Effects of fentanyl on isoflurane minimum alveolar concentration and cardiovascular function in mechanically-ventilated goats

T.B. Dzikiti, G.F. Stegmann, L.N. Dzikiti, L.J. Hellebrekers

T.B. Dzikiti, BVSc, MSc
Department of Companion Animal Clinical Studies, University of Pretoria, P.Bag X04, Onderstepoort 0110, Republic of South Africa.

G.F. Stegmann, BVSc, MMedVet (Anaesth), Diplomate ECVAA
Department of Companion Animal Clinical Studies, University of Pretoria, P.Bag X04, Onderstepoort 0110, Republic of South Africa.

L.N. Dzikiti, BSc (Stats), BSc Hons (Stats)

School of Health Systems and Public Health, University of Pretoria, Bophelo Road, Pretoria, Republic of South Africa.

L.J. Hellebrekers, DVM, PhD, Diplomate ECVAA
Division of Neurophysiology and Anaesthesiology, Faculty of Veterinary Medicine, Utrecht University, P.O. Box 80.153, 3508 TD Utrecht, The Netherlands.

Email for correspondence: brighton.dzikiti@up.ac.za

Summary

Effects of fentanyl on minimum alveolar concentration (MAC) of isoflurane and cardiovascular function in mechanically-ventilated goats were evaluated using six healthy goats (3 does and 3 wethers). Following induction of general anaesthesia with isoflurane, endotracheal intubation was performed and anaesthesia maintained with isoflurane. Baseline isoflurane MAC in response to clamping a claw with a Vulsellum forceps was determined. Immediately after baseline isoflurane MAC determination, the goats then received, on separate occasions, one of three fentanyl treatments intravenously: bolus of 0.005 mg/kg followed by constant rate infusion (CRI) of 0.005 mg/kg/hour (Treatment LFENT), bolus of 0.015 mg/kg followed by CRI of 0.015 mg/kg/hour (Treatment MFENT), bolus of 0.03 mg/kg followed

by CRI of 0.03 mg/kg/hour (Treatment HFENT). Isoflurane MAC was re-determined during fentanyl CRI treatments. Cardiopulmonary parameters were monitored. Quality of recovery was scored. A four-week washout period was allowed between treatments. The observed baseline isoflurane MAC was 1.32 (1.29-1.36)%. Isoflurane MAC decreased to 0.98 (0.92-1.01)%, 0.75 (0.69-0.79)% and 0.58 (0.51-0.65)% following LFENT, MFENT and HFENT respectively. Cardiovascular function was not adversely affected. Quality of recovery from general anaesthesia was good, although exaggerated tail-wagging was observed on some goats following MFENT and HFENT. Fentanyl reduces isoflurane MAC in a dose-dependent manner with minimal adverse cardiovascular effects in healthy, mechanically-ventilated goats.

Introduction

The depth of anaesthesia during surgery is determined by the interaction of hypnotic drugs, analgesic drugs, and the intensity of noxious stimulation (Bouillon and others 2004). General anaesthetic agents, like isoflurane, primarily contribute to anaesthesia through their hypnotic effects, while opioids, like fentanyl, contribute through analgesic effects. The interaction of hypnotic agents and opioid analgesics during general anaesthesia can be schematically described by a hierarchical model, in which, initially a noxious stimuli processed at sub-cortical levels of the central nervous system (CNS) has its nociceptive signal attenuated by opioids and subsequently, when the attenuated signal is projected to the cortical levels, arousal is suppressed by hypnotic agents (Bouillon and others 2004).

Fentanyl, a synthetic μ opioid agonist, is used for the treatment of moderate to severe pain (Carroll and others 1999). Fentanyl is one of several opioids that are suitable for intravenous (IV) infusion because it offers clinically desirable effects over a wide dose range and has a wide therapeutic margin (Meredith and others 2008). The onset of action of fentanyl is rapid following IV (Lamont and Mathews 2007) or intramuscular administration with analgesia and sedation developing in 3 to 8 minutes (Carroll and others 1999). It has a short duration of action, with plasma concentrations decreasing substantially after about 20 minutes (Carroll and others 1999). In goats, fentanyl proved effective against thermal and mechanical stimuli in a nociceptive model study (Valverde and Gunkel 2005). In another study, fentanyl was used satisfactorily supplement nitrous oxide and isoflurane for maintenance of general anaesthesia in goats (Andel and others 2000).

Isoflurane is a commonly used inhalant anaesthetic agent, which has short induction and recovery times because of its low blood/gas solubility coefficient (Antognini and Eisele 1993). It is assumed that the sites of action of isoflurane are the brain and spinal cord (Antognini and Carstens 2002). The most likely mechanism by which isoflurane produces anaesthetic effects is potentiatiation of the GABA (γ-aminobutyric acid) receptor complex (Larsen and others 1998). Isoflurane can be used for induction as well as maintenance of anaesthesia in goats (Antognini and Eisele 1993). Isoflurane

causes several adverse effects such as respiratory depression, hypotension and reduced cardiac output in a dose-dependent pattern (Antognini and Eisele 1993).

