Veterinary Anaesthesia and Analgesia, 2001, **28**, 188–195

RESEARCH PAPER

Pharmacokinetics and selected behavioral responses to butorphanol and its metabolites in goats following intravenous and intramuscular administration

Gwendolyn L Carroll* MS, DVM, **Dawn M Boothe†** DVM, MS, PhD
Sandee M Hartsfield* DVM, MS, **Mandy K Waller*** DVM **& Sue C Geller‡** PhD
*Department of Veterinary Small Animal Medicine and Surgery, Texas A & M University, College Station, TX, USA
†Department of Veterinary Physiology and Pharmacology, Texas A & M University, College Station, TX, USA
‡Department of Veterinary Anatomy and Public Health, Texas A & M University, College Station, TX, USA

Correspondence: Dr Gwendolyn Carroll, Department of Veterinary Small Animal Medicine and Surgery, Texas A & M University, College Station, TX 77843–4474, USA.

Abstract

Objective To evaluate disposition of a single dose of butorphanol in goats after intravenous (IV) and intramuscular (IM) administration and to relate behavioral changes after butorphanol administration with plasma concentrations.

Design Randomized experimental study.

Animals Six healthy 3-year-old neutered goats (one male and five female) weighing 46.5 ± 10.5 kg (mean $\pm$ D).

Methods Goats were given IV and IM butorphanol (0.1 mg kg^{-1}) using a randomized cross-over design with a 1-week interval between treatments. Heparinized blood samples were collected at fixed intervals for subsequent determination of plasma butorphanol concentrations using an enzyme linked immunosorbent assay (ELISA). Pharmacokinetic values (volume of distribution at steady state [Vd_{SS}], systemic clearance [Cl_{TB}], extrapolated peak plasma concentration [C_0] or estimated peak plasma concentration [C_{MAX}], time to estimated peak plasma concentration [T_{MAX}], distribution and elimination half-lives [$t_{1/2}$], and bioavailability) were calculated. Behavior was subjectively scored. A two-tailed paired *t*-test was used to compare the elimination half-lives after IV and IM administration. Behavioral scores are reported as median (range). A Friedman Rank Sums test adjusted for ties was used to analyze the behavioral scores. A logit model was used to determine the effect of time and concentration on behavior. A value of $p < 0.05$ was considered significant.

Results Volume of distribution at steady state after IV administration of butorphanol was 1.27 ± 0.73 L kg^{-1}, and Cl_{TB} was 0.0096 ± 0.0024 L kg^{-1} minute^{-1}. Extrapolated C_0 of butorphanol after IV administration was 146.5 ± 49.8 ng mL^{-1}. Estimated C_{MAX} after IM administration of butorphanol was 54.98 ± 14.60 ng mL^{-1}, and T_{MAX} was 16.2 ± 5.2 minutes; bioavailability was $82 \pm 41\%$. Elimination half-life of butorphanol was 1.87 ± 1.49 and 2.75 ± 1.93 hours for IV and IM administration, respectively. Goats became hyperactive after butorphanol administration within the first 5 minutes after administration. Behavioral scores for goats were significantly different from baseline at 15 minutes after IV administration and at 15 and 30 minutes after IM administration. Both time and plasma butorphanol concentration were predictors of behavior. Behavioral scores of all goats had returned to baseline by 120 minutes after IV administration and by 240 minutes after IM administration.

Conclusions and Clinical Relevance The dose of butorphanol (0.1 mg kg^{-1}, IV or IM) being used clinically to treat postoperative pain in goats has an elimination half-life of 1.87 and 2.75 hours, respectively. Nonpainful goats become transiently excited after

IV and IM administration of butorphanol. Clinical trials to validate the efficacy of butorphanol as an analgesic in goats are needed.

Keywords analgesia, behavior, butorphanol, goats.

Introduction

Opioids are the mainstay of providing perioperative analgesia in many animal species. However, potentially adverse ventilatory, hemodynamic and behavioral changes are associated with the administration of these drugs in ruminants (Randolph 1994); opioid agonist–antagonists may be associated with less marked physiologic changes than pure agonists (Randolph 1994). In studies in cattle (Cornick et al. 1990), sheep (O'Hair et al. 1988) and goats (Carroll et al. 1998a), very few physiologic changes are reported after the administration of butorphanol, a mixed agonist–antagonist.

