CLINICAL EFFICACY AND PHARMACOKINETICS OF HYDROCODONE/ACETAMINOPHEN AND TRAMADOL FOR CONTROL OF POSTOPERATIVE PAIN IN DOGS

by

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Abstract

Hydrocodone and tramadol are opioid analgesics. No studies have been performed to evaluate the clinical efficacy or pharmacokinetics of hydrocodone/acetaminophen and tramadol in a heterogenous population of dogs. The efficacy of tramadol in dogs has been questioned based on previous pharmacokinetic data. The objectives of this study were to evaluate the analgesic effects of hydrocodone/acetaminophen and tramadol measured by a success/failure model and to determine the pharmacokinetic profile of each drug following the second oral drug dose administration.

Fifty client-owned dogs presenting for routine tibial plateau leveling osteotomy were randomized to receive either oral hydrocodone/acetaminophen or tramadol in the postoperative period. A blinded investigator using a modified Glasgow Composite Measure Pain Scale scored each animal. Treatment failures were recorded and compared statistically for differences between the two groups. Blood sampling for pharmacokinetic analysis was initiated after the second oral dose.

Mean ± SE dose of hydrocodone/acetaminophen administered was 0.51 ± 0.04 mg/kg and 16.6 ± 1.41 mg/kg for hydrocodone and acetaminophen, respectively. Mean ± SE dose of tramadol administered was 5.91 ± 0.61 mg/kg. The terminal half life, maximal serum concentration (C_{max}) and time to maximal serum concentration (T_{max}) for tramadol were approximately 1.56 hours, 155.6 ng/mL and 3.90 hours, respectively. Plasma concentrations of the active metabolite O-desmethyltramadol (M1) were low. For hydrocodone, the C_{max} and T_{max} were approximately 7.90 ng/mL and 3.47 hours, respectively. Plasma concentrations of hydromorphone were low after oral hydrocodone administration.

Eighteen of 48 (37.5%) dogs required additional rescue analgesic therapy. This included 10 dogs in hydrocodone group and 8 dogs in the tramadol group ($p=0.628$).

In a group of postoperative patients, no difference in pain scoring could be detected in hydrocodone/acetaminophen and tramadol groups. The pharmacokinetics of tramadol and metabolites were similar to previous studies. Wide variations existed in tramadol drug concentrations and the effects of tramadol are likely independent of the μ-opioid receptor. There

is poor metabolism of hydrocodone to hydromorphone in dogs, however, efficacy may be achieved through hydrocodone. The analgesic efficacy of tramadol, 5-7 mg/kg PO q 8 h, and hydrocodone, 0.5 mg/kg PO q 8 h, should be assessed further prior to widespread use in canine postoperative patients.

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Chapter 1 - Clinical Efficacy of Hydrocodone/APAP and Tramadol for Control of Postoperative Pain in Dogs

INTRODUCTION

Optimal pain relief following surgery is most often provided with the use of opioid analgesics with or without the addition of non-steroidal anti-inflammatory drugs (NSAIDs). Tramadol[a] is a synthetic opioid that is commonly used for analgesia in dogs. Tramadol is reported to have weak μ-receptor affinity as a parent compound, but its metabolites are reported to be more potent.[1] One active metabolite (O-desmethyltramadol or M1) exerts most of its pharmacological effects as a high-affinity opiate μ-receptor agonist and is highly correlated to analgesic activity in humans.[1,2] The metabolite (N-desmethyltramadol or M2) is present in dogs, but is considered an inactive metabolite in several species.[3] Unlike humans, this inactive metabolite (M2) was found to be a major metabolite in dogs that exceeded concentrations of tramadol and M1.[4-6] In addition to its opioid receptor activity, tramadol can act as a serotonin and norepinephrine re-uptake inhibitor. Only a few studies have been conducted to evaluate the pharmacokinetics of tramadol following oral administration in dogs. There are large divergences in reports of the bioavailability of 65%[7] and 10%[5] in regards to the oral tramadol tablets. Given the aforementioned discrepancies in the bioavailability of oral tramadol tablets, many veterinarians anecdotally question its clinical efficacy, despite the frequent clinical use of tramadol.

Hydrocodone[b] (HC) is also an opioid analgesic and is a semisynthetic derivative of codeine. Hydrocodone is metabolized to hydromorphone and is approximately equipotent to morphine in producing opiate effects.[8] Historically, it has been infrequently used as an oral opioid analgesic in veterinary medicine, but it is more commonly used as a potent antitussive agent in both human and veterinary patients. Recently, Kukanich et al. evaluated the pharmacokinetics of HC/acetaminophen and its active metabolite, hydromorphone (HM), after a single oral dose of HC/acetaminophen (0.5 mg/kg) in 6 healthy Greyhound dogs.[9] There are no clinical reports of oral HC/acetaminophen efficacy to treat postoperative pain in dogs.

It is widely accepted that advances in animal welfare and adequate patient care should include effective postoperative pain management. Postoperative pain identification and

administration of adequate analgesics is a necessary skill for any veterinarian practicing surgery. Unfortunately, pain assessment in animals is difficult because of lack of verbal communication with veterinary patients. Attempts to improve pain assessment in veterinary patients include employing the use of pain assessment rating systems such as the simple descriptive scale (SDS), numerical rating scale (NRS), and the visual analog scale (VAS).[10-13] At present, the only validated method for evaluating postoperative pain in dogs is the Glasgow Composite Measure Pain Score (GCMPS).[14,15] Reid et al. have modified the GCMPS for clinical use in the postoperative setting.[16]

The purpose of the present study is to evaluate the pharmacodynamics of multiple dosing of HC/acetaminophen and tramadol in the hospital setting and to compare the analgesic effects of the drugs using a composite pain scale. There are no previous reports of HC/acetaminophen used as a postoperative analgesic in dogs and these analgesics have not been compared clinically in dogs to determine the superior analgesic medication for postoperative patients. We hypothesized that an 8 hour dosing frequency of orally administered HC/acetaminophen would provide better postoperative analgesia than tramadol based on improved pain scores and decreased frequency of rescue therapy.