In the present experimental study, the effects of fentanyl on isoflurane MAC in mechanically-ventilated goats were accessed. Minimum alveolar concentration was defined by Merkel and Eger (1963), as the lowest isoflurane alveolar concentration required to prevent gross purposeful movement in response to a supramaximal stimulus. Isoflurane MAC in goats has been determined in previous studies to be in the range of 1.3 to 1.5% (Antognini and Eisele 1993, Hikasa and others 1998, Antognini and others 2000, Doherty and others 2002, Doherty and others 2004). Combining isoflurane with opioid analgesic drugs like fentanyl potentially reduces the dose of isoflurane required for general anesthesia and consequently may reduce occurrence of adverse dose-dependent cardiopulmonary effects associated with isoflurane anaesthesia. We tested the null hypothesis that fentanyl does not affect isoflurane MAC against alternative hypothesis that fentanyl reduces isoflurane MAC in goats.

Materials and Methods

The present study was approved by both the Animal Use and Care Committee and the Research Committee of my University's Faculty of Veterinary Science (Research Protocol Number: V045/06). Six clinically healthy goats (3 does and 3 wethers) were used. The goats were assigned to three treatments, with order of treatments randomized in a cross-over pattern, with a four-week washout period between treatments. General anaesthesia was achieved with isoflurane only. Following baseline isoflurane MAC determination, MAC of isoflurane was re-determined during maintenance of anaesthesia with isoflurane combined with a CRI of low dose fentanyl (Treatment LFENT), moderate dose fentanyl (Treatment MFENT) or high dose fentanyl (Treatment HFENT). Median (interquartile range) age was 15.5 (14.3-16.0) months for Treatment LFENT, 15.0 (15.0-15.80) months for Treatment MFENT and 14.5 (14.0-15.8) months for Treatment HFENT while weight was 36.7 (29.6-40.7) kg for Treatment LFENT, 36.9 (33.6-38.6) kg for Treatment MFENT and 35.9 (31.1-37.6) kg for Treatment HFENT. Health status was assessed by physical examination, complete blood count and serum biochemical analysis; all findings were normal.

Food and water were withheld for 16–22 hours before anaesthesia. The goats were weighed 30 minutes before the experiment. The auricular artery on the right ear was catheterized using a 24-SWG catheter (Jelco, Medex Medical Ltd) which was then connected to a calibrated transducer (DTX Plus transducer, BD Medical) for measurement of arterial blood pressure. The blood pressure readings were obtained from a recently calibrated electronic strain gauge transducer connected to a multi-parameter monitor (Cardiocarp/5, Datex-Ohmeda Corporation), which had been recently calibrated against a mercury column. For transducer calibration to atmospheric pressure, the scapulo-humeral joint or the point of the sternum were used as zero reference points in sternally-recumbent or laterally-recumbent

goats, respectively. An 18-SWG catheter (Jelco, Medex Medical Ltd) was introduced into the right cephalic vein for administration of intravenous fluids and fentanyl.

Mask induction of the goats with isoflurane (Forane Liquid, Abbott Laboratories Pty Ltd) delivered in oxygen from a circle anaesthetic breathing system with a calibrated Tec 3 out-of-circle vaporiser (Fluotec 3, BOC Health Care) was achieved with the goats restrained in sternal position. A tight-fitting facemask was used. Each goat was accustomed to the mask by initially being allowed to breathe 100% oxygen at 6 L/minute for at least one minute before isoflurane administration was slowly begun with 0.5% increments every 15 seconds until a 3.5% vaporizer setting was reached. This vaporizer setting was then maintained until the jaw was relaxed enough to allow intubation. Placement of the endotracheal tube (silicone tube, internal diameter 7.5 mm) was done with the goats in sternal recumbency using a laryngoscope to facilitate the process. If intubation was not successful due to poor relaxation of the jaws, isoflurane delivery by facemask was continued before attempting again. The cuff of the endotracheal tube was inflated to prevent leakage of gases from the breathing circuit to a pressure of 20 cmH_20.

Immediately after intubation, the goats were placed in left lateral recumbency with fresh oxygen flow set at 2 L/minute and initial end-tidal isoflurane concentration targeted to be 1.6%. Intermittent positive pressure ventilation (Ohmeda 7000 Ventilator, Ohmeda) was used to maintain end-tidal carbon dioxide between 35–45 mmHg throughout the procedure. Ringer Lactate solution (Intramed Ringer-Lactate Fresenius, Bodene Pty Ltd, trading as Intramed) was administered by a pump (Infusomat, BBraun, Melsungen, Germany) at a rate of 4 mL/kg/hr intravenously.