Although minimal cardiopulmonary effects are seen after butorphanol administration, its usefulness as an analgesic for mild to moderate pain in ruminants might be limited by its behavioral side-effects. Butorphanol has been used in goats in combination with detomidine as a premedicant without precipitating excitement (Carroll et al. 1998b). However, when butorphanol (0.1 mg kg^{-1}, IV) was administered to nonpainful goats without administration of a sedative (Carroll et al. 1998a) the goats vocalized, climbed in the restraint chute and nibbled at equipment and clothing (unpublished observations). The purpose of this investigation was to examine the pharmacokinetic profile of IV and IM butorphanol in goats, to describe the behavioral response of goats to butorphanol administration, and to relate the plasma concentrations of butorphanol to the behavioral response.

Materials and methods

Animals and experimental protocol

Six 3-year-old neutered cross-bred meat goats (one male, five females) weighing 46.5 ± 10.5 kg (mean ± SD) and conditioned to handling and restraint for 3 months yearly were used in the study. The goats were determined to be in good health based on physical examination and complete blood counts. Goats had unrestricted access to hay and water and were fed a commercially available chow formulated for goats (Sheep and Goat Pellets [15% crude protein], Producers Co-Operative, Bryan, TX, USA; 0.5 kg $goat^{-1}$ day^{-1}).

The study was approved by the University Laboratory Animal Care and Use Committee. The study was conducted as a randomized cross-over design; the IV and IM administration periods were separated by one week. The goats were not held off feed prior to the study; the time of day for butorphanol administration was standardized for both treatments. On the morning of the first day of each administration period, lidocaine (10 mg) was injected subcutaneously (SC) into the area over the right jugular vein. An 18-SWG, 1.75″ catheter (Jelco, Criticon, Tampa, FL, USA) was placed percutaneously, and an intermittent injection cap (PRN; Jelco, Criticon, Tampa, FL, USA) was connected to the catheter, which was then secured to the goat's skin with tissue adhesive. The catheter was used for the administration of butorphanol and for collection of blood samples, similar to a previously reported study (Carroll et al. 1999). Goats were randomly assigned to receive butorphanol (0.1 mg kg^{-1}) (Torbugesic, Fort Dodge Animal Health, Overland, KS, USA), IV or IM (right or left biceps femoris muscle). The dose of butorphanol [0.1 mg kg^{-1}: IV (Carroll et al. 1997); IM (Carroll et al. 1998b)] that is used as an analgesic in goats has been based on research conducted in sheep (Waterman et al. 1991).

The behavior scoring system was developed but not published during a previous study (Carroll et al. 1998a), in which nonpainful goats were noted to have increased arousal rather than sedation after butorphanol administration. The behavioral scores are: 3 = fractious (jumping, crying); 2 = pulling against leash, shifting weight from limb to limb (fidgety), biting; 1 = standing still or laying down, but eyes wide open; 0 = relaxed normal posture. Scores were assigned at 0 minutes (immediately before butorphanol administration) and at 15, 30, 60, 90, 120 and 240 minutes after butorphanol administration by one observer who was aware of the treatment.

Blood samples

Six-mL blood samples were collected at 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720 and 840 minutes after IV butorphanol administration and at 0, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480, 720 and 840 minutes after IM butorphanol administration. Blood samples were collected in heparinized tubes (Monoject Lithium Heparin,

Sherwood Medical, St. Louis, MO, USA), placed on ice and immediately centrifuged to collect plasma. The plasma was stored in microcentrifuge tubes (PGC Scientific, Frederick, MD, USA) at −80 °C until analyzed.

Sample analysis

Butorphanol concentration in plasma was determined using an enzyme linked immunosorbent assay (ELISA) (Neogen Corporation, Lexington, KY, USA) that was validated in goat plasma. The assay is not specific for butorphanol and has probable cross-reactivity for major metabolites; butorphanol in this study refers to butorphanol plus detectable metabolites. This assay measures both protein-bound and free butorphanol. All samples were assayed in duplicate and the average concentration is reported; only samples that were greater than 3 times the concentration at time 0 are reported. The limit of detection for the ELISA assay was 0.1 ng mL^{-1}; the limit of quantification was 0.2 ng mL^{-1}. The interassay coefficient of variation was 11.3 ± 3.4%.

