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IMMOBILIZATION OF DOMESTIC GOATS (*CAPRA HIRCUS*) USING ORALLY ADMINISTERED CARFENTANIL CITRATE AND DETOMIDINE HYDROCHLORIDE

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Abstract: Eight domestic goats (*Capra hircus*) were anesthetized with a combination of carfentanil citrate and detomidine HCl, each at a dosage of 60 μg/kg, mixed with an equal volume of 0.5% saponin, an absorption enhancer. The drug combination was delivered by hand directly into the buccal cavity. Physiologic parameters were measured prior to drug administration and at 5-min intervals after the goats reached sternal recumbency. Depth of anesthesia was assessed at the same time intervals following drug administration. Blood was drawn prior to drug administration, at initial contact following sustained sternal recumbency, and at 15-min intervals thereafter. Serum carfentanil and detomidine levels were measured using slightly modified commercial enzyme-linked immunosorbent assay kits and techniques. Mean (±SD) induction time (time from drug administration to sternal recumbency) was 22 ± 4.3 min (n = 8), and inductions were characterized by long excitement phases (9.3 ± 5.8 min). There was considerable variation in the depth of anesthesia. Three goats appeared to be lightly anesthetized, two goats showed moderate levels of anesthesia, and three goats attained levels of anesthesia adequate for the performance of minor veterinary procedures. Physiologic changes caused by the drug combination were minor and were consistent with changes seen with parenteral administration of these drugs. Serum carfentanil levels were greatest at the time of initial contact for three goats and greatest 15 min later for two other goats. Levels then decreased slightly during the procedures, suggesting carfentanil absorption in these animals was across the oral mucosa. Serum detomidine levels rose gradually throughout anesthesia. Reversals with naltrexone and yohimbine or atipamezole were rapid and smooth.

Key words: Anesthesia, oral administration, *Capra hircus*, carfentanil, detomidine, goat.

INTRODUCTION

Potent opioids have been used worldwide for the chemical immobilization and capture of a wide variety of zoo and wildlife species. Opioid anesthetic agents have allowed zoo and wild animal veterinarians to restrain animals for a variety of routine and emergency procedures and are essential to the practice of zoological veterinary medicine.[5]

Opioids are usually administered parenterally, either by physically restraining the animal and injecting the drug or by using remote injection delivery systems, such as darts. However, these methods become difficult in free-ranging animals, where physical restraint is often impossible and administration of drugs by darting is not always feasible. Darting also carries the associated risks of injury to the animal, e.g., bone fracture, muscle trauma, and thoracic and abdominal injections. The capture of wild animals is inherently stressful for the animal, particularly if the capture attempt is prolonged, and can lead to a number of complications such as hyperthermia and capture myopathy.[3,5]

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Opioids are effectively absorbed through mucous membranes in human volunteers, and this route of administration provides equal or enhanced bioavailability when compared with oral and parenteral routes.[17–19] Orally administered carfentanil citrate has been used successfully to immobilize white-handed gibbons (*Hylobates lar*)[12] and, in a honey vehicle, to immobilize black bears (*Ursus americanus*).[13] Preliminary studies in elk (*Cervus elaphus*) suggest the potential for use in wild ungulates.[10]

Detomidine is an alpha-2 agonist with sedative, analgesic, and muscle relaxant properties. Alpha-2 agonists are often used in combination with opioids to enhance the quality of immobilization.[4,5] Detomidine is also transmucosally absorbed when administered sublingually for sedation of domestic horses (*Equus caballus*).[9]

The purposes of this study were to evaluate the effectiveness of orally administered carfentanil citrate and detomidine HCl for chemical immobilization of domestic goats, to investigate the use of permeation enhancers to improve these drugs' absorption, and to examine the cardiopulmonary effects of this route of administration. The kinetics of these drugs were studied to identify absorption rates and assist in developing a better dosage regimen. The domestic goat (*Capra hircus*) was chosen as a model for captive and free-ranging exotic ungulates.