Instrumentation for recording of physiological parameters was set up using a multi-parameter monitor (Cardiocap/5, Datex-Ohmeda Corporation). Three electrocardiography (ECG) electrodes were placed on shaven areas (on the middle of the left shoulder, on the midline 2 cm in front of the point of the sternum and on the midline 2 cm cranial to the tip of the xiphoid) to provide a lead II ECG tracing. Haemoglobin oxygen saturation (SpO_2) was measured using a pulse-oximetry infrared probe placed around the tongue. Inspired and expired concentrations of isoflurane, carbon dioxide and oxygen were by side-stream spirometry, with side-stream gas sampler placed between the endotracheal tube and the Y-piece of the breathing system. The gas analyzer had been calibrated with calibration gas as recommended by the manufacturer within recently and would automatically self-calibrate to atmospheric air at the beginning of the experiment. Temperature was measured by an oesophageal probe placed as close to the base of the heart as possible. The targeted oesophageal temperature range was 37.5 and 39.5ºC. The targeted temperature was achieved using a forced warmed air blanket and ordinary blankets placed around the goats. The physiological parameters were measured continuously during the anaesthetic period, but recorded every 15 minutes.

Determination of the baseline isoflurane (control) MAC began 15 minutes after end-tidal isoflurane concentration had been held constant at 1.6%. Isoflurane MAC determination involved application of a noxious stimulus with a Vulsellum forceps clamped to the second ratchet to the claw about 1 cm below the coronary band for 60 seconds or until occurrence of purposeful movement (Fig 1). Purposeful movement was strictly defined as gross movement of the head or limbs, including movement of the limb to which the Vulsellum forceps was being applied. End-tidal isoflurane concentration was then adjusted according to response to noxious stimulation. If no movement occurred, the end-tidal isoflurane concentration was reduced by $1/10^{th}$ and held constant for at least 15 minutes before application of a noxious stimulus again. If movement was noticed, the end-tidal isoflurane concentration was increased by $1/10^{th}$ and held constant for at least 15 minutes before application of a noxious stimulus again. The four claws on the two uppermost limbs were clamped consecutively in a clockwise fashion. Isoflurane MAC was calculated as the average of two successive concentrations: the end-tidal isoflurane concentration at which movement in response to noxious stimulation occurred and the preceeding end-tidal isoflurane concentration at which movement did not occur. The isoflurane MAC was determined in duplicate and the mean of the two MACs was taken as baseline isoflurane MAC for each goat.

Following baseline MAC determination, the goats then received, in a randomized crossover pattern, one of three IV fentanyl treatments (Fentany-Fresenius 10mg/mL, Bodene Pty Ltd, trading as Intramed) administered as a bolus dose manually over a 1 minute period; at 0.005 mg/kg, 0.015 mg/kg, or 0.030 mg/kg; followed by a maintenance dose of 0.005 mg/kg/hour, 0.015 mg/kg/hour, or 0.030 mg/kg/hour as Treatment LFENT, Treatment MFENT and Treatment HFENT, respectively. Fentanyl for maintenance of general anaesthesia was prepared up to 60 mL in normal saline and was administered by CRI from a 60 mL syringe controlled by a syringe-driving pump (Perfusor Compact, BBraun). The fentanyl syringe was connected to the right cephalic vein catheter, to which the Ringer Lactate administration line was also connected, by an extension set via a three-way connection port. The fentanyl loading dose was administered over a period of 1 minute and administration of the maintenance dose started immediately afterwards. The accuracy of delivery of fentanyl by the pump was checked at the end of the experiment by calculating the expected infused amount based on infusion rates and comparing this to actual volume infused from the syringe.

Fentanyl-treatment isoflurane MAC was then determined by applying a noxious stimulus with a Vulsellum forceps after every 15 minutes of end-tidal isoflurane concentration equilibration, and depending on the goat's response, adjusting the end-tidal isoflurane concentration in the same manner as described above.

Since baseline isoflurane MAC was determined each time before a goat underwent one of the three fentanyl treatments, the final baseline isoflurane MAC for each goat was calculated as the

average of the three baseline MAC values obtained. None of the sets of 3 baseline MACs used to calculate the average baseline MAC had a difference of more than 0.1% between each other.

After determination of fentanyl-treatment isoflurane MAC, administration of fentanyl and isoflurane was discontinued simultaneously and the quality of recovery from anaesthesia of the goats observed. The endotracheal tube was removed once the goats regained the swallowing reflex.

Time to extubation, sternal position and standing were recorded. All times were determined as the interval between the time of discontinuation of fentanyl and isoflurane administration and the time a particular event happened.

Quality of recovery from anaesthesia was scored on a 0 – 2 scale where: 0 = restlessness, 1 = relatively smooth, with some restlessness, 2 = smooth.

Statistical analysis

Data were analysed using the R Statistical Software, Version 2.7.2 (The R Foundation for Statistical Computing). All data were assumed to be non-parametric because of the small sample size and are expressed as median and inter-quartile ranges.