MATERIALS AND METHODS

We designed a prospective, randomized, blinded clinical study to compare the pharmacodynamics of hydrocodone/acetaminophen and tramadol in dogs. Fifty client-owned dogs admitted to Kansas State University Veterinary Health Center (KSU VHC) for TPLO to treat unilateral cranial cruciate ligament rupture were included in this study. Written informed consent was obtained from owners prior to enrollment of dogs in the study. This study was performed with approval from KSU Institutional Animal Care and Use Committee (IACUC) and in accordance with applicable local animal use regulations.

For all dogs enrolled, routine physical and orthopedic examinations were performed and recorded. Inclusion criteria consisted of dogs weighing greater than or equal to 10 kg and dogs with confirmed cranial cruciate ligament rupture based on physical examination and diagnostic imaging. Dogs suffering from chronic painful conditions or concurrent metabolic or systemic disorders were excluded from the study. Dogs receiving hydrocodone/acetaminophen or tramadol upon presentation for TPLO surgery were not included in the study. Dogs on non-steroidal anti-inflammatory medication were included in the study following discontinuation of the drug 24 hours prior to surgery and to preoperative pain assessments. Dogs were hospitalized and acclimated to a quiet location in the hospital so that accurate behavioral assessment could be made. A CBC, blood chemistry, and urinalysis were performed preoperatively in all dogs.

Dogs were randomly assigned to receive either HC/acetaminophen[b] (0.5-0.6 mg/kg hydrocodone by mouth every 8 hours; Group H) or tramadol[a] (5-7 mg/kg by mouth every 8 hours; Group T) postoperatively. Treatment variability using this study design was unknown prior to the start of this study. Based on the clinical experience of the investigators, a target enrollment of at least 25 dogs in each treatment group was considered sufficient.

Anesthesia and Surgery Protocol

Each animal was considered an adequate candidate for anesthesia and American Society of Anesthesiologist (ASA) scores were recorded for each patient. Only dogs with an ASA score of 1 or 2 (indicating mild to no systemic disease present) were included in the study. All dogs were treated with a similar anesthetic protocol of morphine in conjunction with acepromazine or midazolam as premedication. Anesthesia was induced with propofol. Dogs were intubated and anesthesia maintained with isoflurane in oxygen. Perioperative decisions requiring a change to

the anesthetic and/or surgical protocol were based on the clinical judgment of the veterinarian assigned to each patient and were based solely in the best interest of the patient. These cases were excluded from the study.

TPLO surgical procedures were performed as described by Slocum and Slocum[17] by a Diplomate of the American College of Veterinary Surgeons or surgical resident with supervision. All dogs were given an intra-articular injection of 0.5% bupivicaine at 0.5-1.5 mg/kg administered prior to the end of the surgery for additional perioperative analgesia. Variations in surgical procedure including arthrotomy, menisectomy, and/or meniscal release were recorded. In addition, length of surgery and surgeon were also recorded.

Analgesic Administration Protocol

The timing of the initial postoperative administration of the drugs varied based on the clinical presentation of the individual patient, however, all dogs were given one dose of morphine 0.25-0.5 mg/kg parenterally immediately following surgery or up to 4 hours postoperatively. Oral administration of analgesic medication began when patients were awake, alert and able to swallow without difficulty, and continued at 8-hour intervals. Heart rate, respiratory rate and temperature were recorded for each patient one hour prior to surgery, and immediately postoperatively followed by every 8 hours until discharge from hospital.

Pharmacodynamic Analysis

Each patient was evaluated by a blinded assessor (XXX) who was thoroughly trained in the use of the modified short form GCMPS.[16] Pain scoring assessments were initiated following the second dose of oral medication administration. Due to the IACUC protocol, each patient was only allotted up to 5 assessment points to minimize handling. Pharmacodynamic analysis was based on a staggered collection of scores from the patient population so that analysis could be performed at times 0, 15 min, 30 min, 45 min, 1, 2, 4, 6, and 8 hours after the second dosage of analgesic. Cumulative scores at individual time points ranged from 0 (least painful) to 24 (most painful) when dogs were mobile and 0 to 20 when dogs were not mobile. A score of greater than or equal to 6/24 or 5/20 was defined as treatment failure and injectable morphine at a dose of 0.25-0.5 mg/kg was given. Both treatment groups were compared for patient, surgical, and drug factors that could affect their postoperative pain scores and a success/failure model was used to

determine the clinical efficacy of oral drug formulation. Pain scores were used to determine the overall efficacy of oral drug formulation.

All dogs were observed for adverse reactions following oral pain medication therapy. Adverse reactions were characterized as minor if they were self-limiting and did not require additional therapy. Minor reactions included sedation, dysphoria, inappetance, constipation without the need for laxatives/stool softeners or manual evacuation, or limited episodes of regurgitation and/or vomiting. Major adverse reactions were those that required active medical intervention and included continued vomiting/regurgitation (>2x in 12 hour period), diarrhea, dysphoria requiring sedation, constipation requiring laxatives/stool softeners or manual evacuation, or seizures.

Statistics

Nonparametric mGCMPS scores were compared between treatment groups at each time period by Mann-Whitney U. Body weight and age were compared between treatment groups by independent group t-test. The number of rescues was compared between treatment groups by independent group t-test. The prevalence of adverse effects, prevalence of rescued versus not rescued, surgery on left versus right limb, procedure by ACVS-boarded surgeon or resident, and dogs receiving arthrotomy or not receiving arthrotomy were compared between groups by Chi-Square analysis. The number of rescued dogs was compared between arthrotomy/nonarthrotomy groups by Chi-Square analysis. Results were considered significant at $p \leq 0.05$.

