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Phenylpiperidine opioid effects on isoflurane minimum alveolar concentration in cats

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Abstract

Different structurally related phenylpiperidine opioids exhibit different isoflurane-sparing effects in cats. Because minimum alveolar concentration (MAC) in cats is affected only by very high plasma concentrations of some phenylpiperidine opioids, we hypothesized these effects are caused by actions on nonopioid receptors. Using a prospective, randomized, crossover design, six cats were anesthetized with isoflurane, intubated, ventilated, and instrumented. Isoflurane MAC was measured in triplicate using a tail-clamp and bracketing technique. A computer-controlled intravenous infusion using prior pharmacokinetic models targeted plasma concentrations of 60 ng/ml fentanyl, 10 ng/ml sufentanil, or 500 ng/ml alfentanil, and isoflurane MAC was measured in duplicate. Next, naltrexone 0.6 mg/kg was administered to cats hourly during the opioid infusion, and isoflurane MAC was measured in duplicate. Blood was collected during MAC determinations to measure opioid concentrations. Responses were analyzed using repeated measures ANOVA with significance at $p < .05$. Alfentanil and sufentanil decreased isoflurane MAC by 16.4% and 6.4%, respectively, and these effects were completely reversed by naltrexone. Fentanyl had no significant effect on isoflurane MAC. Alfentanil and sufentanil modestly reduce isoflurane MAC via agonist effects on opioid receptors. However, these effects are too small to justify clinical use of phenylpiperidine opioids as single agents to reduce MAC in cats.

KEYWORDS

alfentanil, feline, fentanyl, MAC, sufentanil

1 | INTRODUCTION

Fentanyl, sufentanil, alfentanil, and remifentanil are phenylpiperidine opioids and agonists of the μ-opioid receptor (MOR) through which they exert analgesic and anesthetic effects in humans and many animal species. In cats, MOR-agonist opioids are effective analgesics (Carrozzo, Alcorn, & Ambros, 2018;Robertson, Taylor, Sear, & Keuhnel, 2005), but most exhibit little or no effect on the immobilizing potency of volatile anesthetics. Fentanyl doses producing analgesia (Yackey, Ilkiw, Pascoe, & Tripp, 2004) and remifentanil concentrations more than 20 times greater than needed for analgesia (Brosnan, Pypendop, Siao, & Stanley, 2009) do not decrease isoflurane minimum alveolar concentration (MAC) in cats. In contrast, very high concentrations of alfentanil—about 500 ng/ml—significantly decrease isoflurane MAC by 35% in cats (Ilkiw, Pascoe, & Fisher, 1997). This is surprising given the very close structural similarities among fentanyl, remifentanil, and alfentanil molecules.

We hypothesized that the isoflurane MAC-sparing effects observed with some phenylpiperidine opioids might be mediated by nonopioid receptor effects. Fentanyl decreases neuronal release of acetylcholine to reduce muscarinic cholinergic activity (Mortazavi, Thompson, Baghdoyan, & Lydic, 1999), decreases release of

glutamate that may reduce excitatory NMDA receptor currents, and increases release of γ-aminobutyric acid (GABA) that may enhance inhibitory $GABA_A$ receptor currents (Pourzitaki et al., 2018). Additionally, various opioids at sufficient concentrations can directly modulate NMDA receptors (Hahnenkamp et al., 2004), α_1-adrenergic receptors (Toda & Hatano, 1977), α_2-adrenergic receptors (Hocker et al., 2008, 2009), dopamine receptors (Hagelberg et al., 2002), serotonin receptors (Leysen & Gommeren, 1986), voltage-gated sodium channels (Leffler et al., 2012), and potassium channels (Tschirhart, Li, Guo, & Zhang, 2019). Indeed, any hydrocarbon with sufficient molar water solubility, when administered at near-saturated concentrations, can modulate anesthetic–sensitive ion channels and receptors (Brosnan & Pham, 2014, 2016, 2018) and potentially exert anesthetic-like effects. As alfentanil only decreases isoflurane MAC in cats at very high plasma concentrations, we proposed it might do so through similar low-affinity interactions with anesthetic–sensitive ion channels and receptors.