Pharmacokinetic analysis

Plasma drug concentration versus time curves for each goat were subjected to a computerized linear regression program (RSTRIPII, Micromath Scientific Software, Salt Lake City, UT, USA) for one-, two-, three- and four-exponential models having the general mathematical formula:

$$C_p = \sum_{i=0}^{n} A_i e_i^{-k(t)}$$

where C_p is the concentration of butorphanol at any time (t); A_i, is the y-axis intercept of the ith exponential term; and k_i is the slope for the linear regression of the ith exponential term (Gibaldi & Perrier 1982). Selection of the best-fitting model was based on a statistical model selection that related the number of exponential terms in the model to the total variance accounted for by the model (Yamakoa et al. 1978).

The area under the plasma concentration *versus* time curve (*AUC*) and the area under the first moment curve (*AUMC*) were determined using the trapezoidal method to the last time point. Distribution half-life and elimination half-life were determined from the slope of the initial and terminal components of each plasma drug concentration *versus* time curve, respectively. Apparent volume of distribution at a steady state (Vd_{SS}), total body clearance (Cl_{TB}), mean residence time (MRT), y-intercept (A) and slope (k) were calculated for each individual animal using standard model-independent methods (Gibaldi & Perrier 1982). Peak plasma drug concentrations were extrapolated at time 0 (C_0) for the IV study and estimated peak plasma concentration (C_{max}) and time to peak concentration (T_{max}) were determined for the IM study. Bioavailability of butorphanol after IM administration was calculated by comparing the total *AUC* from IM to the total *AUC* after IV administration in each animal using the ratio: AUC_{IM}/AUC_{IV}. Pharmacokinetic data are reported as mean ± SD, except for elimination half-lives which are reported as harmonic mean and pseudo standard deviation. A two-tailed paired t-test was used to compare the elimination half-lives after IV and IM administration.

Behavioral scores are reported as median (range). A Friedman Rank Sums test adjusted for ties was used to analyze the behavioral scores for IV or IM administration of butorphanol (Hollander & Wolfe 1973). A value of $p < 0.05$ was considered significant. If a significant difference was found, a distribution-free multiple comparison test adjusted for ties and based on the Friedman Rank Sums test was conducted (Hollander & Wolfe 1973). A logit model was used to determine the effect of time and concentration on behavior (PROC GENMOD, SAS, version 6.12, SAS Institute, Cary, NC, USA).

Results

Plasma concentrations of butorphanol best fit a two-exponential model after IV administration and a three-exponential model after IM administration (Figs 1 and 2). Pharmacokinetic values were calculated for each method of administration (Tables 1 and 2).

Goats were hyperactive after butorphanol administration; behavior changes were apparent within the first 5 minutes after administration. On both the IV and IM trials, a Friedman Rank Sums test adjusted for ties showed that there were differences among the medians of the behavioral scores ($p = 0.009$ in both cases) (Table 3). The distribution-free multiple comparison test adjusted for ties and based on the Friedman Rank sums showed that behavioral scores for goats were significantly different from baseline at 15 minutes after IV administration and at 15 and 30 minutes after IM administration. Behavioral scores of all goats had returned to

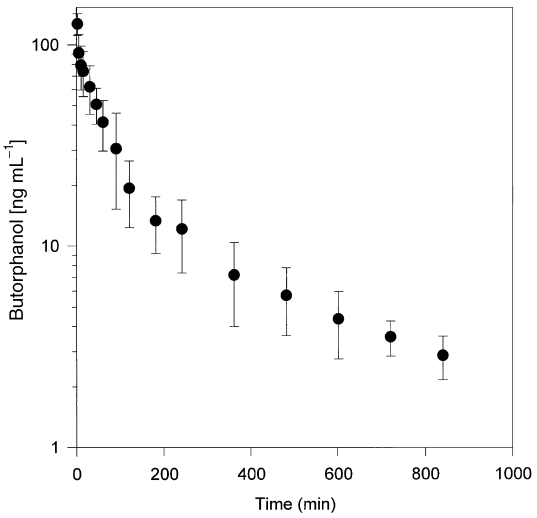

Figure 1 Mean (±SD) plasma concentrations of butorphanol (ng mL^{-1}) after administration of butorphanol (0.1 mg kg^{-1}, IV) to six goats.