RESULTS

Fifty client-owned dogs were enrolled in the study. Forty-eight dogs successfully completed the study with one dog lost from each group. One dog in the hydrocodone group was disqualified due to a breach in the standard anesthetic protocol. One dog in the tramadol group was not amenable to handling in the postoperative period despite additional rescue analgesia. Breeds of dogs included mixed breed dogs (n=16), Labrador Retrievers (n=11), Golden Retrievers (n=4), Rottweilers (n=2), Boxer (n=2), German Shepherd Dog (n=2), German Shorthair Pointer (n=1), Old English Sheepdog (n=1), Chesapeake Bay Retriever (n=1), English Pointer (n=1), Great Dane (n=1), Great Pyrenees (n=1), Doberman Pincher (n=1), English Springer Spaniel (n=1), Giant Schnauzer (n=1), Siberian Husky (n=1), Saint Bernard (n=1), and Viszla (n=1). There was no significant difference in mean body weights between the groups (H 34.4±7.85 kg, T 37.53±11.79 kg, p=0.421). The mean age of dogs enrolled was 5.1 ± 2.4 years. There was no significant difference in age between the drug groups (p=0.433).

Of the surgical and patient factors evaluated, the only statistically significant difference found between groups was the affected side. Eight of 24 dogs in group H had the left leg operated, whereas 18/24 (75%) dogs in group T had the left leg operated (p=0.004). Surgery was performed by an ACVS diplomate in 13/24 dogs in group H versus 10/24 dogs in group T (p=0.386). Based on surgeon preference, an arthrotomy was performed in 17/24 dogs in group H and 11/24 dogs in group T (p=0.234). There was no statistical difference in pain scores and need for rescue analgesic therapy based on whether or not an arthrotomy was performed (p=0.282).

Both drugs were well tolerated throughout the study period. Adverse events occurred in 3/24 (12.5%) dogs in group H versus 6/24 (25%) dogs in group T. This difference was not statistically different (p=0.464). Adverse events included self-limiting regurgitation (n=3 group H, n=5 group T), salivation (n=1 group H), and regurgitation requiring medical therapy (n=1 group T).

Overall, 18/48 (37.5%) dogs required additional rescue analgesic therapy based on their pain scores of ≥ 6/24 (mobile) or ≥ 5/20 (immobile). This included 10 dogs in the hydrocodone group and 8 dogs in the tramadol group (p=0.628). Three dogs in each drug group required more than one rescue analgesic based on the interventional score, though this difference did not reach statistical significance (p=0.566). Pain scores of the two drug groups at each individual time period were recorded (Table 1). During the evaluation period, both groups had similar pain

scores and there was no statistical difference in the score at any of the time points between the two drug groups. The 2-hour post drug administration pain score showed the greatest difference between the two drug groups; however, significance was not reached ($p=0.076$). In this time period of 8 dogs, power analysis at $\alpha=0.05$ indicates that 11 scores would have been needed to find a significant effect. Similar power analysis at other time periods indicated that up to 465 dogs would have been needed to find significant effects.

DISCUSSION

In this study, we compared the effects of HC/acetaminophen and tramadol administered postoperatively as analgesics for dogs undergoing unilateral TPLO. This is the first reported clinical study to evaluate the efficacy of oral HC/acetaminophen for postoperative analgesia in dogs. We found no significant difference in clinical analgesic effects of HC/acetaminophen or tramadol at the dosages administered used in this study. Modified Glasgow Composite Measure Pain Scores throughout the study period were similar between groups. Approximately 38% of dogs were rescued based on score alone. This is an unacceptably large number and may reflect inconsistencies or poor sensitivity in pain assessment by the scoring system or the low cut off levels for rescue analgesia. It may also represent the inability of either drug to produce acceptable levels of analgesia in the immediate postoperative period in this study.

Hydrocodone is a semisynthetic derivative of codeine. Historically, it has been used as an oral opioid analgesic as well as a potent antitussive agent in both human and veterinary patients. Hydrocodone is more bioavailable following oral administration at 39% [18] when compared to codeine (4-6.5%)[18,19] and its bioavailability is less variable than tramadol (10-65%).[5,7] Hydromorphone is a predictable metabolite in clinically relevant concentrations after oral administration of hydrocodone.[8,9,18] Drug concentrations of hydromorphone following hydrocodone administration were found to be 11-20x greater than the concentration of morphine after oral administration of codeine based on previous reports.[18] Kukanich et al. evaluated the pharmacokinetics of HC/acetaminophen and its active metabolite, hydromorphone, using a single dose of 0.5 mg/kg of HC/acetaminophen in 6 healthy Greyhound dogs.[9] From that study, both hydrocodone and its hydromorphone metabolite are present at high concentrations and every 6-8 hour dosing was recommended. Previous studies using intravenous hydromorphone suggest anti-nociceptive effects up to 4 hours with a concentration of hydromorphone near 1.6 ng/mL.[20,21] Based on those results and results from Kukanich's study, plasma concentrations of hydromorphone following oral hydrocodone administration are expected to exceed the previously published 1.6 ng/ml throughout the 8 hour dose interval period.

