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A preliminary study comparing the sedative, cardiorespiratory, and histaminic-releasing effects of intramuscular and intravenous administration of pethidine (meperidine) with midazolam in healthy cats

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ABSTRACT

Pethidine is a synthetic opioid that is widely used in cats. However, the sedative, cardiorespiratory, and histaminic effects following administration of pethidine with midazolam in cats remain unclear. The objectives of this study were to evaluate and compare changes before and after intravenous (IV) and intramuscular (IM) administration of pethidine with midazolam in healthy cats. In this prospective randomized blind study, 12 cats were assigned equally to either the IV or IM treatment group. The IV group received pethidine 3 mg/kg and midazolam 0.1 mg/kg. The IM group received pethidine 6 mg/kg and midazolam 0.2 mg/kg. The sedative effects, heart rate, respiratory rate, non-invasive arterial blood pressures, and behavioral signs were recorded before and at 2, 5, 15, 30, 45, and 60 min after the injection. Blood samples were taken for an ELISA histamine assay at baseline and at 5 and 15 min after treatment. Cats that received IV treatment were rapidly induced a moderate degree of sedation but those received IM treatment were only mildly sedated. There was no significant difference in the cardiorespiratory values within and between the treatments over time. Plasma histamine concentrations increased by 3 and 5 times at 5 and 15 min after IV treatment, respectively, compared to baseline values. IM injections induced minimal changes in the plasma histamine concentration. In summary, intravenous pethidine with midazolam induced potentially superior sedative effects without serious side effects in clinically healthy cats. However, further studies with larger sample sizes are required to validate this finding.

1. Introduction

Pethidine, also known as meperidine and sold under various trade names including Demerol, is a synthetic μ opioid receptor agonist with potency less than morphine. The advantages of using pethidine include a low incidence of inducing emesis (Wilson, Evans & Mauer, 2007) and a short duration of action (30–120 min), which are suitable for short procedures without prolonged recovery. In addition, bradycardia rarely develops after pethidine administration due to its anticholinergic properties (Latta, Ginsberg & Barkin, 2002), therefore, pethidine is considered an opioid of choice for use in patients with chronotropic deficiency (Sanchis-Mora et al., 2014).

Despite the aforementioned unique advantages of pethidine, the hemodynamic changes associated with pethidine-induced histamine release are a major concern for its clinical use (Akcasu, Yillar, Akkan & Küçkhüseyin, 2009; Baldo & Pham, 2012; Flacke, Flacke, Bloor, Van Etten & Kripke, 1987). Pethidine has been shown to induce histamine release in both humans and dogs. The release of histamine can evoke anaphylactoid reactions such as flushing, erythema, and cutaneous edema, as well as hemodynamic changes, including tachycardia and vasodilation (Akcasu & Unna, 1970)(Kaliner et al., 1982). However, the relationship between the opioid-induced increase in plasma histamine concentrations and clinical manifestations is complex, and direct consistent link between the two has not yet been identified (Baldo & Pham, 2012). Studies of horses receiving pethidine have yielded controversial results. In a clinical case report, two horses were found to have tachycardia and hypotension following intravenous administration of pethidine. Adverse side effects were suspected to be linked to histamine release after pethidine administration (Clutton, 1987). In a recent equine study, specific focus was placed on blood parameter level changes associated with pethidine injection. Subcutaneous and

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Abbreviations

IV	intravenous
IM	intramuscular
HR	heart rate
RR	respiratory rate
SAP	systolic arterial blood pressure
MAP	mean arterial blood pressure
DAP	diastolic arterial blood pressure

intramuscular (IM) administration of pethidine did not induce a statistically significant increase in concentration of histamine, tryptase, or IgE compared to the baseline values (Trenholme et al., 2020). However, in all horses, subcutaneous pethidine injection caused localized vasculitis and thrombosis with regional edema and hemorrhage (Trenholme et al., 2020). 4,087,610–01

To the best of our knowledge, no study has been performed to investigate the combined use of pethidine and midazolam in cats, particularly with an intravenous (IV) route of administration to study histamine release. The objectives of this study were to evaluate the sedative, cardiovascular, and histaminic-releasing effects of pethidine combined with midazolam. The study also aimed to identify the differences in histamine release and behavioral changes between IM and IV administration routes. We hypothesized that pethidine combined with midazolam would induce reasonable sedation when administered via either the IM or IV route. In addition, we hypothesized that histamine would increase and induce hypotension and tachycardia following IV administration, while this effect would not be observable in IM pethidine-midazolam-treated cats.