MATERIALS AND METHODS

This study was approved by the University of Tennessee and the Knoxville Zoological Gardens Animal Care and Use committees. Eight female domestic goats weighing 21.8–36.8 kg (29.14 ± 5.5 kg, mean ± SD) and housed in an indoor/outdoor enclosure at the Knoxville Zoological Gardens (Knoxville, Tennessee) were used in the study. They were fed a mixture of hay and a commercial pelleted ration and allowed water ad lib. They were assessed to be healthy by physical examination, complete blood cell count, and serum chemistry analysis. The animals were kept from food for 12–24 hr prior to drug administration.

Preanesthetic rectal temperatures were taken using a thermometer, heart rates were measured by thoracic auscultation using a stethoscope, and respiration rates were measured by observing thoracic movements. The goats were then physically restrained, and the drug mixture was administered directly into the buccal cavity using a 3-ml syringe without a needle.

Based on data from preliminary trials, a combination of carfentanil citrate (Wildlife Laboratories, Fort Collins, Colorado 80524, USA; 3 mg/ml) and detomidine HCl (SmithKline Beecham, West Chester, Pennsylvania 19380, USA; 10 mg/ml), each at a dosage of 60 μg/kg, were used in the study. Saponin (0.5%) (Sigma Chemical Co., St. Louis, Missouri 63178, USA), an absorption enhancer, was added to the drug combination. The volume of saponin added was equal to the volume of the drug combination; total volume delivered to the goats ranged from 1.0 to 1.9 ml.

The depth of anesthesia was assessed every minute during induction. Induction time was defined as the time from administration of the drug to sustained sternal recumbency. Any excitement that occurred during induction was noted. Excitement was defined as excessive vocalization, prancing, ataxia, or hypermetric gait. The animals were not intubated and were allowed to breathe ambient air spontaneously while anesthetized.

Upon adoption of sustained sternal recumbency (time of intial contact = $t - 0$), each animal was manually restrained and positioned in right lateral recumbency. Temperature, pulse and respiration rates were measured every 5 min for 45 min. Indirect systolic, mean, and diastolic blood pressure measurements were made every 5 min for the same duration using an automated blood pressure monitor (Dinamap 8300, Critikon, Tampa, Florida 33634, USA) with a size 5 neonatal cuff attached around the left metacarpal region. Hemoglobin saturation (Spo_2) was also measured at the same intervals using a pulse oximeter (Ohmeda Biox 3700, Ohmeda, Louisville, Colorado 80027, USA), with the probe placed on the buccal mucous membranes. Hemoglobin saturation readings were recorded only if the instrument indicated that an adequate signal was received from the probe. Blood samples were obtained via jugular venipuncture at initial contact and at 15, 30, and 45 min after initial contact.

Depth of anesthesia was assessed every 5 min by recording palpebral reflex, presence of nystagmus, and level of muscle relaxation. A strong, brisk blink elicited by gentle touching of the medial canthus of the eye was considered to be a normal palpebral response. Muscle relaxation was noted as poor, moderate, or good based on the resistance to flexion and extension of a hind limb and on the degree of muscle rigidity. Animals were judged to be lightly anesthetized if they had poor muscle relaxation, varying degrees of body movements, especially head movements and occasional kicking, and lateral nystagmus throughout anesthesia. Normal palpebral reflexes were present in lightly sedated goats. Animals were judged to have a moderate level of anesthesia if muscle relaxation was moderate and occasional nystagmus and delayed palpebral reflexes were present. Animals were considered adequately anesthetized if they permitted the performance of minor veterinary procedures, such as blood collection, without movement and had adequate muscle relaxation and no palpebral reflexes or nystagmus.

At 45 min, the opiate antagonist naltrexone HCl (Wildlife Laboratories) was administered (2.25 mg/kg i.v., 0.75 mg/kg s.c.) with yohimbine (Sigma Chemical Co.; 0.375 mg/kg i.v.) or atipamezole (Antisedan, Norden Laboratories, Stevenage, UK; 0.30 mg/kg i.v.). The stage of recovery was noted at 1-min intervals. Recovery time was defined as time from administration of the reversal agents to when ambulation ability returned.