Hydrocodone is currently a schedule III controlled substance based on the Drug Enforcement Administration (DEA) classification. In general, schedule III substances have abuse potential and the combination of hydrocodone with acetaminophen (aka APAP/paracetamol) is the primary source of the drug.[22] This combination drug formulation is

considered a "diverted pharmaceutical" in order to deter addicts from consuming high doses of the drug. The mechanism of action of acetaminophen remains to be elucidated, but is thought to act in both cyclooxygenase pathway inhibition as well as contain some involvement with the serotonergic pathways. [23] At high doses acetaminophen is known to cause liver toxicity in dogs at dosages near 100 mg/kg.[24] Based on the average dog body weights and dosages used in this study, dosages of acetaminophen did not exceed 18 mg/kg per dose of hydrocodone administered. Acetaminophen in dogs is rapidly absorbed with peak concentrations reached within 60 minutes.[19, 24] Though acetaminophen may have contributed to the analgesic effects of hydrocodone, the drug's half life is short ranging from 0.5-3 hours following oral administration in dogs [19, 24] and it is not likely to contribute to analgesia throughout the entire study period.

Tramadol is a synthetic opioid analgesic that is widely used in human and veterinary medicine. It has a complex mode of action involving opioid receptors and inhibition of serotonin and norepinephrine transporters through its metabolism and available metabolite, O-desmethyltramadol or M1.[2, 25] There are several other metabolites of tramadol, however, the pharmacological effects have only been confirmed with M1 after routine tramadol administration in people. M1 acts as a high affinity opiate mu receptor agonist (>200 times as potent as tramadol) and can also act to inhibit serotonin and norepinenphrine re-uptake.[1, 25]

In humans, the pharmacological effects due to the M1 metabolite are highly related to tramadol's metabolism via cytochrome p450 enzymes, specifically, CYP2D6. This isoenzyme is responsible for tramadol's metabolism, however, it demonstrates extensive genetic polymorphism in humans leading to the belief that there are different phenotypes of the isoenzyme.[26] Phenotypes include ultra, extensive, and poor metabolizers of tramadol based on M1 concentrations following oral administration of tramadol. Previous drug failure rates among humans labeled as poor metabolizers of the drug are reported to be as high as 50%.[2] It is possible that the phenotypic expression of cytochrome p450 enzymes vary in canine species as well and may mimic human failure rates with drug administration if they are unable to metabolize tramadol well. To the authors' knowledge, the cytochrome p450 enzymes responsible for tramadol's metabolism have not been fully elucidated in the dog. Further investigations would be needed to determine the phenotypic expression on the cytochrome p450 enzyme responsible for tramadol metabolism, in order to predict poor metabolizers of the drug in our canine population.

Previous studies in dogs show very low M1 concentrations throughout the 8 hour time course. [4-6, 27] These are exceptionally low concentrations of the drug metabolite and not likely to be contributing to analgesic effects. In a previous study by Kukanich et. al, dogs given an oral tramadol dose close to 10 mg/kg showed minimal, if any, change in the concentrations of the M1 metabolite. However, concentrations of the parent tramadol compound reached very high concentrations >200 ng/ml. In that same study, a von Frey pressure threshold device showed anti-nociceptive effects to exist at 5-6 hour post drug administration. M1 concentrations at that time point were < 1 ng/ml and not believed to be contributing to analgesic effects. [6]

Canine species, unlike humans, must rely on the activity of other potential metabolites and/or the parent tramadol compound for analgesic effects. This may make tramadol a less effective analgesic in dogs than in people. If the antinociceptive effects in dogs are due to tramadol alone and not M1, then the effects may be independent of opioid receptor activity all together. Though the parent compound tramadol acts as a low affinity opiate mu receptor agonist, it can also act as a serotonin and norepinephrine reuptake inhibitor based on the complementary action of its two enantiomers and those actions may play a big role to enhance inhibitory effects on pain transmission. Additionally, previous reports of the large range of bioavailability suggests variable clinical efficacy of tramadol in dogs. The findings of two previous reports of bioavailability of tramadol following oral administration in dogs varied in the method of metabolite analysis. [5,7]

In this study, pain scoring was performed using a modified Glasgow Composite Measure Pain Score under a sole blinded assessor. Accurate pain assessment in veterinary patients is challenging, however, the mGCMPS aims to use an animal's behavior in 6 different categories to detect pain. Using these 6 categories allows for more than one aspect of postoperative pain to be evaluated through spontaneous and evoked behaviors, interactions with people, and clinical observations within a clinical practice setting. The mGCMPS provides a degree of consistency that allows for the adequate evaluation because each behavior category assessed has specific definitions of behavior descriptors that avoids bias. This scoring system also allows for assignment of a number to a behavioral category. Numeric scores allow for an easy method to tabulate a cumulative score. Scores have been shown to provide a descriptive and repeatable assessment of pain. [16] This scoring system has been used successfully in other animal studies to differentiate among severities of pain and to monitor changes in pain intensity over time. [28, 29]

This study required one individual experienced in assessing pain be assigned to evaluate dogs at the designated times in order to reduce the variability in pain assessment scores between observers. Dogs were given rescue analgesics if they scored ≥6/25 or 5/20 on the mGCPS scoring system or if the assessor determined that pain intervention therapy was needed because of discomfort of the dog. This intervention score is corroborated by previous work demonstrating the same intervention decision point using the mGCPS scoring system.[16]

Though the mGCPS scoring system was developed to decrease variability in pain assessments, like other pain scales, it still relies on subjective evaluations to measure treatment outcomes. Inability of the pain score in this study to detect a clinical difference in the efficacy of the two drugs may have been because the scoring system was not sufficiently sensitive to detect differing levels of pain in some dogs, differences between how dogs interacted with the blinded assessor, differences between how the assessor interpreted the scoring criteria, or that some dogs did not show signs of pain, or were truly not painful. Additionally, all dogs received intra-articular bupivacaine which may have provided analgesia that made differentiation of the effects of oral tramadol and hydrocodone more difficult. The use of other markers of pain could have been attempted in this study (pressure threshold devices, vital parameters, biochemical markers, and force plate gait analysis), however, each suffers from inconsistent data regarding the efficacy and use of those markers in recognition of pain in veterinary patients.