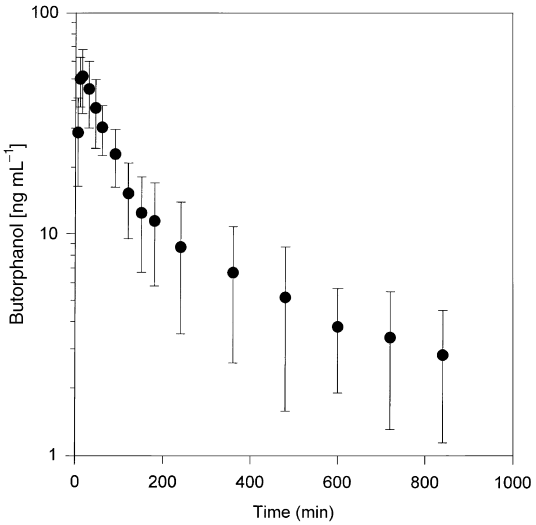

Figure 2 Mean (±SD) plasma concentrations of butorphanol (ng mL^{-1}) after administration of butorphanol (0.1 mg kg^{-1}, IM) to six goats.

baseline by 120 minutes at a plasma concentration of 19.4 ± 7.8 ng mL^{-1} after IV administration and by 240 minutes at a plasma concentration of 8.7 ± 5.7 ng mL^{-1} after IM administration. A logit model was fitted for each of the IV and IM data sets for behavior as a function of time and concentration. Both time and plasma butorphanol concentration were

Table 1 Pharmacokinetic values after administration of butorphanol (0.1 mg kg^{-1}, IV) to six goats

	Range	Mean (±SD)
BW (kg)	36.9–65.5	46.1 ± 10.2
A_1 (ng mL^{-1})	63.7–790.8	213.5 ± 284.3
A_2 (ng mL^{-1})	11.3–101.9	50.7 ± 35.4
$t_{1/2}A_1$ (minutes)	0.6–34.1	2.1 ± 0.3
$t_{1/2}A_2$ (minutes)	60.1–396.9	112.4 ± 89.4
k_1 (minute^{-1})	0.020–1.192	0.331 ± 0.452
k_2 (minute^{-1})	0.002–0.012	0.006 ± 0.004
C_0 (ng mL^{-1})	90.5–221.5	146.5 ± 49.8
AUC (ng L^{-1} minute^{-1})	8.1–16.1	11.1 ± 3.1
AUMC (ng minute^2 L^{-1})	559.5–2456.8	1488.8 ± 759.7
MRT (minutes)	81.9–210.5	145.7 ± 54.0
Vd_{SS} (L kg^{-1})	0.63–2.52	1.27 ± 0.73
Cl_{TB} (L kg^{-1} minute^{-1})	0.0062–0.0012	0.0096 ± 0.0024

BW = body weight; A_1 = intercept of initial phase of biexponential curve; A_2 = intercept of terminal phase of biexponential curve; $t_{1/2}A_1$ and $t_{1/2}A_2$ = harmonic means of the respective half-lives (minutes); k_1 = slope (rate constant) for initial phase; k_2 = slope (rate constant) for terminal (elimination) phase; C_0 = extrapolated peak plasma concentration; *AUC* = plasma concentration *versus* time curve; *AUMC* = area under the first moment curve; MRT = mean residence time; Vd_{SS} = apparent volume of distribution at a steady state; Cl_{TB} = total body clearance.