2. Materials and methods

2.1. Animals

This study was approved by the National Chung Hsing University Institutional Animal Care and Use Committee (no. 109–035). A total of 12 cats (11 females and 1 male) admitted to the National Chung Hsing University Veterinary Medical Teaching Hospital were enrolled in this study. Client consents were obtained prior to the study. The cats weighed between 2.2 and 4.4 kg and were 2 to 6 years old. The cats belonged to breeds American shorthair (3/12), British shorthair (2/12), Persian (5/12), Munchkin (1/12), and domestic shorthair (1/12). The cats were considered apparently healthy with no signs of heart failure based on their medical history and physical examinations, including cardiovascular variables such as heart rate and blood pressure, complete blood count, and serum biochemistry analysis.

2.2. Treatment procedures

The 12 cats were randomly assigned to either the IM or IV treatment groups, with six cats in each group. The cats in the IM group received 6 mg/kg pethidine (Pethidine; National Bureau of Controlled Drugs, Department of Health, Taipei, Taiwan) and 0.2 mg/kg midazolam (Dormicum; Roche, Switzerland) while the cats in the IV group received 3 mg/kg pethidine and 0.1 mg/kg midazolam.

The cats were fasted for 8 h before the study, but had free access to water. A catheter (Introcan Certo, 24 gage, 19 mm; B Braun Melsungen AG, Germany) was placed in the cephalic vein and the cat was placed in a quiet room for at least 10 min before the baseline data measurement. The baseline sedation score, heart rate (HR), respiratory rate (RR), and non-invasive blood pressure (Vet-HDO-Monitor, $S + B$ MedVET; Babenhausen, Germany) were obtained. For blood pressure measurement, a cuff of size C1 was applied in all cats at the tail base, and the pressure was measured by a single person. For the sedation score, a composite simple description system (see Table 1) modified from previous studies (Gurney, Cripps & Mosing, 2009; Kuusela et al., 2000; Nagore et al., 2013) was used. The scores ranged from 0 (no sedation) to 15 (profoundly sedated) based on spontaneous posture, palpebral reflex, eye position, response to sound (handclap), resistance to being placed in lateral recumbency, and overall appearance. In addition, the cat's sedative degree was assessed based on the suitability of IV puncture for histamine blood sampling at 5 and 15 min after the drug treatments. The cats' sedation scores and behaviors were evaluated by the same observer who was blinded to the treatments.

After drug administration, HR, RR, blood pressure, and sedation score were reassessed at 2, 5, 15, 30, 45, and 60 min. Behavioral changes including nausea, vomiting, defecation, salivation, purring, kneading, vocalization, restlessness, and agitation were noted during the 60-minute study duration. Blood samples for the histamine assay were collected via direct venipuncture of a peripheral vein at baseline, and then at 5 and 15 min after drug administration. The sedative suitability induced by the drugs was assessed during venipuncture for blood sampling. Venipuncture was always performed after all physiologic variables had been obtained at each timepoint.

2.3. Histamine assay

Blood samples were collected in ethylenediaminetetraacetic acid tubes, immediately placed on ice, and centrifuged within one hour. After centrifugation, the plasma was separated and frozen at −80 °C until the assay was performed. A commercial immunoassay kit (Histamine ELISA kit, Beckman Coulter; Marseille, France) was used to determine plasma histamine concentration with a sensitivity of 0.05 ng/mL. The samples were run in duplicate, and the results were averaged.

2.4. Statistical analysis

Data were analyzed using SPSS version 26 for Windows (IBM SPSS Statistics 26; NY, USA). Statistical significance was set at $p < 0.05$. Age and weight were analyzed using an independent sample *t*-test to compare the differences between treatment groups. The effects of behaviors were analyzed using Fisher's exact test. Continuous data including sedation score, systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), diastolic arterial pressure (DAP), HR, RR, and plasma histamine concentration were analyzed using a mixed-design two-way ANOVA. Further comparisons were conducted to

Table 1
Composite simple descriptive sedation score system with an overall score from 0 (no sedation) to 15 (profound sedation).

Variable		Score
Spontaneous posture	Standing	0
	Sternally recumbent	1
	Laterally recumbent	2
Palpebral reflex	Brisk	0
	Slow	1
	Absent	2
Eye position	Forward	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 physical restraint required	1
	Mild physical restraint required	2
	No resistance	3
Overall appearance	No sedation apparent	0
	Mild sedation	1
	Moderate sedation	2
	Profound sedation	3

determine the differences within groups at each time point in cases where there was a significant interaction between the two factors.