Other limitations of this study include the use of enrolled dogs of varied breed. Despite this limitation, it accurately represents the population of dogs presenting for cruciate rupture at our hospital. Additionally, only 50 dogs were included for enrollment in this study. Based on the IACUC protocol, each patient was only allotted 5 assessment points in the postoperative period to minimize handling. A recent study by Coleman et al. evaluated wound sensitivity using a mechanical stimulus in order to detect postoperative pain.[30] In that study, the authors concluded that learning occurred over repeated collection time points, with dogs anticipating the stimulus and reacting at lower thresholds.[30] Because of that report and the IACUC protocol, assessments were limited per dog in order to avoid the anticipatory effects from the patients undergoing pain assessment. This, however, decreased the total number of dogs assessed at each individual time period. In addition, lingering effects of anesthesia and/or dysphoria also remain a concern for many postoperative pain studies. In this study, the first pain assessments were performed following the second dose of oral pain medication therapy. This allowed for pain scoring to

occur anywhere from 8 to 12 hours postoperatively. This includes a time in which the effects of anesthesia and injectable medication are expected to be negligible, but individual differences in the pharmacokinetics and effects of these drugs could have resulted in effects persisting in a small number of dogs in the assessment period.

Assessment of effective pain management relies on comparisons to treatments that may not have been definitively demonstrated to relieve pain (use of a positive control), or comparisons to animals that have not received perioperative pain management (use of a negative control group). Due to animal welfare reasons, a negative control group was not included in the study. Likewise, a gold standard analgesic has not been definitively demonstrated to serve as a positive control for use in this study and positive controls do not account for the sensitivity of the pain assessment method to determine truly effective analgesia versus inability to identify pain in stoic patients. The lack of a control group makes it difficult to conclude that either treatment provides the best analgesia for this procedure. Based on results from this study, the hypothesis was rejected that HC/acetaminophen could be detected as a clinically superior drug based on pain scores and need for rescue analgesic therapy.

CONCLUSIONS

This study represents the first clinical investigation of HC/acetaminophen for clinical analgesia in dogs. The analgesic effects of HC/acetaminophen and tramadol at the doses used in this study could not be differentiated based on pain score and the number of rescue drug therapies needed. Based on this study, HC/acetaminophen and tramadol are equipotent for postoperative analgesia. Considerations of need for analgesia, dosage and route requirements, and drug bioavailability in the individual dog should ultimately determine the best agent for analgesic therapy of a specific patient.

ABBREVIATIONS

TPLO, tibial plateau leveling osteotomy

mGCMPS, modified Glasgow Composite Measure Pain Scale

NSAIDs, non-steroidal anti-inflammatory drugs

HC, hydrocodone

HM, hydromorphone

SDS, simple descriptive scale

NRS, numeric rating scare

VAS, visual analog scale

IACUC, Institutional Animal Care and Use Committee

CBC, complete blood count

ASA, American Society of Anesthesiologist

APAP, acetaminophen/paracetamol

ACVS, American College of Veterinary Surgeons

DEA, Drug Enforcement Administration

FOOTNOTES

[a] Tramadol hydrochloride 50 mg, Amneal Pharmaceuticals LLC, Paterson, NJ, 07504, USA.

[b] Hydrocodone bitartrate 5 mg and 10 mg/Acetaminophen 325 mg, Qualitest Pharmaceuticals, Huntsville, AL, 35811, USA.

TABLES

Table 1—1 Median Modified Glasgow Composite Pain Scores (mGCPS) at individual time periods per drug group. H, hydrocodone; T, tramadol.

	Hydrocodone	Tramadol	P value	# dogs H	# dogs T
Pain Pre	1	1	0.477	24	24
Pain O min	3	3	0.725	10	17
Pain 15 min	4	3	0.759	16	8
Pain 30 min	2.5	3	0.462	8	16
Pain 45 min	3	3	0.951	16	8
Pain 1h	3	3	0.426	8	17
Pain 2h	3	4	0.076	16	8
Pain 4H	3	3	0.739	8	18
Pain 6H	3	3	0.877	16	9
Pain 8H	3	3	0.912	22	24

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Chapter 2 - Pharmacokinetics of Hydrocodone and Tramadol for Control of Postoperative Pain in Dogs

INTRODUCTION

Tramadol is a synthetic opioid that is commonly used for analgesia in dogs. It is reported to have very weak μ-receptor affinity as a parent compound, but one of its metabolites is reported to be more potent at the μ-receptor.[1] The active metabolite (O-desmethyltramadol or M1) exerts pharmacological effects as a high-affinity opiate μ-receptor agonist and is highly correlated to analgesic activity in humans.[1,2] The metabolite (N-desmethyltramadol or M2) is present in dogs, but is considered an inactive metabolite in several species.[3] Unlike humans, this inactive metabolite (M2) was found to be a major metabolite in dogs that exceeded concentrations of tramadol and M1.[4-6] In addition to its weak opioid receptor activity, tramadol can act as a serotonin and norepinephrine re-uptake inhibitor.[1,7] Only a few studies have been conducted to evaluate the pharmacokinetics of tramadol following oral administration in dogs and none in a heterogeneous clinical population.

Hydrocodone (HC) is also a μ opioid analgesic and is a semisynthetic derivative of codeine. Hydrocodone is metabolized in part to hydromorphone (HM) and is approximately equipotent to morphine in producing opiate effects.[8] Historically, it has been infrequently used as an oral opioid analgesic in veterinary medicine. Recently, Kukanich et al. evaluated the pharmacokinetics of HC and its active metabolite, HM, after a single oral dose of HC/acetaminophen (0.5 mg/kg) in 6 healthy greyhound dogs.[9] From that study, both HC and HM were present at clinically useful concentrations and every 6-8 hour dosing was recommended.