Data on isoflurane MAC, isoflurane MAC reduction after fentanyl treatment, isoflurane MAC determination time, time to extubation, time to sternal position, time to standing and recovery scores were tested for statistically significant differences between treatments using the Friedman test. If statistically significant differences were found between treatments, post-hoc analysis (pair-wise Wilcoxon test with a Bonferroni adjustment for multiple testing) was conducted.

Medians of repeatedly measured variables (heart rate, mean arterial blood pressure, SpO_2 and body temperature) were tested for statistically significant differences between and within groups using repeated measures analysis of variance (ANOVA) by ranks. If statistically significant differences were found, a post-hoc analysis (pair-wise Wilcoxon test with a Bonferroni adjustment for multiple testing) was conducted. A value of $P < 0.05$ was considered significant.

Results

Mask induction of anaesthesia using isoflurane was satisfactorily achieved in about 10 minutes with minimal struggling of the goats throughout the induction period. Data on observed isoflurane MACs, changes in isoflurane MAC after treatment with fentanyl and the time it took to determine isoflurane MAC are summarized in Table 1. The observed median baseline MAC of isoflurane in goats of 1.32 (1.29-1.36)% volume was statistically significantly higher than the median MACs obtained after intravenous administration of each of the fentanyl treatments (P =0.013 all round). The median isoflurane MAC following LFENT treatment was statistically significantly higher than those observed following MFENT treatment (P = 0.013) and HFENT treatment (P = 0.013). The differences in MAC

percent reductions were all statistically significantly different from each other. The magnitude of MAC reduction following fentanyl administration was dose-related. The time it took to determine baseline isoflurane MAC was 67.5 minutes. The median time taken to determine isoflurane MAC for HFENT treatment and MFENT treatment was significantly longer than the time it took to determine baseline isoflurane MAC (P = 0.027 for both) and the time it took to determine isoflurane MAC following LFENT treatment (P = 0.024 and 0.047 respectively).

The data obtained for cardiovascular system and respiratory system variables did not show many statistically significant differences between groups or between the baseline reading and any subsequent points within a group. The only differences observed were on heart rate and mean arterial blood pressure which were statistically significantly lower (P = 0.042 and 0.0004 respectively) at 2 minutes following HFENT bolus administration when compared to baseline reading (Table 2). At all time points, mean arterial blood pressure was above 60 mmHg and SpO_2 above 90%. The end-tidal carbon dioxide concentration was successfully maintained within the normal range of 35-45 mmHg by adjusting respiratory rate and intrathoracic pressure settings on the mechanical ventilator. The body temperature of the goats was maintained between 37.5–39.3ºC.

The quality of recovery from anaesthesia was good for all the three treatment groups. The variables used to assess quality of recovery from anaesthesia did not show any statistically significant differences between treatments, except the time taken for the goats to stand, which showed significant differences between treatments (P = 0.04), but did not show any two specific groups to be different when pair-wise comparisons were performed (Table 3). Although the recovery from anaesthesia was smooth following all three fentanyl treatments, it was noticed that 4 out of 6 times, the goats indiscriminately showed exaggerated intermittent tail-waging at recovery following MFENT and HFENT treatment.

Discussion

The median baseline isoflurane MAC in goats of 1.32 (1.29–1.36)% observed in the present study lies with the range reported by previous studies. Antognini and Eisele (1993) reported isoflurane MAC in goats as 1.5%, while other research teams reported isoflurane MACs in goats ranging from 1.23% to 1.29% (Doherty and others 2002, Hikasa and others 1998). The similarity of isoflurane MAC in goats across the different studies is to be expected since MAC of an inhalation anaesthetic agent is expected to remain the same within any species if physiological states like body temperature, blood pressure, haematocrit and tissue perfusion are maintained within normal levels (Quasha and others 1980).

The reductions in isoflurane MAC by 27.6%, 40.7% and 56.6% observed in the present study after administration of Treatment LFENT, Treatment MFENT and Treatment HFENT respectively show

that fentanyl administered intravenously reduces isoflurane MAC in a dose-dependent manner and could have a role as an analgesia adjunct in balanced anaesthesia protocols in goats. There is little information to date on the interaction of opioids with volatile anaesthestic agents in goats. Data from studies in humans, and less consistently so in animals, have shown that the interaction between opioids and potent inhaled anaesthetics result in a dose-dependent reduction of inhaled anaesthestic requirements for general anaesthesia (Criado and Gomez de Segura 2003, Hendrickx and others 2008). In dogs, fentanyl administered transdermally at 0.003 mg/kg/hour reduced isoflurane MAC by approximately 37% (Wilson and others 2006). In the horse, fentanyl administered at 0.00469 mg/kg bolus followed by continuous infusion at about 0.0678 mg/kg/hour resulted in an 18% reduction in isoflurane MAC (Thomas and others 2006). In swine, fentanyl administered at 0.05 mg/kg/hour, 0.1 mg/kg/hour and 0.2 mg/kg/hour reduced isoflurane minimum alveolar concentration by 24.5%, 29.9% and 45.9% respectively (Moon and others 1995). Fentanyl seems to be less potent in reducing isoflurane MAC in goats than in dogs, but is more potent in reducing isoflurane MAC in goats when compared to the horse and swine. These differences in degree of isoflurane MAC reduction by fentanyl in various species show the existence of species difference in pharmacologic actions of fentanyl. The dosages of fentanyl used in the present study are extrapolated from those of other species and are not based on pharmacokinetic data for goats since this kind of data is presently unavailable. The value of the present study could have been greatly improved if the plasma concentration of fentanyl had been determined as this would have ascertained whether steady state had been reached at the time of isoflurane MAC determination during fentanyl CRI.