The aim of this study was to test whether fentanyl, sufentanil, or alfentanil decreased isoflurane MAC in cats using intravenous infusions that targeted constant high plasma concentrations. To test whether MAC-sparing effects were due to actions on opioid receptors, the MOR-antagonist naltrexone would then be administered during the opioid infusion. If naltrexone returned isoflurane MAC to baseline values, then phenylpiperidine MAC-sparing was due to agonist effects on opioid receptors. If naltrexone did not, then phenylpiperidine MAC-sparing must be mediated, at least in part, by non-opioid mechanisms.

2 | MATERIAL AND METHODS

Six healthy adult cats weighing 4.9 ± 0.7 kg (mean ± *SD*) were studied using a randomized crossover design that was approved by the Animal Care and Use Committee at the University of California, Davis. Each cat was anesthetized three times, two weeks apart, using a Latin square design. Food, but not water, was withheld overnight prior to study.

Unsedated cats were anesthetized with isoflurane in oxygen in an acrylic chamber. Cats were then intubated with a cuffed 4.5 mm endotracheal tube with a sampling port that extended to the distal tip, and anesthesia was maintained using isoflurane in oxygen delivered via a coaxial Mapleson F circuit. Breathing was controlled using a pressure-cycled flow-controlled ventilator (Mark 7, Bird Corporation) to achieve a 10 cm H_2O peak inspiratory pressure and a rate sufficient to maintain normocapnia, as measured using a Raman scatter analyzer (Rascal II, Ohmeda); however, cats were allowed to breathe spontaneously during the expiratory pause. Percent hemoglobin saturation with oxygen (S_pO_2) was estimated using a pulse oximeter placed on the tongue (Rascal II, Ohmeda). End-tidal isoflurane was hand-sampled in glass syringes and measured using an infrared analyzer (Beckman LB2, Sensormedics) that was calibrated daily against multiple standard gases that spanned the range of study concentrations. Systolic arterial blood pressure was measured using a Doppler probe (Model 811-BTS, Parks Medical Electronics) over the radial artery and a sphygmomanometer with a cuff width equal to 40% of the antebrachial circumference. Body temperature was measured using an esophageal thermistor probe (400 series, YSI) that was calibrated daily against a certified standard mercury thermometer (SRM934-FC, ERTCO). Heating pads and forced air warming or cooling were used to maintain body temperature between 38 and 39°C. A 22-gauge, 4.8-cm catheter in the medial saphenous vein was used to administer either lactated Ringer's solution at 10 ml kg^{-1} hr^{-1}or opioid infusions. A 20-gauge, 10-cm catheter placed percutaneously in the jugular vein was used for blood sampling.

Baseline isoflurane MAC in each cat was calculated as the average of triplicate measurements using a bracketing experimental design (Sonner, 2002). After a 20-min equilibration period at a constant end-tidal isoflurane concentration and recording of physiologic responses, a Martin forceps was clamped to the first ratchet on the distal tail for 1 min or until the cat exhibited nonreflexive movement. End-tidal isoflurane concentration then was either increased 10% if the cat moved or was decreased 10% if the cat did not move. After 20 min equilibration at the new isoflurane concentration, movement in response to forceps clamping was assessed at a site immediately proximal to the previous tail test. A single MAC value equaled the mean of the highest and lowest isoflurane concentrations that respectively allowed and prevented movement in response to noxious stimulation. After the final baseline MAC measurement, jugular venous blood was collected for drug analysis.

Continuing isoflurane anesthesia, a syringe pump (PHD 2000; Harvard Apparatus) and target-controlled infusion computer software (Rugloop I, Demed) were used with individual-specific pharmacokinetic models to intravenously administer fentanyl citrate (Baxter), sufentanil citrate (Baxter), or alfentanil hydrochloride (Baxter) to target drug plasma concentrations of 60, 10, and 500 ng/ml, respectively. Distribution volumes and elimination rate constants used to achieve plasma concentrations for each opioid were previously modeled for each individual cat in this study during isoflurane anesthesia (Pypendop, Brosnan, Majewski-Tiedeken, Stanley, & Ilkiw, 2014). Phenylpiperidine concentrations studied are approximately equipotent (Glass, Gan, Howell, & Ginsberg, 1997;Mather, 1983;Wilde et al., 2019) and are similar in potency to the highest effective remifentanil concentrations (Brosnan et al., 2009) and alfentanil concentrations (Ilkiw et al., 1997) previously reported in cats. Twenty minutes after the start of the opioid infusion, isoflurane MAC was measured in duplicate using the same tail-clamp technique. Jugular venous blood was collected for drug analysis after each MAC determination.