Interval data were evaluated for normal distribution. Mean values for heart rate, respiratory rate, body temperature, systolic, diastolic, and mean blood pressure, and Spo_2 prior to and upon induction of anesthesia and at specific time intervals up to 45 min after induction of anesthesia were analyzed with analysis of variance for repeated measurements. Fisher's LSD test was used to examine specific contrasts.[14] Other statistical comparisons were performed using unpaired t-tests. $P \leq 0.05$ was considered statistically significant.

All samples were analyzed using specific detomidine and carfentanil enzyme-linked immunosorbent assays (ELISAs) (ELISA Technologies, Lex-

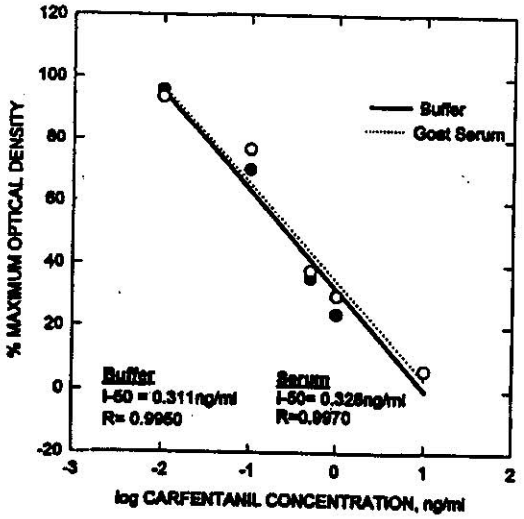

Figure 1. Carfentanil ELISA standard curves determined in phosphated buffer solution and goat serum.

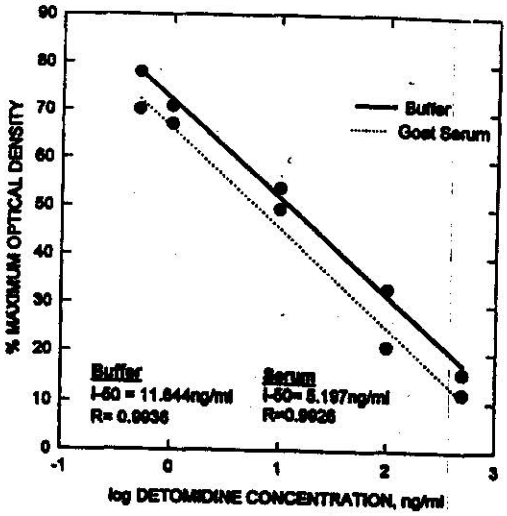

Figure 2. Detomidine ELISA standard curves determined in phosphated buffer solution and goat serum.

ington, Kentucky 40505, USA). Authentic detomidine or carfentanil standards were prepared in methanol and diluted to appropriate concentrations in assay buffer (0.1 M potassium phosphate-buffered saline (PBS), pH 7.4, with 0.1% bovine serum albumin).

All assays were performed at room temperature, using a method similar to one previously described.[15] For each assay, 20 µl of standard, test, or control samples was added to each well with 160 µl of detomidine– or carfentanil–horseradish peroxidase (HRP) conjugate solution and 20 µl of blank goat serum. After 1 hr incubation, the wells were washed with wash buffer (0.01 M phosphate buffer, pH 7.4, with 0.05% Tween-20), and 150 µl of Kentucky (KY) blue substrate (ELISA Technologies) was added to each well. The optical density (OD) of each well was read at a wavelength of 650 nm with an automated microplate reader (EL310 Microplate Autoreader, Bio-Tek, Winooski, Vermont 05404, USA) approximately 60 min after addition of the substrate. Samples exceeding the OD of the high standard were diluted appropriately with assay buffer and reanalyzed.

During the assay, the presence of unbound detomidine or carfentanil in the standard or test sample competitively prevented the binding of the detomidine–or carfentanil–HRP complex to the antibody present in the antiserum. Because the reaction of KY blue substrate with HRP was responsible for the color (blue) production in the ELISA, the apparent concentration of detomidine or carfentanil in the sample was inversely related to the OD of the well. Apparent detomidine or carfentanil concentrations in biologic specimens were calculated based on the results of standards that were run in duplicate with each individual assay in addition to 20 µl of blank goat serum.