The results on the effects of fentanyl administration on cardiovascular parameters show that fentanyl can substantially reduce isoflurane required to maintain general anesthesia in goats without causing severe adverse effects on cardiovascular function. Lower heart rate and arterial blood pressure readings were obtained 2 minutes following administration of fentanyl bolus at the highest bolus dose of 0.03 mg/kg. Such high dosages of fentanyl would usually not be used in already anaesthetised patients in clinical situations. The arterial blood pressure and SpO_2 observed even after administration of the highest dose of fentanyl in this study were within normal physiological limits. Fentanyl is known to cause clinically desirable effects over a wide dose range as it has a wide therapeutic margin (Meredith and others 2008). The minimal cardiovascular effects obtained in this study confirm a widely accepted view that opioids result in minor changes in cardiovascular function if used in combination with low doses of inhalation anaesthetics for maintenance of general anaesthesia (Shibutani and others 1999). A well known adverse effect of high doses of fentanyl is bradycardia (Criado and Gomez de Segura 2003). In the present study, heart rate decreased in a dose-dependent manner after the beginning of fentanyl administration, but even the lowest heart rates observed were within physiological limits. A more detailed assessment of the effects of isoflurane-fentanyl anaesthesia on

cardiopulmonary function in goats is required as a follow-up to the present study. It must be taken into consideration that the goats in the present study were all mechanically ventilated so as to standardize the effects of ventilation on isoflurane uptake. Mechanical ventilation also allowed maintenance of eucapnoea, which is vital because abnormal carbon dioxide levels can affect MAC (Quasha and others 1980).

The oesophageal temperature decreased gradually over the anaesthetic period during all three treatments, but stayed within physiologically acceptable limits, with the lowest median oesophageal temperature of 37.7ºC observed in the group that received the lowest dose of fentanyl. This shows that heat conservation methods employed (covering with ordinary blankets and warming with a warm-air heating blanket) were successful in preventing excessive heat loss. The normal physiological body temperature range for goats is 37.2–39.7ºC (Ayo and others 1998). Hypothermia is known to cause a reduction in MAC (Quasha and others 1980, Satas and others 1996); consequently the small decreases in body temperature observed in the present study could still have affected isoflurane MAC. However, this decrease in body temperature was consistent across the three groups.

The period of recovery from anaesthesia was short following all three treatments, with all goats attaining sternal recumbency within 4 minutes and standing within 10 minutes of termination of general anaesthesia. In goats, fentanyl has an extremely short duration of action due to the rapid elimination rate and clearance coupled with a large apparent volume of distribution at steady state (Carroll and others 1999). Exaggerated tail-wagging was observed in the majority of goats that received higher doses of fentanyl, but the general behaviour of the goats was acceptable at all times during recovery. Carroll and others (1999) also reported a different form of abnormal behaviour in the form of increased vocalisation and activity during the first hour after IV administration of a single bolus of fentanyl in conscious goats. We did not observe this type of abnormal behaviour may be because the goats in our study were unconscious during the first hour of fentanyl administration.

In conclusion, fentanyl reduced isoflurane MAC in a dose-dependent manner with minimal adverse effects on cardiovascular function in goats. The results indicate that, fentanyl administered intravenously as a CRI following a bolus dose, may be a useful analgesic adjunct to general anesthesia in goats.

Acknowledgements

This study was jointly funded by the University of Pretoria, the South African Veterinary Foundation (SAVF) - laboratory costs, Fresenius Kabi South Africa - propofol and Ringer Lactate and the University of Pretoria - Utrecht University Memorandum of Understanding (UP-UU) MSc/PhD Research Fund - purchase and upkeep of the goats. Gratitude is expressed to Ms Lebo Sentle and Monicca Ngobeni of

the University of Pretoria Biomedical Centre who worked tirelessly offering technical support to the research.