To test whether opioid drug effects on isoflurane MAC were due to actions on opioid receptors, the opioid infusion was continued, and cats were administered 0.6 mg/kg naltrexone through the saphenous vein once hourly until the end of the study. Naltrexone administered at this dose and frequency is sufficient to antagonize remifentanil infusions equipotent to the phenylpiperidines used in the present study (Pypendop, Brosnan, & Ilkiw, 2011) but does not affect isoflurane MAC (Brosnan, Pypendop, Majewski-Tiedeken,

Shilo-Benjamini, & Ilkiw, 2013). Fifteen minutes after naltrexone administration, isoflurane MAC measurements using the tail-clamp procedure began. Subsequent tests used 20 min equilibration periods and were identical to the bracketing design described for measurements during baseline and opioid infusions. MAC was measured in duplicate, jugular venous blood was collected after each determination, and cats were recovered from anesthesia at the end of the experiments.

Fentanyl, alfentanil, and sufentanil were measured in plasma by liquid chromatography–mass spectrometry (LCMS) analysis of protein-precipitated samples using materials, methods, equipment, and facilities identical to those described in a prior publication (Thomasy, Mama, Whitley, Steffey, & Stanley, 2007). D5-fentanyl was the internal standard for fentanyl and alfentanil, and d5-sufentanil was used as the internal standard for sufentanil. The limit of quantitation was 0.05 ng/ml for all phenylpiperidines. Measurement accuracy as a percent of nominal standard 1.5 and 20 ng/ml concentrations was within 98%-to-116% for all three opioids. Measurement precision as a percent relative standard deviation was within 3%-to-5% for these same standard concentrations of all three opioids.

Data were summarized using mean ± *SD*. Shapiro–Wilk tests were used to verify normal distribution for variables. Repeated measures analyses of variance and Holm–Šidák post hoc tests were used to detect differences from baseline during opioid and opioid + naloxone administration for MAC and physiologic responses, as well as differences between opioid and opioid + naltexone for physiologic responses. Significance was set at an adjusted familywise Type I error rate < 0.05.

3 | RESULTS

During opioid infusions without naltrexone, mean plasma concentrations deviated 3%–10% from the target concentrations for the three phenylpiperidines (Table 1). With the addition of hourly naltrexone during the infusion, mean plasma opioid concentrations deviated 7%–10% from target values. The pharmacokinetic model used for target-controlled infusions also produced reasonably stable plasma opioid concentrations over time. For fentanyl, sufentanil, and alfentanil, respectively, the lowest measured opioid concentration was within 92%, 82%, and 94% of the plasma target, and the highest opioid concentration was within 112%, 99%, and 117% of the plasma target (Table 1).

TABLE 1 Mean (±*SD*) plasma concentrations (ng/ml) during target-controlled opioid infusions in cats

Phenylpiperidine	Fentanyl	Sufentanil	Alfentanil
Baseline	0 ± 0	0 ± 0	0 ± 0
Opioid	55.4 ± 6.9	8.96 ± 1.24	513 ± 93
Opioid + Naltrexone	66.2 ± 11.3	9.12 ± 2.92	535 ± 128
Target concentration	60	10	500
Low concentration	54.0 ± 6.0	8.18 ± 1.03	472 ± 98
High concentration	67.3 ± 11.4	9.87 ± 2.39	584 ± 120

Note: The mean (±*SD*) low and high concentrations are calculated as the average of the highest and lowest measured concentrations, respectively, for each cat during each opioid infusion.