There are no previous reports of HC/acetaminophen used as a postoperative analgesic in dogs and the pharmacokinetics of both HC and tramadol have not been evaluated in a heterogenous population of dogs. The purpose of the present study is to determine the pharmacokinetics of multiple dosing of HC and tramadol in a heterogenous population of dogs in a clinical setting. We hypothesize that both drugs would be metabolized to active compounds. We hypothesize that tramadol concentrations would vary widely after oral administration and mimic previously described drug metabolite concentrations including low M1 concentrations and high M2 concentrations. We also hypothesize that HC would be metabolized to HM and be

present in measurable drug concentrations acceptable for clinical analgesia after oral HC administration.

MATERIALS AND METHODS

Animals

Fifty client-owned dogs admitted to Kansas State University Veterinary Health Center (KSU VHC) for TPLO to treat unilateral cranial cruciate ligament rupture were included in this study. Written informed consent was obtained from owners prior to enrollment of dogs in the study. This study was performed with approval from KSU Institutional Animal Care and Use Committee (IACUC) and in accordance with applicable local animal use regulations.

For all dogs enrolled, routine physical and orthopedic examinations were performed and recorded. Inclusion criteria consisted of dogs weighing greater than or equal to 10 kg and dogs with confirmed cranial cruciate ligament rupture based on physical examination and diagnostic imaging. Dogs suffering from chronic painful conditions or concurrent metabolic or systemic disorders were excluded from the study. Dogs with a history of recent HC or tramadol administration upon presentation for TPLO surgery were not included in the study. Dogs on non-steroidal anti-inflammatory medication were included in the study following discontinuation of the drug 24 hours prior to surgery. A CBC, blood chemistry, and urinalysis were performed preoperatively in all dogs.

Dogs were randomly assigned to receive either HC/acetaminophen[a] (0.5-0.6 mg/kg HC by mouth every 8 hours; Group H) or tramadol[b] (5-7 mg/kg by mouth every 8 hours; Group T) postoperatively.

Anesthesia and Surgery Protocol

Each animal was considered an adequate candidate for anesthesia and American Society of Anesthesiologist (ASA) scores were recorded for each patient. Only dogs with an ASA score of 1 or 2 (indicating mild or no systemic disease present) were included in the study. All dogs were treated with a similar anesthetic protocol of parenteral morphine in conjunction with acepromazine or midazolam as premedication. Anesthesia was induced with propofol to effect. Dogs were intubated and anesthesia maintained with isoflurane in oxygen. Perioperative decisions requiring a change to the anesthetic and/or surgical protocol were based on the clinical judgment of the veterinarian assigned to each patient and were based solely in the best interest of the patient. These cases were excluded from the study.

TPLO surgical procedures were performed as described by Slocum and Slocum[10] by a Diplomate of the American College of Veterinary Surgeons (ACVS) or surgical resident with supervision. All dogs were given an intra-articular injection of 0.5% bupivacaine at 0.5-1.5 mg/kg administered prior to the end of the surgery for additional perioperative analgesia.

Analgesic Administration Protocol

The timing of the initial postoperative administration of the drugs varied based on the clinical presentation of the individual patient, however, all dogs were administered one dose of morphine 0.25-0.5 mg/kg parenterally immediately following surgery or up to 4 hours postoperatively. Oral administration of the assigned test analgesic medication began when patients were awake, alert and able to swallow without difficulty, and continued at 8-hour intervals.

Blood Sample Collection and Rescue Therapy Protocol

For pharmacokinetic analysis, approximately 2-3 mls of venous blood was collected from a jugular or peripheral vein (cephalic and/or saphenous veins) by a surgical staff member following the second dose of oral medication administration. Samples were transferred into non-heparinized tubes and centrifuged. The serum was collected and stored in polypropylene vials at –80°C until the serum drug concentrations were determined.

Based on the IACUC approval, each patient was only allotted up to 5 blood samples postoperatively to minimize animal handling. Pharmacokinetic analysis was based on a staggered collection of blood samples from the patient population so that analysis could be performed at times 0, 15 min, 30 min, 45 min, 1, 2, 4, 6, and 8 hours after the second dosage of analgesic. In addition, each patient was evaluated at those time points by a blinded investigator (MB) with experience in evaluating pain in dogs in a clinical setting. The investigator was thoroughly trained in the use of the modified short form Glasgow Composite Measure Pain Scale (mGCMPS).[11] Cumulative scores had a possible range from 0 (least painful) to 24 (most painful) when mobility can be assessed and up to 20 when mobility cannot be assessed. A score of greater than or equal to 6/24 or 5/20 was defined as treatment failure and injectable morphine of 0.25-0.5 mg/kg was administered subcutaneously as rescue intervention. An additional blood sample was obtained at time of drug rescue therapy to determine the systemic drug concentration

at time of failure. Pharmacokinetic analyses were conducted after the second dose of oral medication.

Serum Drug Concentrations

Serum drug concentrations were determined using liquid chromatography with triple quadruple mass spectrometry according methods previously published in detail. [6,9] Standard curves for serum tramadol, M1, M2, and M5 were linear from 1-500 ng/mL and were accepted if the measured concentrations were within 15% of the actual concentrations. The accuracy of the assay for tramadol was 102, 103 and 95% and the coefficient of variation was 5, 1, and 3% on replicates of 5 at 1, 10, and 500 ng/mL, respectively. The accuracy of the assay for M1 was 103, 97 and 104% and the coefficient of variation was 5, 4, and 3% on replicates of 5 at 1, 10, and 500 ng/mL, respectively. The accuracy of the assay for M2 was 94, 100 and 96% and the coefficient of variation was 10, 4, and 4% on replicates of 5 at 1, 10, and 500 ng/mL, respectively. The accuracy of the assay for M5 was 101, 92, and 108% and the coefficient of variation was 5, 4, and 4% on replicates of 5 at 1, 10, and 500 ng/mL, respectively.