3. Results

The sedative, respiratory, cardiovascular, and histaminic-releasing effects induced by pethidine and midazolam are presented in Table 2. No significant differences were found in age or weight between the treatment groups. IV pethidine with midazolam rapidly induced a moderate degree of sedation, which lasted for 30 min. The degree of sedation was suitable for venipuncture at 5 and 15 min with minimal physical restraint. The sedation quality was reduced after 30 min and reached a minimum level at 60 min (Table 2) after IV injection. IM treatment induced a mild degree of sedation, which peaked at 2 and 5 min; thereafter, the sedation quality was minimal. Sedation degrees were highly variable among the individual cats in the IM treatment group. Two cats did not appear to be sedated with mean total sedation score of 1.5 and 2.5 at 2 and 5 min, respectively, whereas the other four cats were sedated with quality similar to the IV-treated cats (mean total sedation score of 6 and 7). The sedative scores in the IV group at 15 and 30 min were significantly higher than those in the IM group.

No significant changes in heart and respiratory rates or blood pressures were observed over time within and between the treatment groups. None of the cats developed hypotension except for one cat in the IV treatment group, who developed transient hypotension (SAP = 89 mmHg, MAP = 53 mmHg, DAP = 33 mmHg) at 5 min. Blood pressure returned to normal in the following measurements.

The overall plasma histamine concentration was significantly higher ($p = 0.002$) in the IV group than in the IM group, while the average levels in the IV and IM groups were 0.124 and 0.064 ng/mL, respectively

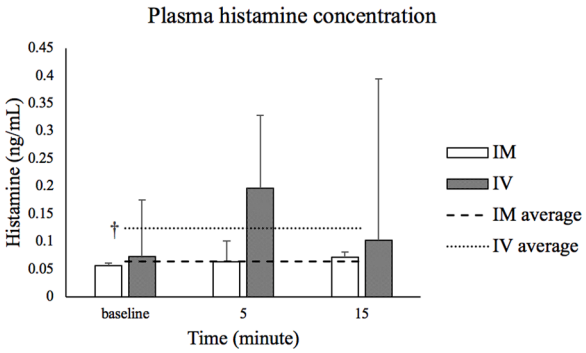

Fig. 1. Plasma histamine concentration in cats before (baseline) and after receiving intramuscular ($n = 6$ cats; pethidine 6 mg/kg and midazolam 0.2 mg/kg, IM) or intravenous ($n = 6$ cats, pethidine 3 mg/kg and midazolam 0.1 mg/kg, IV) treatments. † indicates statistically different from IM average.

(Fig. 1). The histamine concentration increased from the baseline values of 0.07 ± 0.10 ng/ml – 0.20 ± 0.13 ng/ml at 5 min and 0.10 ± 0.29 ng/ml at 15 min after IV treatment. However, this increase was not statistically significant. The cat that developed transient hypotension also had the highest histamine concentration (0.45 ng/ml) at 5 min after IV injection.

Number of cats in the IV and IM groups exhibiting behavioral changes and the types of behavioral changes after drug administration included kneading (3/6; 0/6), purring (2/6; 0/6), vocalization (2/6; 2/6), and restlessness (1/6; 3/6), respectively. None of the cats developed salivation, nausea, vomiting, or defecation during the study.

Table 2
Values of the sedation score, heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), diastolic arterial blood pressure (DAP) and plasma histamine concentration before (baseline) and 60 min after receiving either intramuscular ($n = 6$, pethidine 6 mg/kg and midazolam 0.2 mg/kg, IM) or intravenous ($n = 6$, pethidine 3 mg/kg and midazolam 0.1 mg/kg, IV) treatments in healthy cats. Values are presented in mean ± standard deviation [range]. [a] Statistically different from IM treatment at the same time ($p < 0.05$); [b] Statistically different from baseline within the same treatment ($p < 0.05$); No statistically significant difference was detected for HR, SAP, MAP and SAP ($p > 0.05$) among the groups.