Although fentanyl had no significant effect on isoflurane concentrations needed for immobility, sufentanil decreased isoflurane MAC by 6.4%, and alfentanil decreased isoflurane MAC by 16.4% (Table 2). Isoflurane MAC-sparing effects for both sufentanil and alfentanil were reversed by naltrexone.

Opioid infusions increased heart rate compared to baseline responses, and blood pressure was higher during fentanyl and alfentanil infusions when compared to responses measured during naltrexone reversal (Table 3). During baseline measurements, average systolic arterial pressure was ≤70 mmHg for 3/6 of cats prior to receiving sufentanil or alfentanil. During naltrexone administration, 1/6 cats had an average systolic arterial pressure ≤70 mmHg for the fentanyl and alfentanil treatments, and 2/6 cats had blood pressures within this range for the sufentanil treatment.

Cats typically breathed between ventilator cycles when anesthetized with isoflurane alone or during opioid reversal with naltrexone. However, opioid infusions caused respiratory depression which allowed ventilation to be controlled for greater periods of time by the ventilator without patient-initiated breaths between ventilator cycles. As a result, respiratory frequency was lower and end-tidal CO_2 higher during opioid infusions than during either baseline isoflurane anesthesia or during naltrexone reversal (Table 3).

4 | DISCUSSION

High plasma concentrations of alfentanil and sufentanil caused a statistically significant decrease in isoflurane MAC that was completely reversed by naltrexone administration. Consequently, we conclude that the modest MAC-sparing effects of alfentanil and sufentanil result from actions on opioid receptors and not through lower-affinity interactions with nonopioid targets. However, alfentanil effects on MAC in the present study are only about one-half the magnitude of previously reported effects (Ilkiw et al., 1997) which could reflect response variability between different cat populations. Moreover, as with remifentanil (Brosnan et al., 2009), fentanyl had no effect on isoflurane requirement. It is unknown whether plasma concentrations of these opioids were insufficient to observe MAC-sparing effects or whether these opioids simply lack any immobilizing potency in cats.

In contrast, phenylpiperidine opioids produced important cardiovascular effects. Heart rate increased after opioid administration, and naltrexone reversal returned both heart rate and blood pressure back to baseline levels. Pressor and chronotropic effects reflect an increase in sympathetic tone caused by opioid stimulation of catecholamine release that exceeds replacement. Although release can lead to brain catecholamine depletion, this does not occur uniformly in cats where intravenous morphine has been shown to actually increase norepinephrine in regions of the

TABLE 2 Mean (±*SD*) isoflurane MAC (% of 1 atmosphere) in 6 cats before and during target-controlled opioid infusions with and without hourly naltrexone administration

Phenylpiperidine	Baseline	Opioid	Opioid + Naltrexone
Fentanyl	1.97 ± 0.22	1.90 ± 0.09	2.16 ± 0.24
Sufentanil	2.03 ± 0.16	1.90 ± 0.17*	2.19 ± 0.18
Alfentanil	2.14 ± 0.18	1.79 ± 0.17*	2.20 ± 0.18

Note: MAC values during opioid infusions that are significantly different (adjusted $p < .05$) than repeated baseline measurements are indicated by an asterisk (*).

TABLE 3 Physiologic responses (mean ± *SD*) measured in cats during baseline (B), opioid infusions (O), and opioid infusions with hourly administration of naltrexone (N)