Standard curves for serum HC and HM were linear from 1-100 ng/mL and were accepted if the measured concentrations were within 15% of the actual concentrations. The accuracy of the assay for HC was 97, 102, and 106% and the coefficient of variation was 2, 4, and 5% on replicates of 5 at 1, 10, and 100 ng/mL, respectively. The accuracy of the assay for HM was 106, 98, and 104% and the coefficient of variation was 1, 2, and 5% on replicates of 5 at 1, 10, and 100 ng/mL, respectively.

Pharmacokinetic Analysis

Naïve pooled pharmacokinetic analysis was performed with computer software (WinNonLin 5.2, Pharsight Incorporated, Cary, NC, USA) using a one compartment first order model with absorption, no lag time and first order elimination. Uniform weighting was used. Population pharmacokinetic modeling of tramadol was performed with computer software (WinNonMix 2.0 Pharsight Incorporated, Cary, NC, USA) using a one compartment first order model with absorption, no lag time and first order elimination. The model equations for the primary model parameters were: V_F=V_F_0*exp(V_F_eta0) ; K01=K01_0*exp(K01_eta0) ; K10=K10_0*exp(K10_eta0).

RESULTS

Forty-eight client-owned dogs successfully completed the study. One dog in group H was disqualified due to a breach in the standard anesthetic protocol. One dog in group T was not amenable to blood sampling in the postoperative period. Breeds of dogs included mixed breed dogs (n=16), Labrador Retrievers (n=11), Golden Retrievers (n=4), Rottweilers (n=2), Boxers (n=2), German Shepherd Dogs (n=2), German Shorthair Pointer (n=1), Old English Sheepdog (n=1), Chesapeake Bay Retriever (n=1), English Pointer (n=1), Great Dane (n=1), Great Pyrenees (n=1), Doberman Pincher (n=1), English Springer Spaniel (n=1), Giant Schnauzer (n=1), Siberian Husky (n=1), Saint Bernard (n=1), and Viszla (n=1). There was no significant difference in mean body weights between the groups (H 34.4±7.85 kg, T 37.5±11.8 kg, p=0.42). The mean age of dogs enrolled was 5.1 ± 2.4 years. There was no significant difference in age between the drug groups (p=0.433).

Mean ± SE dose of HC/acetaminophen administered was 0.51 ± 0.04 mg/kg and 16.6 ± 1.41 mg/kg for HC and acetaminophen, respectively. Mean ± SE dose of tramadol administered was 5.91 ± 0.61 mg/kg.

The serum concentration–time profiles of tramadol (population pharmacokinetic model) and metabolites M1 and M5 (naïve pooled pharmacokinetic model) after administration were shown graphically (Figure 1 and 2, respectively). The metabolite M2 was not modeled as plasma concentrations continued to increase throughout the 8 hour sample collection interval (Figure 2). The associated pharmacokinetic parameters for tramadol (population and naïve pooled models) and M1 and M5 (naïve pooled model) were summarized in Tables 1 and 2, respectively. The parent compound tramadol, the active metabolite M1 and inactive metabolites M2 and M5 are illustrated in Figure 3. The inactive metabolite concentrations for M2 and M5 far exceeded the active metabolite concentrations for M1. The geometric mean population pharmacokinetics was similar to the naïve pooled pharmacokinetics for tramadol, despite the different methods of analysis (Tables 1-2). Based on the naïve pooled results for tramadol, the terminal half life, maximal serum concentration and time to maximal serum concentration were approximately 1.56 hours, 155.6 ng/mL and 3.90 hours, respectively. For M1, the terminal half life, maximal serum concentration and time to maximal serum concentration were approximately 4.67 hours, 4.6 ng/mL and 2.82 hours, respectively. The inactive metabolite, M2, was found in

high concentrations with no elimination or terminal phase noted and as such pharmacokinetic modeling was not performed.

Population pharmacokinetics were able to be fit to the data of the parent compound tramadol after oral administration (Table 1). The mean and associated ranges for terminal half life, maximal serum concentration and time to maximal serum concentration were approximately 1.58 hours (range, 0.78-3.93), 195.0 ng/mL (range, 46.8-613.0) and 3.54 hours (range, 1.77-6.96), respectively.

The serum concentration–time profile of HC after administration was presented graphically in Figure 4. The associated naïve pooled pharmacokinetic parameters of HC were summarized (Table 3). A population pharmacokinetic model did not fit the HC data. Hydromorphone (HM) metabolite was too infrequently measured to appropriately assess pharmacokinetic parameters and was only isolated in 3 of 24 dogs receiving HC analgesia. Based on the naïve pooled results for HC, the terminal half life, maximal serum concentration and time to maximal serum concentration were approximately 15.85 hours, 7.90 ng/mL and 3.47 hours, respectively.

The median drug serum concentrations at the time of rescue drug therapy were 232 (range 20.2 – 398 ng/mL) and 4.3 ng/mL (range <1 – 9.1 ng/mL) for tramadol and M1, respectively. The median HC serum concentration at the time of rescue drug therapy was 8.2 ng/mL (range 4.5 – 36.1 ng/mL). All doses had HM concentrations ≤ 1.1 ng/mL at the time of rescue drug therapy.

DISCUSSION

In this study, we evaluated the pharmacokinetics of hydrocodone and its metabolite, hydromorphone, after oral hydrocodone/acetaminophen and tramadol and its metabolites after oral tramadol administered postoperatively as analgesics for dogs undergoing unilateral TPLO. This is the first reported study to evaluate the pharmacokinetics after oral HC and tramadol administered for postoperative analgesia in a diverse group of dogs in a clinical study. Previous pharmacokinetic studies of HC and tramadol used healthy research dogs, which may not represent the true clinical population of dogs.