Table 2 Pharmacokinetic values after administration of butorphanol (0.1 mg kg^{-1}, IM) to six goats

	Range	Mean (±SD)
BW (kg)	38.7–67.7	46.8 ± 10.8
A_1 (ng mL^{-1})	−2488.6–40.0	−1042.2 ± 1129.4
A_2 (ng mL^{-1})	36.9–2460.5	1023.7 ± 1129.3
A_3 (ng mL^{-1})	3.1–52.5	24.2 ± 18.0
$t_{1/2}A_1$ (minutes)	0.8–16.1	2.8 ± 1.3
$t_{1/2}A_2$ (minutes)	2.7–60.8	8.5 ± 3.4
$t_{1/2}A_3$ (minutes)	76.4–685.1	165.1 ± 115.9
k_1 (minute^{-1})	0.043–0.842	0.249 ± 0.302
k_2 (minute^{-1})	0.011–0.253	0.082 ± 0.090
k_3 (minute^{-1})	0.001–0.009	0.004 ± 0.004
C_{max} (ng mL^{-1})	30.9–69.2	55.0 ± 14.6
T_{max} (minutes)	7.5–20.6	16.2 ± 5.2
Bioavailability percentage	31–151	82 ± 41
AUC (ng L^{-1} minute^{-1})	4.1–14.1	8.0 ± 3.7
AUMC (ng minute^2 L^{-1})	78.6–3548.7	1509.5 ± 1402.6
MRT (minutes)	110.8–274.6	187.8 ± 68.8

BW = body weight (kg); A_1, A_2 and A_3 = intercepts of respective phase of curve; $t_{1/2}A_1$, $t_{1/2}A_2$ and $t_{1/2}A_3$ = harmonic means of the respective half-lives (minutes); k_1, k_2 and k_3 = slope (rate constant) for respective phase; C_{max} = estimated peak plasma concentration; T_{max} = time to peak plasma concentration; *AUC* = plasma concentration *versus* time curve; *AUMC* = area under the first moment curve; MRT = mean residence time.

Table 3 Behavioral scores and plasma butorphanol concentrations (ng mL^{-1}) after IV and IM administration of butorphanol (0.1 mg kg^{-1})

	After IV administration		After IM administration	
Time period	Behavioral score (median; range)	Plasma butorphanol concentration ng mL^{-1} (mean ± SD)	Behavioral score (median; range)	Plasma butorphanol concentration ng mL^{-1} (mean ± SD)
0	0	0.5 ± 0.2	0	0.4 ± 0.3
15	2 (1–2)*	74.0 ± 20.3	2.5 (2–3)**	51.4 ± 18.0
30	1 (1–2)	62.0 ± 18.0	2 (1–3)**	45.0 ± 16.5
60	1 (0–1)	41.4 ± 12.7	1 (0–2)	30.2 ± 8.5
90	0.5 (0–1)	30.6 ± 16.8	1 (0–1)	22.9 ± 7.4
120	0	19.4 ± 7.8	0 (0–1)	15.1 ± 6.2
240	0	12.2 ± 5.2	0	8.7 ± 5.7

*After IV administration, behavioral scores in the 15-minute time period are different from 0-,120- and 240-minute periods.
**After IM administration, behavioral scores in the 15-minute and 30-minute time periods were different from those at 0 and 240 minutes.

predictors ($p < 0.0001$) of behavior after IV and IM administration of butorphanol.

Discussion

A number of different assays have been used to detect butorphanol in other species. The ELISA assay for butorphanol is an easy, commercially available assay with a sufficiently low limit of quantification that pharmacokinetics can be characterized in many species once the assay is validated in the species of interest. One alternative to ELISA is high performance liquid chromatography (HPLC) with electrochemical detection (Besner et al. 1989), a method which requires a tedious sample preparation and expensive equipment. Additionally, the detection level necessary to describe the plasma concentration–time profile of butorphanol after the administration of clinical doses cannot be achieved using HPLC (Court et al. 1992). In the laboratory used for this investigation, the limit of quantification of butorphanol using HPLC is 6.7 ng mL^{-1}. A third alternative is radioimmunoassay (RIA), which is expensive and difficult to perform and, although it does not cross-react with the two known metabolites (hydroxybutorphanol and norbutorphanol), it does significantly cross-react with unidentified metabolites of butorphanol (Pittman et al. 1980).