Inter- and intra-assay precision levels for these tests were, respectively, 2.93% and 3.63% for detomidine and 6.02% and 3.68% for carfentanil. Intra-assay precision was based on comparisons of 96 data points, and interassay precision was based on comparisons among 12 data sets per assay. All precision assays were carried out in the absence of biologic matrices. All standard curves were first determined in the absence of biologic matrices in PBS and then in the presence of the biologic matrix being evaluated.

Goat serum showed no significant biologic matrix effects in these assays. For the carfentanil assay, the drug concentration that showed 50% the color activity of the zero standard (I-50) was 0.311 ng/ml; the r value in PBS was 0.995. These data (Fig. 1) show no influence of goat serum on the efficacy of the carfentanil ELISA. Similarly for the detomidine assay (Fig. 2), the standard curve in PBS yielded I-50 and r values of 11.6 ng/ml and 0.993, respectively; the standard curve in goat serum yielded a similar r value and slightly greater I-50 value. Goat serum did not significantly reduce the ability of either of these tests to detect carfentanil or detomidine in goat serum, when compared with the efficacy of these tests in PBS.

The carfentanil ELISA was raised against an antibody to parent carfentanil and is exceptionally sensitive to parent carfentanil, with an apparent I-50 for this agent of about 100 µg/ml and no cross-

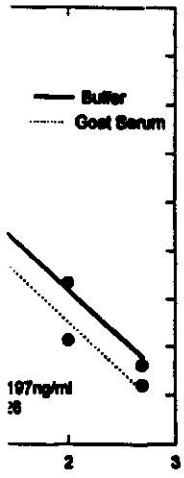

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Table 1. Cross-reactivity of carfentanil ELISA with related compounds.

Compound	Cross-reactivity (%)
Carfentanil	100
Sufentanil	0.5
Alfentanil	0.2
Fentanyl	0.06
Lofentanil	0.04
Norsufentanil	<0.05
-Methylfentanyl	<0.01
3-Methylfentanyl	<0.01
p-Methylfentanyl	<0.01
Thienylfentanyl	<0.01

Table 2. Cross-reactivity of detomidine ELISA with related compounds.

Compound	Cross-reactivity (%)
Detomidine metabolite	100
Detomidine	75
Medetomidine	11.3
Xylazine	0.02
Acepromazine	<0.01
Epinephrine	<0.01

reactivity for related agents (Table 1).[2] As such, the material detected in goat serum shortly after oral administration of this agent is likely to be predominantly parent carfentanil. The detomidine ELISA, however, was raised against a detomidine metabolite hapten.[16] The antibody cross-reacts strongly (75% cross-reactivity; Table 2)[2] with parent detomidine, and the detomidine metabolite is unlikely to develop substantial steady-state concentrations early in the drug absorption process.

RESULTS

Results are reported as means ± SD (n = 8). The induction time was 22.0 ± 4.3 min. Onset of anesthesia was characterized by an excitement phase lasting 9.3 ± 5.8 min. Bruxism was seen during induction in approximately half of the goats immobilized. There was also considerable variability in depth of anesthesia. Three animals were assessed as lightly anesthetized. Two animals appeared to have moderate depths of anesthesia. Three animals had anesthesia levels that were adequate for the performance of minor veterinary procedures. No anesthetic complications were seen, although occasional mild abdominal distention was observed in some goats but resolved upon anesthetic reversal.

There was a gradual but significant decrease in temperature over the duration of immobilization (Fig. 3). There were also significant decreases in heart rates at 10–45 min postcontact compared with the precontact and t −0 heart rates (Fig. 3). No abnormalities in heart rhythm were detected during thoracic auscultation. The mean respiratory rate remained steady throughout the anesthetic periods (25.0 ± 2.1 breaths/min), and no abnormal breathing patterns were observed. The Spo_2 remained >90% throughout the procedures (92.3% ± 0.9%). There were no significant changes in respiratory rate or Spo_2. There was an initial but nonsignificant rise in the mean blood pressure 10 min after initial contact, followed by a gradual decline (Fig. 3). The mean blood pressure at t −10 was significantly different from the mean pressures measured at t −30 and t −45.