References

ANDEL, H., BAYER, G. S., CIOVICA, R., MONSIVAIS, J., BASCO, M., ZEMPFER, M. & TURKOF, E. I. (2000) Depressive effect of isoflurane on motor evoked potentials in the Nubian goat. *Canadian Journal of Anesthesia* **47**, 81-86

ANTOGNINI, J. F. & CARSTENS, E. (2002) In vivo characterization of anaesthesia and its components. *British Journal of Anaesthesia* **89**, 156-166

ANTOGNINI, J. F. & EISELE P. H. (1993) Anaesthetic potency and cardiopulmonary effects of enflurane, halothane, and isoflurane in goats. *Laboratory Animal Science* **43**, 607-610

ANTOGNINI, J. F., WANG, X. W. & CARSTENS, E. (2000) Isoflurane anaesthetic depth in goats monitored using the bispectral index of the electroencephalogram. *Veterinary Research Communications* **24**, 361-370

AYO, J. O., OLADELE, S. B., NGAM, S. FAYON, A. & AFOLAYAN, S. B. (1998) Diurnal fluctuations in rectal temperature of the Red Sokoto goat during the harmattan season. *Research in Veterinary Science* **66**, 7-9

BOUILLON, T. W., BRUHN, J., RADULESCU, L., ANDRESEN C., SHAFER, T. J., COHANE, C. & SHAFER, S. L. (2004) Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance to laryngoscopy, bispectral index, and electro-encephalographic approximate entropy. *Anesthesiology* **100**, 1353-1372

CARROLL, G. L., HOOPER, R. N., BOOTHE, D. M., HARTSFIELD, S. M. & RANDOLL, L. A. (1999) Pharmacokinetics of fentanyl after intravenous and transdermal administration in goats. *American Journal of Veterinary Research* **60**, 986-991

CRIADO, A. B. & GOMEZ DE SEGURA, I. A. (2003) Reduction of isoflurane MAC by fentanyl and remifentanil in rats. *Veterinary Anaesthesia and Analgesia* **30**, 250-256

DOHERTY, T. J., ROHRBACH, B. W. & GEISER, D. R. (2002) Effect of acepromazine and butorphanol on isoflurane minimum alveolar concentration in goats. *Journal of Veterinary Pharmacoogy and Therapeutics* **25**, 65-67

DOHERTY, T. J., WILL, W. A., ROHRBACH, B. W. & GEISER, D. R. (2004) Effect of morphine and flunixine meglumine on isoflurane minimum alveolar concentration in goats. *Veterinary Anaesthesia and Analgesia* **31**, 97-101

HENDRICKX, J. F. A., EGER II, E. I., SONNER, J. M. & SCHAFER, S. L. (2008) Is synergy the rule: a review of anaesthetic interactions producing hypnosis and immobility. *Anesthesia and Analgesia* **107**, 494-506

HIKASA, Y., OKUYAMA, K., KAKUTA, T., TAKASE, K. & OGASAWARA, S. (1998) Anesthetic potency and cardiopulmonary effects of sevoflurane in goats: Comparison with isoflurane and halothane. *Canadian Journal of Veterinary Research* **62**, 299-306

LARSEN, M., HAUGSTAD, T. S., BERG-JOHNSEN, J. & LANGMOEN, I. A. (1998) Effect of isoflurane on release and uptake of γ-aminobutyric acid from rat cortical synaptosomes. *British Journal of Anaesthesia* **80**, 634-638

LAMONT, L. A. & MATHEWS, K. A. (2007) Opioids, nonsteroidal anti-inflammatories, and analgesic adjuvants. In Lumb and Jones's Veterinary Anaesthesia and Analgesia. 4th edn. Eds W. J. Tranquilli, J. C. Thurmon, K. A. Grimm. Iowa, Blackwell Publishers. pp 241-271

MEREDITH, J.R., O'KEEFE, K.P., GALWANKAR, S. (2008) Pediatric procedural sedation and analgesia. *Journal of Emergencies, Trauma, and Shock* **1**, 88-96

MERKEL, G. M., EGER II, E. I. (1963) A comparative study of halothane and halopropane anesthesia including method for determining equipotency. *Anesthesiology* **24**, 346-357

MOON, P. F., SCARLETT, J. M., LUDDERS, J. W., CONWAY, T. A. & LAMB, S. V. (1995) Effect of fentanyl on minimum alveolar concentration of isoflurane in swine. *Anesthesiology* **83**, 535-542

QUASHA, A.L., EGER II, E.I., TINKER, J.H. (1980) Determination and applications of MAC: Review. *Anesthesiology* **53**, 315-334

SATAS, S., HAALAND, K., THORESEN, M., STEEN, P.A. (1996) MAC for halothane and isoflurane during normothermia and hypothermia in the newborn piglet. *Acta Anaesthesiologica Scandinavia* **40**, 452-456

SHIBUTANI, K., KATOH, T., KOMATSU, T., SAWADA, K. & FROST, E. A. M. (1999) Clinical applications of fentanyl pharmacokinetics and pharmacodynamics: roles of fentanyl in anesthesia. *Journal of Anesthesia* **13**, 209 – 216