Variable	Group	Time (minutes) Baseline	2	5	15	30	45	60
Sedation score	IM	0.5 ± 0.8 [0–2]	4.5 ± 2.7 [1–5]	5.5 ± 2.7 [1–8]	2 ± 1.7 [0–1]	0.7 ± 0.5 [0–3]	1.5 ± 1.4 [0–3]	0.8 ± 1.3 [0–3]
	IV	0.7 ± 0.8 [0–2]	6.8 ± 2.3 [3–10][b]	6.2 ± 3.1 [3–11][b]	5.2 ± 1.6 [2–6][a,b]	5.7 ± 2.3 [2–9][a,b]	4.2 ± 2.9 [0–8]	1.5 ± 2.3 [0–6]
HR (beats per minutes)	IM	190 ± 22 [160–216]	170 ± 15 [156–196]	177 ± 38 [124–240]	190 ± 21 [152–232]	185 ± 21 [148–240]	177 ± 24 [160–220]	173 ± 31 [148–232]
	IV	213 ± 27 [160–236]	197 ± 21 [176–232]	196 ± 25 [160–222]	192 ± 21 [172–224]	186 ± 13 [168–208]	194 ± 31 [144–220]	184 ± 29 [136–216]
RR (breaths per minutes)	IM	38 ± 14 [22–56]	45 ± 22 [28–88]	37 ± 8 [28–48]	47 ± 15 [28–68]	41 ± 14 [28–60]	47 ± 22 [28–88]	46 ± 19 [24–76]
	IV	40 ± 10 [28–57]	39 ± 10 [28–56]	47 ± 5 [40–52]	40 ± 9 [28–52]	44 ±11 [32–64]	37 ± 9 [24–44]	31 ± 6 [24–40]
SAP (mmHg)	IM	136 ± 19 [102–154]	145 ± 23 [119–175]	139 ± 19 [108–164]	117 ± 13 [100–134]	137 ± 14 [122–156]	122 ± 16 [102–138]	133 ± 11 [123–150]
	IV	143 ± 10 [132–159]	111 ±12 [98–130]	112 ± 12 [89–120]	131 ± 22 [103–170]	117 ± 12 [96–132]	142 ± 25 [115–183]	136 ± 20 [113–174]
MAP (mmHg)	IM	98 ± 8 [84–104]	103 ± 16 [81–124]	101 ± 14 [75–109]	84 ± 5 [77–89]	99 ± 12 [83–120]	88 ± 8 [80–99]	94 ± 10 [81–109]
	IV	98 ± 6 [90–109]	82 ± 9 [73–97]	80 ± 14 [53–90]	90 ± 14 [65–105]	85 ± 10 [71–100]	93 ± 12 [76–107]	98 ± 6 [90–107]
DAP (mmHg)	IM	75 ± 5 [70–82]	80 ± 15 [67–102]	80 ± 13 [57–95]	66 ± 6 [57–71]	77 ± 16 [61–105]	70 ± 8 [56–79]	72 ± 11 [58–91]
	IV	74 ± 7 [63–82]	64 ± 9 [54–79]	63 ± 15 [33–74]	68 ± 13 [44–79]	67 ± 9 [57–82]	67 ± 10 [57–81]	77 ± 7 [68–87]
Histamine (ng/mL)	IM	0.06 ± 0.01 [0.05–0.07]	–	0.06 ± 0.04 [0.05–0.07]	0.07 ± 0.01 [0.06–0.09]	–	–	–
	IV	0.07 ± 0.10 [0.06–0.09]	–	0.20 ± 0.13 [0.08–0.45]	0.10 ± 0.29 [0.06–0.15]	–	–	–

4. Discussion

In the current study, we evaluated the sedative quality of IV and IM administration of pethidine in combination with midazolam in healthy cats. The sedative quality of pethidine in combination with dexmedetomidine or acepromazine has been evaluated in cats with satisfactory results (Nagore et al., 2013; Vettorato & Bacco, 2011). The potential advantage of combining pethidine with midazolam in cats is that it offers minimal cardiorespiratory depression, nausea, and vomiting side effects while providing a reasonably short duration of sedation without hanging over after the procedure is completed.

Our results showed that moderate sedation occurred rapidly after IV injection in cats. The sedative quality induced by IV pethidine and midazolam allowed for venipuncture in cats with minimal physical restraint. In contrast to the IV treatment, the IM treatment, despite having twice the dosage of pethidine and midazolam than that of the IV treatment, induced less optimal and highly variable sedative quality. In dogs, highly variable bioavailability was reported after IM administration of pethidine (Waterman & Kalthum, 1990). The same phenomena may have occurred in these cats, which resulted in variable sedative quality among IM-treated cats. Furthermore, midazolam is not a reliable sedative. Healthy cats that received midazolam have been reported to develop excitement and agitation (Ilkiw, Suter, Farver, McNeal & Steffey, 1996). This unique effect of midazolam might also occur when it is co-administered intramuscularly with pethidine, resulting in a poor sedative quality observed in cats assigned to the IM group.