All reversals were rapid and smooth. The mean recovery time was 3.2 ± 2.2 min (n = 5) for goats given naltrexone and yohimbine and 1.7 ± 0.9 min (n = 3) for goat given naltrexone and atipamezole. There was no significant difference in mean recovery times between animals given yohimbine and those given atipamezole. Excessive salivation was seen in approximately half of the goats immediately after anesthetic reversal. There were no episodes of renarcotization, although a few of the goats appeared sedate for 1–2 hr after reversal.

Carfentanil was rapidly absorbed in some goats and poorly absorbed in others (Fig. 4). The two goats with the highest serum carfentanil levels at t −0 (>15 mg/ml) also showed the most rapid inductions and best muscle relaxation of all the goats anesthetized. The two goats with the lowest peak serum carfentanil levels were considered the most lightly anesthetized. One goat with an early, large serum concentration (17.4 mg/ml at t −15) experienced light anesthesia, and one goat with a relatively low peak serum carfentanil concentration (6.0 mg/ml at t −30) was adequately anesthetized.

Serum detomidine levels rose gradually for all goats throughout the study (Fig. 5). In only one goat did serum detomidine levels peak prior to the 45-min sample. There did not appear to be any clear correlation between serum detomidine absorption and either induction time or depth of anesthesia.

DISCUSSION

The induction time for orally administered carfentanil and detomidine immobilization of domestic goats was markedly longer than that for parenteral administration of the same drugs in goats and in captive nondomestic hoofstock (JMS, unpubl.

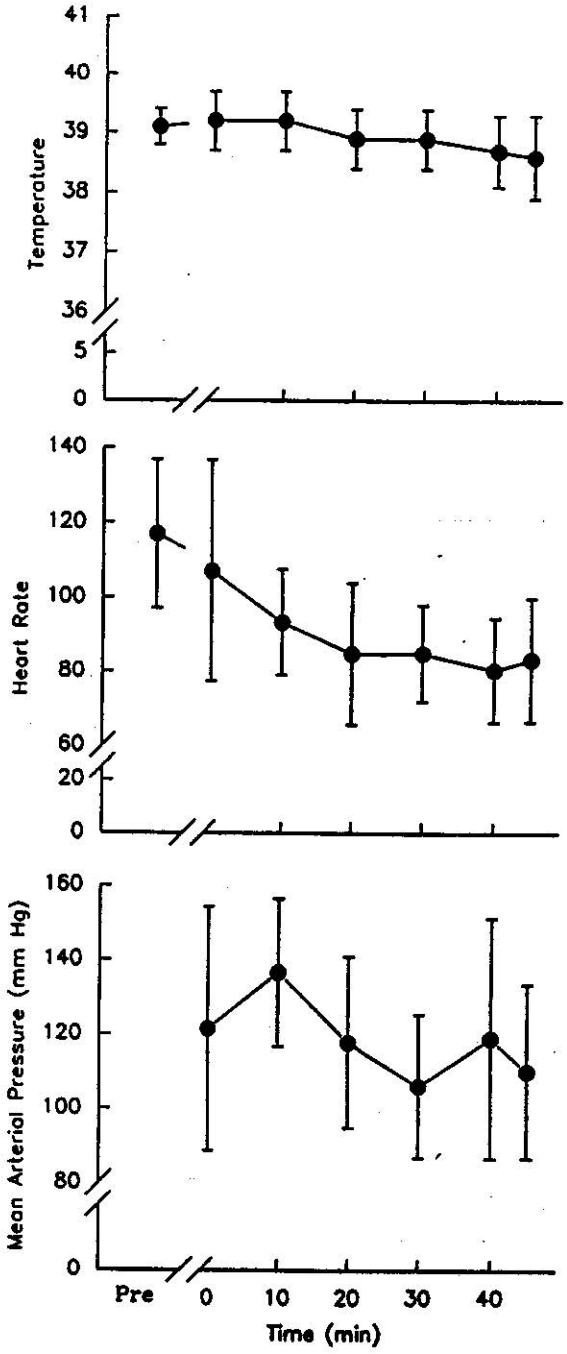

Figure 3. Changes in temperature, heart rate, and arterial pressure (mean ± SD) in eight goats after oral administration of 60 μg/kg each of carfentanil citrate and detomidine HCl plus a saponin solution. Measurements were made prior to drug administration (Pre), at initial contact (sustained sternal recumbency, min 0), and at indicated intervals thereafter.

data).[1] More excitation was present during induction than desired. Excitement during induction was characterized by a prolonged period of prancing and hypermetria. Prolonged inductions and excitement phases were some of the specific side effects this delivery technique was intended to avoid.