THOMAS, S. M., STEFFEY, E. P., MAMA, K. R., SOLANO, A. & STANLEY, S. D. (2006) The effects of i.v. fentanyl administration on minimum alveolar concentration of isoflurane in horses. *British Journal of Anaesthesia* **97**, 232-237

VALVERDE, A. & GUNKEL, C. I. (2005) Clinical Practice Review: Pain management in horses and farm animals. *Journal of Veterinary Emergency and Critical Care* **15**, 295-307

WILSON, D., PETTIFER, G. R. & HOSGOOD, G. (2006) Effect of transdermally administered fentanyl on minimum alveolar concentration of isoflurane in normothermic and hypothermic dogs. *Journal of the American Veterinary Medical Association* **228**, 1042-1046

Tables

TABLE 1 Effect [median (inter-quartile range)] of intravenously administered fentanyl: 0.005 mg/kg bolus followed by CRI at 0.005 mg/kg/hour (LFENT Treatment), 0.015 mg/kg bolus followed by CRI at 0.015 mg/kg/hour (MFENT Treatment), or 0.03 mg/kg bolus followed by CRI at 0.03 mg/kg/hour (HFENT Treatment) on the MAC of isoflurane in goats.

Treatment	Isoflurane MAC (%vol)	Change post-treatment (%)	MAC determination time (minutes)
Control	1.32 (1.29-1.36) [*]	Not applicable	67.5 (65.0-70.0)
LFENT	0.98 (0.92-1.01) [*]	-27.6 (24.9-29.3)[*]	75.0 (75.0-75.0)
MFENT	0.75 (0.69-0.79) [#]	-40.7 (40.0-47.7)[*]	97.5 (90.0-116.3)[#]
HFENT	0.58 (0.51-0.65) [#]	-56.6 (51.9-60.8)[*]	120.0 (108.8-120.0)[#]

[*]: statistically significantly different ($P < 0.05$) from all other groups
[#]: statistically significantly different ($P < 0.05$) from Control treatment and LFENT treatment

TABLE 2 Physiological parameters [median (inter-quartile range)] observed following IV administration of fentanyl: 0.005 mg/kg bolus followed by CRI at 0.005 mg/kg/hour (LFENT Group), 0.015 mg/kg bolus followed by CRI at 0.015 mg/kg/hour (MFENT Group), or 0.03 mg/kg bolus followed by CRI at 0.03 mg/kg/hour (HFENT Group) in isoflurane-anaesthetised goats.