Despite the significant advantages of pethidine, there are major concerns regarding histamine release and hemodynamic impact after pethidine administration (Akcasu et al., 2009; Clutton, 1987; Flacke et al., 1987). Histamine release following pethidine administration is well documented in both humans and dogs (Akcasu et al., 2009; Flacke et al., 1987) but not in cats. Controversial data exist when evaluating histamine release in horses after pethidine administration. Trenholme et al. (Trenholme et al., 2020) showed that IM or subcutaneous administration of pethidine did not induce histamine release, whereas a clinical case report from Clutton (Clutton, 1987) strongly suspected that histaminic effects led to hypotension and tachycardia in two horses.

The heart rates of the cats in this study were well maintained, and the values after administration were similar to their baseline values. Possible reasons for the relatively high heart rate in the treated cats observed in previous studies were likely the anticholinergic property of pethidine (Latta et al., 2002), the lack of cardiovascular depressive effect of midazolam (Frölich, Arabshahi, Katholi, Prasain & Barnes, 2011), or a combination of these two factors.

In this study, the plasma histamine concentrations increased from baseline values at 5 and 15 min after IV injection. Although these histamine releases did not reach a statistically significant level when compared with the baseline values, they were cause for clinical concern. The cat in the IV group that developed transient hypotension also had the highest histamine release (7.5 times its baseline value) at 5 min after IV injection of pethidine and midazolam. Although the hypotension in this cat was self-limiting and subsided thereafter, the risk of persistent hypotension could develop in non-healthy cats. The histamine concentration only changed minimally from the baseline in the IM group. It has been reported that IV administration of opioids evokes opioid-driven mast cell degranulation; however, this degranulation can be avoided if the opioid is administered intramuscularly (Guedes, Papich, Rude & Rider, 2007; Smith, Yu, Bjorling & Waller, 2001). The histamine release observed in our study is consistent with these findings. In a dog study, a sharp but transient elevation of histamine level was recorded after IV morphine administration, with a peak concentration occurring within 2 min but rapidly declining 5 min later (Guedes, Rudé & Rider, 2006). A similar pattern of increase and decrease in histamine concentrations after pethidine-midazolam IV injection was also noted in the current study on cats. Further studies are warranted to investigate the dose-dependent effects on the duration of histamine release in cats.

This study had several limitations. We only evaluated a single-dose regimen of pethidine and midazolam in the IV and IM treatment groups, and the histamine concentration was only measured at 5 and 15 min after co-administration of drugs. The histamine concentration was measured throughout the study for 60 min. However, there were minimal changes in the histamine concentrations after IM treatment and highly variable values observed in the IV group, suggesting that histamine concentrations might not have changed further after 15 min. In addition, the short duration of pethidine-midazolam-induced sedative quality decreased drastically after 15–30 min, which could make the venipunctures for histamine blood sampling stressful to these cats. Second, a relatively small sample size was used in this study. This minimized the chance of detecting the true impact of histamine release and hemodynamic changes in these cats. However, in the IV treatment group, one out of six cats developed transient hypotension, which could serve as an indication that the risk of such hemodynamic impacts exists in healthy cats and, furthermore, could serve as a warning for cats with cardiovascular compromises.

5. Conclusion

Our study demonstrated that administering pethidine (3 mg/kg) with midazolam (0.1 mg/kg) intravenously induces a reasonable but short duration (~30 min) of sedation that is suitable for minor invasive procedures (e.g., thoracentesis, abdominocentesis, cystocentesis) and other non-invasive procedures (i.e. proper radiographic position) in cats. Caution should be taken in using this sedative protocol in cardiovascular-compromised cats because of the risk of histamine-induced hypotension. Furthermore, the IM route of pethidine-midazolam at the dosage used in this study only induced a mild degree of sedation with minimal histamine release. It should be anticipated that some physical restraint to the cat must be applied when performing blood sampling and other non-invasive procedures with the IM protocol. Finally, no hypersalivation, nausea, vomiting, or bradycardia was noted in any of the cats treated with these sedative protocols.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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References

Akcasu, A., & Unna, K. R. (1970). The role of mast cell disruption in the acute manifestations of the intravenous injection of morphine in dogs. *European Journal of Pharmacology, 13*, 103–107.

Akcasu, A., Yillar, D. O., Akkan, A. G., & Küçkhüseyin, C. (2009). The role of mast cells in the genesis of acute manifestations following the intravenous injection of meperidine in dogs. *Journal of Basic and Clinical Physiology and Pharmacology, 20*, 67–72.