The degree of cross-reactivity between butorphanol and its metabolites has not been established for the ELISA assay. Cross-reactivity is not necessarily a disadvantage in species in which the metabolites are unknown. In human beings, butorphanol is extensively metabolized in the liver to hydroxybutorphanol, with smaller amounts of norbutorphanol produced (Vachharajani et al. 1996). In human beings, these metabolites are inactive; in other animal studies, butorphanol metabolites have demonstrated some analgesic activity (Physician Desk Reference 1998). Metabolites of butorphanol and their activity apparently have not been characterized in goats. If these metabolites are found not to be analgesic in goats, the interpretation of the data presented here may need to be altered. However, selected samples in this study were also subjected to HPLC with no evidence of the presence of metabolites, suggesting that the formation and subsequent detection of metabolites had little impact in this study. Another potential limitation of the sampling technique relates to venous sampling verses arterial sampling for pharmacokinetic modeling (Jacobs & Nath 1995). Traditional pharmacokinetic studies use venous samples because of the lack of invasiveness of venous sampling as opposed to arterial sampling. Some drugs, particularly drugs that are lipophilic and those that are metabolized by tissue, may be characterized by differences in arterial and venous sampling. The use of either arterial or venous sampling is based on the assumption that plasma samples from either site correlate with but may not be equal to tissue drug concentrations. In this study, the same catheter was used for administration of the drug and sampling,

which might lead to abnormally high measured values. This did not appear to be the case in this study.

Butorphanol has been studied in several veterinary species. Dosing schemes for many drugs are often extrapolated from one species to another despite differences in pharmacokinetics. This study documents that the disposition of butorphanol in goats differs from that in other species, including other small ruminants, human beings and dogs – species from which data might be used as a basis for extrapolation of butorphanol dosing schemes in goats. Goats have a lower rate of clearance (9.6 mL kg^{-1} $minute^{-1}$) of butorphanol than other species, including rabbits (75.46 mL kg^{-1} $minute^{-1}$) (Portnoy & Hustead 1992), dogs (57.5 mL kg^{-1} $minute^{-1}$) (Pfeffer et al. 1980), cows (34.6 mL kg^{-1} $minute^{-1}$) (Court et al. 1992), sheep (63.7 mL kg^{-1} $minute^{-1}$) (Maduska et al. 1980) and human beings (29 mL kg^{-1} $minute^{-1}$) (Ramsey et al. 1986). In addition, the Vd_{SS} of butorphanol is smaller in goats (1.27 L kg^{-1}) compared with that in rabbits (10.76 L kg^{-1}: Portnoy & Hustead 1992), dogs (7.51 L kg^{-1}: Pfeffer et al. 1980), cows (4.178 L kg^{-1}: Court et al. 1992) and human beings (8.3 L kg^{-1}: Ramsey et al. 1986). The lower *Vd* suggests that drug concentrations will be higher in goats compared with other species when given an equivalent dose, indicating a need to lower the doses in goats if they were to respond to butorphanol as other species do. Elimination half-life, a hybrid parameter that is indirectly proportional to clearance and directly proportional to half-life, was different in goats than other species. For example, the elimination half-life after IV administration in goats (1.87 hours) is shorter than reported for human beings (3.67 hours: Ramsey et al. 1986; to 4.56 hours: Physician Desk Reference 1998) but is similar to that reported for rabbits (1.64 hours: Portnoy & Hustead 1992). Compared with other ruminants, the elimination half-life of butorphanol in goats appears to be slightly longer than that reported for cows, 1.37 hours (Court et al. 1992), and almost twice as long as in pregnant anesthetized sheep, 0.82 hours (Maduska et al. 1980).

With respect to parenteral administration of butorphanol, the half-life in goats (2.75 hours after IM administration) was longer than reported for dogs (1.62 hours after IM or SC administration: Pfeffer et al. 1980) and similar to that reported in rabbits (3.16 hours after SC administration: Portnoy & Hustead 1992). Thus the duration of effect of butorphanol in goats might be expected to be shorter than in human beings, but longer than that in a number of other species.