Phenylpiperidine	Fentanyl	Sufentanil	Alfentanil
f_H (min^{-1})	B: 167 ± 31 O: 215 ± 46* N: 166 ± 20	B: 164 ± 19 O: 214 ± 25* N: 174 ± 24†	B: 159 ± 32 O: 217 ± 21* *N*: 182 ± 17†
SAP (mmHg)	B: 96 ± 22 O: 104 ± 21 N: 76 ± 7†	B: 71 ± 7 O: 86 ± 22 N: 78 ± 16	B: 76 ± 24 O: 103 ± 24 N: 74 ± 12†
f_R (min^{-1})	B: 20 ± 11 O: 20 ± 11 N: 16 ± 7	B: 18 ± 5 O: 14 ± 8 N: 22 ± 13	B: 12 ± 7 O: 22 ± 14* N: 16 ± 14
S_pO_2 (%)	B: 98 ± 1 O: 98 ± 1 N: 98 ± 1	B: 98 ± 1 O: 98 ± 1 N: 98 ± 1	B: 98 ± 1 O: 99 ± 1 N: 98 ± 1
$P_{E'}CO_2$ (mmHg)	B: 30 ± 7 O: 37 ± 5 N: 27 ± 4†	B: 30 ± 5 O: 36 ± 5 N: 23 ± 4†	B: 28 ± 5 O: 37 ± 2* N: 25 ± 6†
T_b (°C)	B: 38.5 ± 0.3 O: 38.7 ± 0.3 N: 38.8 ± 0.6	B: 38.4 ± 0.2 O: 38.8 ± 0.2* N: 38.4 ± 0.2†	B: 38.2 ± 0.2 O: 38.8 ± 0.1* N: 38.6 ± 0.1*

Note: Statistically significant differences from repeated baseline (*) or opioid infusion values (†) are indicated by superscripts.

Abbreviations: f_H, heart frequency; f_R, respiratory frequency; SAP, systolic arterial pressure; S_pO_2, hemoglobin-oxygen saturation estimate by pulse oximetry; T_b, body temperature.

hypothalamus and telencephalon (Reis, Rifkin, & Corvelli, 1969). Fentanyl also stimulates norepinephrine release in the spinal cord (Bouaziz, Tong, Yoon, Hood, & Eisenach, 1996) which plausibly could play a role in helping sustain cardiovascular stimulation. Likewise, high doses of opioids can stimulate serotonin release that can produce similar cardiovascular effects, along with hyperthermia and mania observed in awake animals (Bardon & Ruckebusch, 1984).

Published pharmacokinetic models (Pypendop et al., 2014) were used to determine infusion rates for target phenylpiperidine concentrations. Measured opioid concentrations were reasonably close to target values and remained stable over the course of an approximately 3 hr infusion period, thereby serving to validate the models. However, during sufentanil infusions prior to naloxone, only 1/6 cats achieved or exceeded the target sufentanil concentration, and measured plasma concentrations averaged approximately 10% lower than target values. This finding probably reflects a 10% underestimation of the sufentanil volume of distribution in cats. Accordingly, these data can be used to further refine the pharmacokinetic model and improve target accuracy of sufentanil concentrations.

Even with extremely high plasma concentrations, MAC-sparing effects of alfentanil and sufentanil were quantitatively small and of limited clinical utility. Although phenylpiperidines may provide benefits during anesthesia through antinociception and blunting of autonomic responses to surgical stimuli, present findings leave us to conclude that these opioids should not be used as sole agents in cats for the purpose of decreasing volatile anesthetic requirements.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Brosnan conceived and helped design the study, analyzed data, and wrote the manuscript. Pypendop helped design the study, conducted the study, tabulated data, and revised the manuscript draft. Stanley analyzed drug concentrations and revised the manuscript draft.

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REFERENCES

Bardon, T., & Ruckebusch, M. (1984). Changes in 5-HIAA and 5-HT levels in lumbar CSF following morphine administration to conscious dogs. *Neuroscience Letters*, *49*(1–2), 147–151. https://doi.org/10.1016/0304-3940(84)90151-4

Bouaziz, H., Tong, C., Yoon, Y., Hood, D. D., & Eisenach, J. C. (1996). Intravenous opioids stimulate norepinephrine and acetylcholine release in spinal cord dorsal horn. Systematic studies in sheep and an observation in a human. *Anesthesiology*, *84*(1), 143–154. https://doi.org/10.1097/00000542-199601000-00017

Brosnan, R. J., & Pham, T. L. (2014). Hydrocarbon molar water solubility predicts NMDA vs. GABAA receptor modulation. *BMC Pharmacol Toxicol*, *15*, 62. https://doi.org/10.1186/2050-6511-15-62

Brosnan, R. J., & Pham, T. L. (2016). GABAA receptor modulation by phenyl ring compounds is associated with a water solubility cut-off value. *Pharmacology*, *98*(1–2), 13–19. https://doi.org/10.1159/000444935