Baldo, B. A., & Pham, N. H. (2012). Histamine-releasing and allergenic properties of opioid analgesic drugs: Resolving the two. *Anaesthesia Intensive Care, 40*, 216–235.

Clutton, R. E. (1987). Unexpected responses following intravenous pethidine injection in two horses. *Equine Veterinary Journal, 19*, 72–73.

Flacke, J. W., Flacke, W. E., Bloor, B. C., Van Etten, A. P., & Kripke, B. J. (1987). Histamine release by four narcotics: A double-blind study in humans. *Anesthesia and Analgesia, 66*, 723–730.

Frölich, M. A., Arabshahi, A., Katholi, C., Prasain, J., & Barnes, S. (2011). Hemodynamic characteristics of midazolam, propofol, and dexmedetomidine in healthy volunteers. *Journal of Clinical Anesthesia, 23*, 218–223.

Guedes, A. G., Rudé, E. P., & Rider, M. A. (2006). Evaluation of histamine release during constant rate infusion of morphine in dogs. *Veterinary Anaesthesia and Analgesia, 33*, 28–35.

Guedes, A. G. P., Papich, M. G., Rude, E. P., & Rider, M. A. (2007). Comparison of plasma histamine levels after intravenous administration of hydromorphone and morphine in dogs. *Journal of Veterinary Pharmacology and Therapeutics, 30*, 516–522.

Gurney, M., Cripps, P., & Mosing, M. (2009). Subcutaneous pre-anaesthetic medication with acepromazine–buprenorphine is effective as and less painful than the intramuscular route. *Journal of Small Animal Practice, 50*, 474–477.

Ilkiw, J. E., Suter, C. M., Farver, T. B., McNeal, D., & Steffey, E. P. (1996). The behaviour of healthy awake cats following intravenous and intramuscular administration of midazolam. *Journal of Veterinary Pharmacology and Therapeutics, 19*, 205–216.

Kaliner, M., Shelhamer, J. H., & Ottesen, E. A. (1982). Effects of infused histamine: Correlation of plasma histamine levels and symptoms. *The Journal of Allergy and Clinical Immunology, 69*, 283–289.

Kuusela, E., Raekallio, M., Anttila, M., Falck, I., Mölsä, S., & Vainio, O. (2000). Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. *Journal of Veterinary Pharmacology and Therapeutics, 23*, 15–20.

Latta, K. S., Ginsberg, B., & Barkin, R. L. (2002). Meperidine: A critical review. *American Journal of Therapeutics, 9*, 53–68.

Nagore, L., Soler, C., Gil, L., Serra, I., Soler, G., & Redondo, J. I. (2013). Sedative effects of dexmedetomidine, dexmedetomidine-pethidine and dexmedetomidine-butorphanol in cats. *Journal of veterinary pharmacology and therapeutics, 36*, 222–228.

Sanchis-Mora, S., Viscasillas, J., Mathis, A., Palacios, C., Brodbelt, D. C., & Alibhai, H. I. (2014). Anaesthetic management and complications of pacemaker implantation in dogs. *The Veterinary record, 175*, 303.

Smith, L. J., Yu, J. K., Bjorling, D. E., & Waller, K. (2001). Effects of hydromorphone or oxymorphone, with or without acepromazine, on preanesthetic sedation, physiologic values, and histamine release in dogs. *Journal of the American Veterinary Medical Association, 218*, 1101–1105.

Trenholme, H. N., Sakai, D. M., Berghaus, L. J., Hanafi, A. L., Knych, H. K., Ryan, C. A., et al. (2020). Effect of meperidine on equine blood histamine, tryptase, and immunoglobulin-E concentrations. *Frontiers in Veterinary Science, 7*, Article 584922.

Vettorato, E., & Bacco, S. (2011). A comparison of the sedative and analgesic properties of pethidine (meperidine) and butorphanol in dogs. *Journal of Small Animal Practice., 528*, 426–432.

Waterman, A. E., & Kalthum, W. (1990). Pharmacokinetics of pethidine administered intramuscularly and intravenously to dogs over 10 years old. *Research in Veterinary Science, 48*, 245–248.

Wilson, D. V., Evans, A. T., & Mauer, W. A. (2007). Pre-anesthetic meperidine: Associated vomiting and gastroesophageal reflux during the subsequent anesthetic in dogs. *Veterinary. Anaesthesia and Analgesia, 34*, 15–22.