There was also considerable variability in the depth of the anesthesia. Serum drug concentrations suggest that the initial anesthetic effects were largely due to the carfentanil. Individual variation in carfentanil absorption appears to be one of the most important factors affecting immobilization. Goats judged to have moderate or adequate levels of anesthesia generally had higher serum carfentanil levels than did goats that were only lightly anesthetized. The effects of detomidine early in the immobilizations were probably minimal. Many animals seemed to become more sedate over the monitoring period possibly because of the calming effects of detomidine as it was absorbed over time. One goat with high serum carfentanil and detomidine levels became only lightly anesthetized, and one goat with low serum levels of both drugs was considered adequately anesthetized, suggesting that individual variation is a major factor in determining response to this method of anesthetic drug administration.

Permeation enhancers, i.e., surfactants that improve the absorption of compounds across mucous membranes, have been used to promote the transmucosal absorption of many polypeptide drugs, such as insulin.[11] During the preliminary trials, the absorption enhancer appeared to slightly decrease the induction times, but too few trials were performed to allow a statistical comparison. The choice of concentration of the absorption enhancer solutions was based on previously established effective concentrations for the ocular absorption of insulin in domestic cats (*Felis domesticus*).[11] These concentrations or compounds may be inappropriate for the buccal absorption of opioids. Further studies are needed to investigate possible methods of reducing induction times.

Other factors, such as the pH of the drug mixture and of the animal's saliva and mucous membranes, were not considered in this study. Nonpolar molecules penetrate more readily than do ions, and therefore the pH will affect the absorption by determining the relative concentration of ionized and un-ionized forms.[20] Opioids are weak bases; therefore, in a basic environment, the un-ionized form is favored, theoretically improving transmucosal absorption. The fate of the drug if swallowed may also affect induction time and depth of anesthesia. The serum carfentanil levels were greatest in most

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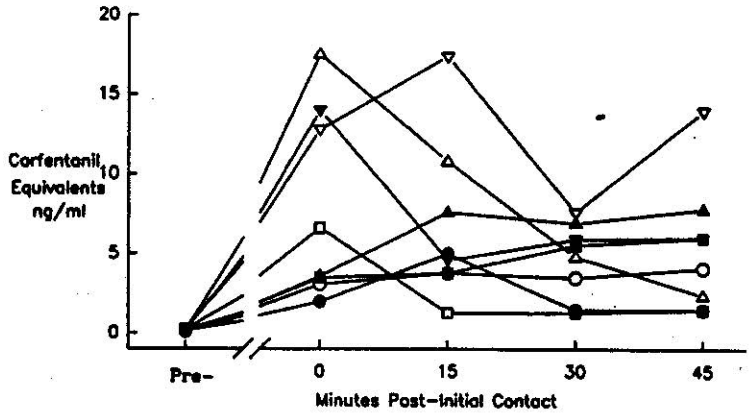

Figure 4. Mean (±SD) serum concentrations of apparent carfentanil equivalents from eight goats after oral administration of 60 µg/kg each of carfentanil citrate and detomidine HCl plus a saponin solution. The drug combination was administered after the pretreatment blood samples were drawn. Samples were drawn prior to drug administration (Pre), at initial contact (sustained sternal recumbency, min 0), and at 15-min intervals thereafter.

goats in this study at time of initial contact, suggesting that maximum drug absorption occurred in the first 20 min after administration. Absorption appears to take place primarily in the oral mucosa rather than in the lower gastrointestinal tract.

The physiologic changes observed in this study were similar to those seen in previous studies of parenteral administration of these two drugs. There appear to be few novel physiologic side effects associated with oral administration. Although the decrease in body temperature was significant, the 0.5°C drop is probably not clinically important. However, if the anesthesia were prolonged, any further drop in temperature could lead to hypothermia.