Variable		Treatment	Time	Period of Baseline Isoflurane MAC Determination (minutes)				Period of Fentanyl-treatment Isoflurane MAC Determination (minutes)				
			Baseline	2	15	30	45	2	15	30	45	60
Heart Rate	(beats min^{-1})	LFENT	86 (81-88)	89 (78-91)	88 (85-94)	90 (85-98)	90 (88-95)	76 (67-83)	77 (71-82)	75 (68-83)	76 (65-84)	86 (73-87)
		MFENT	90 (82-99)	86 (82-93)	87 (85-90)	89 (85-97)	88 (85-98)	68 (65-73)	74 (68-76)	67 (61-75)	69 (61-74)	69 (62-74)
		HFENT	90 (76-11)	88 (75-99)	87 (73-104)	88 (73-103)	88 (76-111)	62 (47-72)*	69 (56-81)	71 (55-78)	71 (54-82)	71 (54-76)
SAP	(mmHg)	LFENT	120 (106-133)	86 (85-109)	98 (94-105)	101 (94-103)	98 (96-101)	95 (88-100)	97 (92-99)	96 (90-98)	95 (90-100)	96 (87-103)
		MFENT	110 (104-115)	103 (88-111)	102 (90-109)	104 (89-106)	103 (96-109)	88 (71-100)	94 (89-97)	100 (93-103)	103 (99-106)	96 (97-106)
		HFENT	127 (113-135)	102 (90-120)	102 (94-117)	102 (100-105)	99 (95-103)	78 (70-81)	97 (93-108)	98 (97-104)	96 (90-113)	98 (87-119)
DAP	(mmHg)	LFENT	74 (68-77)	56 (51-81)	63 (60-73)	70 (61-76)	78 (65-82)	63 (62-73	70 (64-75)	71 (67-76)	75 (65-80)	71 (66-79)
		MFENT	77 (73-80)	64 (50-76)	74 (57-80)	79 (63-84)	80 (65-85)	58 (54-65)	70 (67-74)	74 (73-75)	76 (73-79)	75 (72-79)
		HFENT	79 (77-90)	71 (62-87)	71 (63-83)	74 (72-76)	70 (64-76)	54 (51-57)	69 (68-80)	71 (68-77)	66 (64-80)	65 (64-85)
MAP	(mmHg)	LFENT	98 (90-104)	70 (64-90)	77 (72-85)	85 (74-90)	88 (79-92)	78 (71-84)	82 (75-88)	81 (76-86)	84 (77-88)	82 (74-89)
		MFENT	96 (90-98.8)	90 (69-94)	88 (70-91)	92 (72-94)	91 (79-95)	71 (62-77)	80 (79-82)	85 (83-87)	88 (83-91)	84 (81-92)
		HFENT	109 (97-115)	83 (74-102)	84 (75-98)	87 (86-87)	83 (78-87)	63 (61-65)*	82 (80-95)	84 (82-91)	79 (77-96)	80 (76-103)
SpO_2	(%)	LFENT	-	99 (98-99)	99 (98-99)	98 (97-98)	98 (97-98)	98 (97-98)	97 (96-98)	97 (96-99)	97 (97-98)	97 (96-98)
		MFENT	-	98 (97-99)	99 (98-100)	98 (97-99)	98 (96-98)	98 (96-98)	97 (95-99)	97 (95-98)	96 (94-98)	95 (94-97)
		HFENT	-	98 (93-98)	98 (96-98)	98 (96-98)	98 (95-98)	98 (96-98)	99 (98-99)	98 (97-98)	98 (97-98)	98 (98-99)
$PE'CO_2$	(mmHg)	LFENT	-	45.3 (42.2-46.9)	43.9 (42.4-44.8)	42.3 (40.3-43.5)	40.5 (38.1-43.5)	39.8 (36.9-43.1)	41.6 (37.9-44.8)	34.9 (34.5-35.3)	36.7 (34.9-38.4)	37.5 (36.0-39.6)
		MFENT	-	41.0 (36.9-44.1)	44.2 (38.0-45.6)	45.6 (44.5-45.6)	43.7 (43.3-45.2)	43.7 (40.9-44.9)	41.0 (41.0-42.2)	41.0 (39.3-43.3)	42.6 (42.0-43.7)	43.3 (42.8-43.9)
		HFENT	-	44.1 (40.5-45.4)	43.2 (41.0-43.9)	44.8 (40.7-45.6)	44.5 (37.2-45.4)	41.4 (38.0-44.8)	42.2 (37.8-45.4)	44.1 (41.0-45.4)	40.3 (35.5-44.5)	44.5 (43.3-45.6)
Temp	(ºC)	LFENT	39.1 (39.0-39.2)	38.5 (38.4-38.5)	38.3 (38.3-38.6)	38.3 (38.1-38.5)*	38.1 (38.0-38.5)*	38.1 (37.9-38.4)*	37.8 (37.7-38.3)*	37.8 (37.6-38.2)*	37.7 (37.6-38.1)*	37.6 (37.5-38.0)*
		MFENT	39.1 (38.8-39.3)	38.6 (38.2-38.8)	38.5 (38.2-38.8)	38.4 (38.1-38.6)	38.4 (38.0-38.6)	38.3 (38.1-38.5)*	38.2 (37.9-38.4)*	38.1 (37.8-38.3)*	38.0 (37.8-38.3)*	38.0 (37.9-38.3)*
		HFENT	39.1 (39.0-39.2)	38.5 (38.4-38.8)	38.5 (38.3-38.8)	38.4 (38.1-38.7)	38.3 (38.1-38.5)	38.3 (38.0-38.5)*	38.1 (37.9-38.3)*	38.1 (37.9-38.1)*	38.0 (37.9-38.0)*	38.0 (37.8-38.0)*

*: statistically significantly different ($P < 0.05$) from baseline reading within treatment

SAP - systolic arterial pressure; DAP - diastolic arterial pressure; MAP - mean arterial pressure; SpO_2 - saturation of haemoglobin with oxygen in peripheral blood; $PE'CO_2$ - end-tidal carbon dioxide partial pressure; Temp - body temperature.

TABLE 3 Quality of recovery from anaesthesia [median (inter-quartile range)] observed in a study where the effects of intravenously administered fentanyl: 0.005 mg/kg bolus followed by CRI at 0.005 mg/kg/hour (LFENT Treatment), 0.015 mg/kg bolus followed by CRI at 0.015 mg/kg/hour (MFENT Treatment), or 0.03 mg/kg bolus followed by CRI at 0.03 mg/kg/hour (HFENT Treatment) on the MAC of isoflurane in goats were investigated.

Treatment	Time to Extubation (minutes)	Time to Sternal Position (minutes)	Time to Standing (minutes)	Recovery Score
LFENT	2.0 (2.0-2.8)	3.0 (3.0-4.5)	5.0 (5.0-7.3)	2 (2-2)
MFENT	3.0 (3.0-3.0)	4.0 (3.0-5.0)	9.0 (7.25-11.5)	2 (2-2)
HFENT	3.0 (3.0-3.0)	3.0 (3.0-4.5)	10.0 (8.5-10.0)	1.5 (1-2)

Note: No statistically significant differences ($P < 0.05$) between any treatments

List of Figures

FIGURE 1 Vulsellum forceps clamped to the claw for noxious stimulation.