Butorphanol was absorbed quickly following IM administration, with a T_{max} of 16.2 minutes resulting in a C_{max} of 55.0 ng mL^{-1}. Absorption was nearly complete (bioavailability = 82%), suggesting that IM administration of butorphanol is a viable route for clinical use in goats. The higher C_{max} of the butorphanol in goats at a dose of 0.1 mg kg^{-1}, IM compared with a C_{max} of 25.1 ng mL^{-1} in dogs 0.7 hours after IM administration of 0.25 mg kg^{-1} and 33.3 ng mL^{-1} 0.5 hours after SC administration of 0.25 mg kg^{-1} (Pfeffer et al. 1980), probably reflects both differences in rate of absorption (faster in goats) and in the *Vd* of butorphanol (smaller in goats). Thus, dosing following IM administration in goats may need to be reduced compared with dogs in order to avoid potential adverse side-effects.

Although the analgesia and cardiovascular stability provided by butorphanol are desirable, there are behavioral changes associated with central nervous system excitement reported in ruminants (Randolph 1994), sheep (Waterman et al. 1991; O'Hair et al. 1988), human beings (Bailey et al. 2000) and horses (Kalpravidh et al. 1984), but not cats (Branson et al. 1995). In our goats, behavioral effects were noted within 5 minutes of butorphanol administration and persisted for at least 90 minutes after IV butorphanol administration and at least 2 hours after IM administration. The goats demonstrated heightened awareness to their surroundings and increased activity; none of the goats became sedated. These behavioral changes may be overcome by administering a lower dose, as has been demonstrated in sheep (Waterman et al. 1991), or by coadministration of a sedative, as demonstrated in horses (Kalpravidh et al. 1984) and goats (Carroll et al. 1998b).

All goats' behaviors fit within the scores used in this study. When plasma concentrations are examined, it appears that more profound behavioral changes are associated with lower plasma concentrations after IM administration than after IV administration. However, the observer was not naive to the route of administration which could lead to observer bias. The observer who scored behavior noted that the goats receiving butorphanol IV demonstrated their greatest change in behavior within the first 5 minutes; by the time of the first official observation and blood sampling time, the goats were much calmer. Thus, the behavioral scores after the IV administration are not a complete reflection of the behavioral changes. It is possible that the IM injection might cause some behavioral changes not seen in the goats after receiving an IV injection. Although

analgesia was not tested in this study, in sheep analgesia persists for longer than behavioral changes (Waterman et al. 1991).

Therapeutic plasma concentration for analgesia varies with species and with the pain model. In human beings, peak serum levels after a therapeutic dose are 1–2 ng mL^{-1} (Gaver et al. 1980). In the dog, minimum therapeutic plasma concentrations of approximately 9 ng mL^{-1} were extrapolated from the results of Pfeffer et al. (1980) by Troncy et al. (1996). Plasma concentrations of butorphanol associated with analgesia have not been established in the goat, but were equal to about 9 ng mL^{-1} for 240 minutes.

This study supports the importance of pharmacokinetic studies in the targeted species of interest rather than using data extrapolated from other species. Because butorphanol produces relatively minor physiologic changes (Carroll et al. 1998a) and has an acceptable half-life for ease of dosing, butorphanol may be a good alternative for analgesia in goats. In our experience, butorphanol does not produce the behavioral changes seen in this study when administered to goats with pain. Alternatively, the coadministration of a sedative may decrease the potential for excitement in nonpainful goats. Clinical trials that assess analgesic efficacy and behavioral responses in goats with pain are needed.

Acknowledgements

Supported by Texas A & M University, College of Veterinary Medicine. The authors acknowledge Dr Albert Boeckh for assistance with the butorphanol assay.

References

Bailey PL, Egan TD, Stanley TH (2000) Intravenous opioid anesthetics. In: Anesthesia, 5th edn. Miller RD (ed.). Churchill Livingstone, Philadelphia, USA, pp. 273–376.

Besner JG, Band CJ, Rondeau JJ, et al. (1989) Determination of opiates and other basic drugs by high-performance liquid chromatography with electrochemical detection. J Pharm Biomed Anal 7, 1811–1817.

Branson KR, Gross ME, Booth NH (1995) Opioid agonists and antagonists. In: Veterinary Pharmacology and Therapeutics, 7th edn. Adams HR (ed.). Iowa State University Press, Ames, pp. 274–310.