A significant bradycardia occurred, with the drop in heart rate occurring during induction and during early anesthesia, from t −0 to t −15. Given the serum levels of the two drugs, this effect can most likely be attributed to the carfentanil. In our study, a decrease in heart rate was observed in domestic goats given i.v. and i.m. etorphine or carfentanil.[6,7] The effect was not significant when the drugs were given i.v. but was significant when they were given i.m. These results contrast with those from another study, which showed an increase in heart rate in domestic sheep given i.m. carfentanil and xylazine[4] and from a study in which impala were given i.m. carfentanil by dart.[8] These differences may be due to species-specific responses to the drugs.

In previous studies, a significant bradypnea has been reported in domestic goats given parenteral carfentanil;[6,7] however, in the present study there

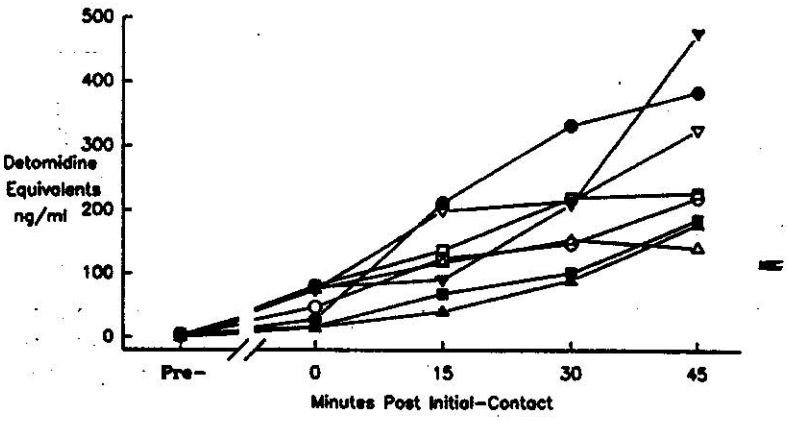

Figure 5. Mean (±SD) serum concentrations of apparent detomidine equivalents from eight goats after oral administration of 60 µg/kg each of carfentanil citrate and detomidine HCl plus a saponin solution. The drug combination was administered after the pretreatment blood samples were drawn. Samples were drawn prior to drug administration (Pre), at time of initial contact (sustained sternal recumbency, min 0), and at 15-min intervals thereafter.

was no change in the mean respiratory rate. The mean Spo_2 remained >90% during anesthesia, and the goats remained reasonably well oxygenated. Few studies have measured peripheral oxygen saturation in animals anesthetized with carfentanil. The results reported here are in contrast with the marked hypoxemia seen in impala immobilized with carfentanil.[8] However, no mention was made of the signal quality in that study, and the low relative oxygen saturation may be a result of inadequate probe placement or may have been compromised by intense peripheral vasoconstriction. The changes in blood pressure measurements were also similar to those described in domestic goats given i.v. and i.m. carfentanil.[6,7]

Because of the uncertainty of the identity of the materials reacting in the immunoassays, all data based on immunoassay tests must be interpreted with caution. Here, we present all data points as drug equivalents. However, because of the very low concentrations of reactive material in these samples and the limited volume of sample available, immunoassay testing is essentially the only viable approach. For the carfentanil data the material interacting with the ELISA test probably is predominantly carfentanil, because of the high sensitivity of this assay and the likelihood of rapid absorption of the carfentanil. Interpretation of the detomidine data is less clear cut; this antibody reacts slightly more readily with an equine urinary metabolite of detomidine than with the parent detomidine. Again, values at the earlier times probably are predominantly due to parent detomidine, because absorption of this drug is rapid and detomidine metabolites probably would not attain significant early serum concentrations after oral administration.

The oral administration of carfentanil may be a useful alternative in ungulates in certain circumstances but currently appears to have few advantages over darting. For oral detomidine to contribute to anesthesia in the goat, it should be given ≥1 hr prior to administration of carfentanil. The development of formulations that enhance absorption and of bait systems that would be taken free choice would improve the usefulness of this technique. Exploration of other more rapidly absorbed supplemental drugs may also be useful and allow immobilization trials to be extended to captive nondomestic hoofstock and free-ranging ungulates.

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