Brosnan, R. J., & Pham, T. L. (2018). Anesthetic-sensitive ion channel modulation is associated with a molar water solubility cut-off. *BMC Pharmacol Toxicol*, *19*(1), 57. https://doi.org/10.1186/s40360-018-0244-z

Brosnan, R. J., Pypendop, B. H., Majewski-Tiedeken, C. R., Shilo-Benjamini, Y., & Ilkiw, J. E. (2013). Naltrexone does not affect isoflurane minimum alveolar concentration in cats. *Veterinary Anaesthesia and Analgesia*, *40*(2), 225–228. https://doi.org/10.1111/vaa.12004

Brosnan, R. J., Pypendop, B. H., Siao, K. T., & Stanley, S. D. (2009). Effects of remifentanil on measures of anesthetic immobility and analgesia in cats. *American Journal of Veterinary Research*, *70*(9), 1065–1071. https://doi.org/10.2460/ajvr.70.9.1065

Carrozzo, M. V., Alcorn, J., & Ambros, B. (2018). Effects of two fentanyl constant rate infusions on thermal thresholds and plasma fentanyl concentrations in awake cats. *Veterinary Anaesthesia and Analgesia*, *45*(6), 831–838. https://doi.org/10.1016/j.vaa.2018.06.006

Glass, P. S., Gan, T. J., Howell, S., & Ginsberg, B. (1997). Drug interactions: Volatile anesthetics and opioids. *Journal of Clinical Anesthesia*, *9*(6 Suppl), 18S–22S. https://doi.org/10.1016/s0952-8180(97)00122-0

Hagelberg, N., Kajander, J. K., Nagren, K., Hinkka, S., Hietala, J., & Scheinin, H. (2002). Mu-receptor agonism with alfentanil increases striatal dopamine D2 receptor binding in man. *Synapse (New York, N. Y.)*, *45*(1), 25–30. https://doi.org/10.1002/syn.10078

Hahnenkamp, K., Nollet, J., Van Aken, H. K., Buerkle, H., Halene, T., Schauerte, S., … Hoenemann, C. W. (2004). Remifentanil directly activates human N-methyl-D-aspartate receptors expressed in Xenopus laevis oocytes. *Anesthesiology*, *100*(6), 1531–1537. https://doi.org/10.1097/00000542-200406000-00028

Hocker, J., Bohm, R., Meybohm, P., Gruenewald, M., Renner, J., Ohnesorge, H., … Bein, B. (2009). Interaction of morphine but not fentanyl with cerebral alpha2-adrenoceptors in alpha2-adrenoceptor knockout mice. *Journal of Pharmacy and Pharmacology*, *61*(7), 901–910. https://doi.org/10.1211/jpp/61.07.0009

Hocker, J., Weber, B., Tonner, P. H., Scholz, J., Brand, P. A., Ohnesorge, H., & Bein, B. (2008). Meperidine, remifentanil and tramadol but not sufentanil interact with alpha(2)-adrenoceptors in alpha(2A)-, alpha(2B)- and alpha(2C)-adrenoceptor knock out mice brain. *European Journal of Pharmacology*, *582*(1–3), 70–77. https://doi.org/10.1016/j.ejphar.2007.12.022

Ilkiw, J. E., Pascoe, P. J., & Fisher, L. D. (1997). Effect of alfentanil on the minimum alveolar concentration of isoflurane in cats. *American Journal of Veterinary Research*, *58*(11), 1274–1279.