Carroll GL, Hartsfield SM, Hambleton R (1997) Anesthetic effects of tiletamine–zolazepam, alone or in combination with butorphanol, in goats. J Am Vet Med Assoc 211, 593–597.

Carroll GL, Hartsfield SM, Champney TH (1998a) Stress-related and metabolic response to restraint, with and without butorphanol administration, in preconditioned goats. Laboratory Anim Sci 48, 387–390.

Carroll GL, Hooper RN, Slater MR, et al. (1998b) Detomidine-butorphanol-propofol for carotid artery translocation and castration or ovariectomy in goats. Vet Surg 27, 75–82.

Carroll GL, Hooper RN, Boothe DM, et al. (1999) Pharmacokinetics of fentanyl after intravenous and transdermal administration in goats. Am J Vet Res 60, 986–991.

Cornick JL, Hartsfield SM, Taylor TS, et al. (1990) Cardiopulmonary effects of butorphanol tartrate intravenously administered for placement of duodenal cannulae in isoflurane-anesthetized yearling steers. Am J Vet Res 51, 1062–1064.

Court MH, Dodman NH, Levine HD, et al. (1992) Pharmacokinetics and milk residues of butorphanol in dairy cows after single intravenous administration. J Vet Pharmacol Therap 15, 28–35.

Gaver RC, Vasiljev M, Wong H, et al. (1980) Disposition of parenteral butorphanol in man. Drug Metab Dispos 8, 230–235.

Gibaldi M, Perrier D (1982) Multicompartment models. In: Pharmacokinetics, 2nd edn. Marcell Dekker, New York, pp. 45–109.

Hollander M, Wolfe DA (1973) The two-way layout. In: Nonparametric Statistical Methods. John Wiley & Sons, New York, USA, pp. 138–154.

Jacobs JR, Nath PA (1995) Compartment model to describe peripheral arterial-venous drug concentration gradients with drug elimination from the venous sampling compartment. J Pharm Sci 84, 370–375.

Kalpravidh M, Lumb WV, Wright W, et al. (1984) Analgesic effects of butorphanol in horses: dose–response studies. Am J Vet Res 45, 211–216.

Maduska AL, Pittman KA, Ahokas RA, et al. (1980) Placental transfer and other physiologic studies with intravenous butorphanol in the anesthetized pregnant ewe. Res Commun Chem Pathol Pharmacol 29, 229–241.

O'Hair K, Dodd KT, Phillips YY, et al. (1988) Cardiopulmonary effects of nalbuphine hydrochloride and butorphanol tartrate in sheep. Lab Anim Sci 38, 58–61.

Pfeffer M, Smyth RD, Pittman KA, et al. (1980) Pharmacokinetics of subcutaneous and intramuscular butorphanol in dogs. J Pharm Sci 69, 801–803.

Physician Desk Reference (52nd edn) (1998). Stadol. Montvale, Medical Economics Co, pp. 817–820.

Pittman KA, Smyth RD, Mayol RF (1980) Serum levels of butorphanol by radioimmunoassay. J Pharm Sci 69, 160–163.

Portnoy LG, Hustead DR (1992) Pharmacokinetics of butorphanol in rabbits. Am J Vet Res 53, 541–543.

Ramsey R, Higbee M, Maesner J, et al. (1986) Influence of age on the pharmacokinetics of butorphanol. Acute Care 12, 6–16.

Randolph MM (1994) Post-operative care and analgesia of farm animals used in biomedical research. Animal Welfare Information Center Newsletter 5, 11–13.

Troncy E, Besner J-G, Charbonneau R, et al. (1996) Pharmacokinetics of epidural butorphanol in isoflurane-anaesthetized dogs. J Vet Pharmacol Therap 19, 268–273.

Vachharajani NN, Shyu WC, Garnett WR, et al. (1996) The absolute bioavailability and pharmacokinetics of butorphanol nasal spray in patients with hepatic impairment. Clin Pharmacol Ther 60, 283–294.

Waterman AE, Livingston A, Amin A (1991) Analgesic activity and respiratory effects of butorphanol in sheep. Res Vet Sci 51, 19–23.

Yamakoa K, Nakagawa T, Uno T (1978) Application of Aikake's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 6, 165–175.

Received 27 July 2000; accepted 5 February 2001.