 2000; 217(3):342–5. https://doi.org/10.2460/javma.2000.217.3.342 PMID: 10935036

36. Marjani M, Akbarinejad V, Bagheri M. Comparison of intranasal and intramuscular ketamine-midazolam combination in cats. Vet Anaesth Analg. 2015; 42(2):178–81. https://doi.org/10.1111/vaa.12183 PMID: 24986665

37. Weiland LC, Kluge K, Kutter APN, Kronen PW. Clinical evaluation of intranasal medetomidine–ketamine and medetomidine–S(+)-ketamine for induction of anaesthesia in rabbits in two centres with two different administration techniques. Vet Anaesth Analg [Internet]. 2017; 44(1):98–105. Available from: https://doi.org/10.1111/vaa.12408 PMID: 27374385

38. Orr H, Roughan J, Flecknell P. Assessment of ketamine and medetomidine anaesthesia in the domestic rabbit. Vet Anaesth Analg [Internet]. 2005; 32(5):271–9. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L41467465 https://doi.org/10.1111/j.1467-2995.2005.00211.x PMID: 16135208

39. Canpolat I, Karabulut E, Cakir S. The efficacy of intranasal administration of dexmedetomidine, ketamine and morphine combination to rabbit. Int J Dev Res. 2016; 6(7):8634–6.

40. Gurney M, Cripps P, Mosing M. Subcutaneous pre-anaesthetic medication with acepromazine-buprenorphine is effective as and less painful than the intramuscular route. J Small Anim Pract. 2009; 50(9):474–7. https://doi.org/10.1111/j.1748-5827.2009.00786.x PMID: 19769668

41. Devreese M, Rodrigo D, Schauvliege S, Gasthuys F, De Backer P, Croubels S. Quantification of ketamine and norketamine in bovine plasma by liquid chromatography-tandem mass spectrometry. J Iran Chem Soc [Internet]. 2015; 12(8):1357–62. Available from: http://dx.doi.org/10.1007/s13738-015-0601-4

42. Malinovsky JM, Servin F, Cozian a, Lepage JY, Pinaud M, Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996; 77(2):203–7. https://doi.org/10.1093/bja/77.2.203 PMID: 8881626

43. Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharm Drug Dispos. 2003; 24(1):37–43. https://doi.org/10.1002/bdd.336 PMID: 12516077

44. Wong YC, Zuo Z. Intranasal delivery-Modification of drug metabolism and brain disposition. Pharm Res. 2010; 27(7):1208–23. https://doi.org/10.1007/s11095-010-0127-5 PMID: 20372990

45. Romagnoli N, Bektas RN, Kutter AP, Barbarossa A, Roncada P, Hartnack S, et al. Pharmacokinetics of ketamine and norketamine enantiomers after racemic or S-ketamine IV bolus administration in dogs during sevoflurane anaesthesia. Res Vet Sci [Internet]. 2017;112(December 2016):208–13. Available from: http://dx.doi.org/10.1016/j.rvsc.2017.05.005
48. Sandbaumhüter FA, Theurillat R, Bektas RN, Kutter APN, Bettchart-Wolfensberger R, Thormann W. Pharmacokinetics of ketamine and three metabolites in Beagle dogs under sevoflurane vs. medetomidine comedication assessed by enantioselective capillary electrophoresis. J Chromatogr A [Internet]. 2016; 1467:436–44. Available from: https://doi.org/10.1016/j.chroma.2016.07.060 PMID: 27485149

49. Pyependop BH, Ilkiv JE. Pharmacokinetics of ketamine and its metabolite, norketamine, after intravenous administration of a bolus of ketamine to isoflurane-anesthetized dogs. Am J Vet Res. 2005; 66(12):2034–8. https://doi.org/10.2460/ajvr.2005.66.2034 PMID: 16379643

50. Björkman S, Redke F. Clearance of Fentanyl, Alfentanil, Methohexitone, Thiopentone and Ketamine in Relation to Estimated Hepatic Blood Flow in Several Animal Species: Application to Prediction of Clearance in Man. J Pharm Pharmacol. 2000; 52(9):1065–74. https://doi.org/10.1211/0022357001774985 PMID: 11045886

51. Murrell J. Pre-anesthetic medication and sedation. In: Duke-Novakovski T, de Vries M, Seymour C, editors. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia. third. Gloucester: British Small Animal Veterinary Association; 2016. p. 170–89.

52. Lawrence C, Prinzen F, de Lange S. The Effect of Dexmedetomidine on Nutrient Organ Blood Flow. Anesth Analg. 1996; 83:1160–5. https://doi.org/10.1097/00000542-199612000-00005 PMID: 8942579

53. Bührer M, Mapses A, Lauber R, Stanski D, Maitre P. Dexmedetomidine decreases thiopeptone dose requirement and alters distribution pharmacokinetics. Anesthesiology. 1994; 80(6):1216–27. https://doi.org/10.1097/00000542-199406000-00008 PMID: 7912044

54. Bergadano A, Andersen OK, Arendt-Nielsen L, Theurillat R, Thormann W, Spadavecchia C. Plasma levels of a low-dose constant-rate-infusion of ketamine and its effect on single and repeated nociceptive stimuli in conscious dogs. Vet J [Internet]. 2009; 182(2):252–60. Available from: https://doi.org/10.1016/j.tvjl.2008.06.003 PMID: 18706837

55. Kaka U, Saifullah B, Abubakar AA, Goh YM, Fakurazi S, Kaka A, et al. Serum concentration of ketamine and antinociceptive effects of ketamine and ketamine-lidocaine infusions in conscious dogs. BMC Vet Res [Internet]. 2016; 12(1):1–10. Available from: http://dx.doi.org/10.1186/s12917-016-0815-4

56. Kästner S. Injectable anaesthetics. In: Duke-Novakovski T, de Vries M, C S, editors. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia. third. Gloucester: British Small Animal Veterinary Association; 2016. p. 190–206.

57. Charalamous M, Bhatti SFM, Van Ham L, Platt S,Jeffery ND, Tipold A, et al. Intranasal Midazolam versus Rectal Diazepam for the Management of Canine Status Epilepticus: A Multicenter Randomized Parallel-Group Clinical Trial. J Vet Intern Med. 2017; 31(4):1149–58. https://doi.org/10.1111/jvim.14734 PMID: 28543780

58. Musulin SE, Mariani CL, Papich MG. Diazepam pharmacokinetics after nasal drop and atomized nasal administration in dogs. J Vet Pharmacolocol [Internet]. 2011; 34(1):17–24. https://doi.org/10.1111/j.1239-1669.2011.01186.x PMID: 21219339

59. Nielsen BN, Friis SM, Remsing J, Schmiegelow K, Anderson BJ, Ferreirós N, et al. Intranasal sufentanil/ketamine analgesia in children. Paediatr Anaesth. 2014; 24(2):170–80. https://doi.org/10.1111/pa n.12268 PMID: 24118506

60. Trivedi S, Kumar R, Tripathi AK, Mehta RK. A comparative study of dexmedetomidine and midazolam in reducing delirium caused by ketamine. J Clin Diagnostic Res. 2016; 10(8):UC01–4.

61. Tobias JD. Dexmedetomidine and ketamine: An effective alternative for procedural sedation? Pediatr Crit Care Med. 2012; 13(4):423–7. https://doi.org/10.1097/PCC.0b013e318238b81c PMID: 22067985