Leffler, A., Frank, G., Kistner, K., Niedermirtl, F., Koppert, W., Reeh, P. W., & Nau, C. (2012). Local anesthetic-like inhibition of voltage-gated Na(+) channels by the partial mu-opioid receptor agonist buprenorphine. *Anesthesiology*, *116*(6), 1335–1346. https://doi.org/10.1097/ALN.0b013e3182557917

Leysen, J. E., & Gommeren, W. (1986). Drug-receptor dissociation time, new tool for drug research: Receptor binding affinity and drug-receptor dissociation profiles of serotonin-S2, dopamine-D2, histamine-H1 Antagonists, and Opiates. *Drug Development Research*, *8*(1–4), 119–131. https://doi.org/10.1002/ddr.430080115

Mather, L. E. (1983). Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clinical Pharmacokinetics*, *8*(5), 422–446. https://doi.org/10.2165/00003088-198308050-00004

Mortazavi, S., Thompson, J., Baghdoyan, H. A., & Lydic, R. (1999). Fentanyl and morphine, but not remifentanil, inhibit acetylcholine release in pontine regions modulating arousal. *Anesthesiology*, *90*(4), 1070–1077. https://doi.org/10.1097/00000542-199904000-00021

Pourzitaki, C., Tsaousi, G., Papazisis, G., Kyrgidis, A., Zacharis, C., Kritis, A., … Kouvelas, D. (2018). Fentanyl and naloxone effects on glutamate and GABA release rates from anterior hypothalamus in freely moving rats. *European Journal of Pharmacology*, *834*, 169–175. https://doi.org/10.1016/j.ejphar.2018.07.029

Pypendop, B. H., Brosnan, R. J., & Ilkiw, J. E. (2011). Use of naltrexone to antagonize high doses of remifentanil in cats: A dose-finding study. *Veterinary Anaesthesia and Analgesia*, *38*(6), 594–597. https://doi.org/10.1111/j.1467-2995.2011.00649.x

Pypendop, B. H., Brosnan, R. J., Majewski-Tiedeken, C. R., Stanley, S. D., & Ilkiw, J. E. (2014). Pharmacokinetics of fentanyl, alfentanil, and sufentanil in isoflurane-anesthetized cats. *Journal of Veterinary Pharmacology and Therapeutics*, *37*(1), 13–17. https://doi.org/10.1111/jvp.12047

Reis, D. J., Rifkin, M., & Corvelli, A. (1969). Effects of morphine on cat brain norepinephrine in regions with daily monoamine rhythms. *European Journal of Pharmacology*, *8*(1), 149–152. https://doi.org/10.1016/0014-2999(69)90140-x

Robertson, S. A., Taylor, P. M., Sear, J. W., & Keuhnel, G. (2005). Relationship between plasma concentrations and analgesia after intravenous fentanyl and disposition after other routes of administration in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *28*(1), 87–93. https://doi.org/10.1111/j.1365-2885.2004.00628.x

Sonner, J. M. (2002). Issues in the design and interpretation of minimum alveolar anesthetic concentration (MAC) studies. *Anesthesia and Analgesia*, *95*(3), 609–614.

Thomasy, S. M., Mama, K. R., Whitley, K., Steffey, E. P., & Stanley, S. D. (2007). Influence of general anaesthesia on the pharmacokinetics of intravenous fentanyl and its primary metabolite in horses. *Equine Veterinary Journal*, *39*(1), 54–58. https://doi.org/10.2746/042516407x153011

Toda, N., & Hatano, Y. (1977). Alpha-adrenergic blocking action of fentanyl on the isolated aorta of the rabbit. *Anesthesiology*, *46*(6), 411–416. https://doi.org/10.1097/00000542-197706000-00007

Tschirhart, J. N., Li, W., Guo, J., & Zhang, S. (2019). Blockade of the Human Ether A-Go-Go-Related Gene (hERG) potassium channel by fentanyl. *Molecular Pharmacology*, *95*(4), 386–397. https://doi.org/10.1124/mol.118.114751

Wilde, M., Pichini, S., Pacifici, R., Tagliabracci, A., Busardo, F. P., Auwarter, V., & Solimini, R. (2019). Metabolic pathways and potencies of new fentanyl analogs. *Frontiers in Pharmacology*, *10*, 238. https://doi.org/10.3389/fphar.2019.00238

Yackey, M., Ilkiw, J. E., Pascoe, P. J., & Tripp, L. D. (2004). Effect of transdermally administered fentanyl on the minimum alveolar concentration of isoflurane in cats. *Veterinary Anaesthesia and Analgesia*, *31*(3), 183–189. https://doi.org/10.1111/j.1467-2987.2004.00125.x

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