Hydrocodone is commonly used as an analgesic in human postoperative patients, but information about its use as an analgesic has been limited in veterinary species. The first report on the metabolism of HC in several species including two dogs showed HC being metabolized to hydromorphone (HM) via O-demethylation when using a dose near 1.0 mg/kg subcutaneously.[8] In addition, the analgesic activities of the O-demethylated metabolites including HM were found to be significantly greater (2- to 7-fold) than that of HC and likely to be an important factor in the development of analgesia in domestic species.[8] Findlay et al. also examined the oral bioavailability and metabolism of HC equivalent to 3.1 mg/kg hydrocodone bitartrate in a crossover study in two fasted male beagles. The absolute oral bioavailability of HC was 44% and 34% in dogs 1 and 2, respectively.[12] Other results from that study showed the amount of free HM in dog plasma following oral HC ranged 17 to 24 ng/ml.[12] This is proportionally compared to the concentrations achieved in the clinical population of dogs in this study. Hydromorphone was infrequently detected in this study, with quantifiable concentrations only occurring in 5 dogs. The amount of HM detected in our samples was approximately less than or equal to 1.1 ng/ml throughout the 8 hour dosing range after the second dose of oral HC administration at 0.5 mg/kg of HC given postoperatively. The dosage used in the aforementioned study was nearly 6-fold the drug amount used in the current study and it is possible that using a higher dose may influence the amount of serum HM concentrations.

Kukanich et al. evaluated the pharmacokinetics of HC and its active metabolite, HM, after a single oral dose of HC/acetaminophen in 6 healthy Greyhound dogs using a comparable dosing regime of 0.5 mg/kg of HC.[9] From that study, both HC and HM were present and every 6-8 hour dosing was recommended. In that study, the mean maximum concentration (C_{max}) of HC was 11.73 ng/ml at a T_{max} of 0.74 hr.[9] The mean C_{max} of HM was 5.2 ng/ml at 1.37 hr.[9]

Though HM levels were too low to distinguish pharmacokinetic parameters in the present study, it is worth noting that the C_{max} of HC in the current study was 8.9 ng/ml at a T_{max} of 3.47 hours. Though the C_{max} is comparable, the time to reach maximum serum drug concentrations may be influenced by recent anesthesia, rescue morphine administration and delays in gastrointestinal transit time in the heterogenous population of dogs undergoing a routine procedure.

Li et al. evaluated the metabolite profile of HC administered to an unstated number of dogs of unstated breed at 60 or 120 mg/day (weight, dose, and dosing frequency was not stated) for a period of 13 weeks.[13] Norhydrocodone and N-oxide metabolites of hydrocodone were the predominant metabolites. Hydromorphone and hydromorphone glucuronide were identified as minor metabolites.[13]

Given the discrepancies in HM concentrations with results of the various studies, it is possible that several other mechanisms may have influenced our ability to detect the active HM metabolite. First, dogs used in this study were under the influence of other drugs including premedications and inhalants for general anesthesia. It is possible that concurrent use of other drugs may have altered drug metabolism in such a way that HM was no longer produced via O-demethylation pathways. Though routine screening of patients was performed to rule out systemically unhealthy animals, it is also possible, but unlikely, that undetected systemic diseases including chronic inflammation from cranial cruciate ligament rupture also influenced the normal metabolism of HC to measureable amounts of HM. Breed specific differences in the metabolism of HC to HM may also occur. Findlay et al and Kukanich & Spade assess the pharmacokinetics of HC in beagle and greyhound dogs, respectively.[9, 12] No beagles or greyhounds were enrolled in the current study. Although these breeds were not excluded, no dogs of these breeds presented for TPLO surgery during the study period. Additionally, Findlay et al administered a much higher dose of HC (~6x higher) which may have altered the metabolite profile by saturating other metabolism pathways shunting metabolism to hydromorphone.

A population pharmacokinetic model could not be fit to the HC data. The lack of a model fit may have been due to the sampling protocol (limited to 8 hours prior to administration of the next dose) , the total number of samples, the variability of the data, the relatively small number of animals including in the study (n=25 for group H), or the effects of anesthesia and analgesics on HC pharmacokinetics among other factors. Further studies including a larger number of dogs may be able to better fit a population pharmacokinetic model for oral HC in dogs.

The terminal half-life of HC based on the naïve pooled pharmacokinetic model was 15.85 hr. This estimate should be interpreted cautiously and may not reflect the true terminal half-life of HC in dogs. In order to robustly estimate the terminal half-life, samples should be collected for a period at least 3x the terminal half-life; in this case samples should have been collected for approximately 48 hours during the terminal portion of the curve. However, samples were only collected during the 8 hour dosing interval and as such the estimate for the terminal half-life may not be robust. Further studies assessing accumulation of HC over 48–72 hours would better assess if the terminal half-life is truly 15.85 hours in clinical patients or if the estimate of the terminal half-life in this study is not robust due to limitations of study design.

Tramadol is widely used in human and veterinary medicine as an opioid analgesic, however, it has a complex mode of action involving opioid receptors and inhibition of serotonin and norepinephrine transporters. Its mechanisms of action are wildly believed to be related to the drug's metabolism and available active metabolite, O-desmethyltramadol or M1.[1,2,7]

Tramadol is atypical of other opioids, and its metabolism through hepatic cytochrome p450 enzymes is quite unique when compared to traditional opioids. Specifically, the cytochrome p450 isoenzyme, CYP2D6, has been extensively evaluated in humans as the isoenzyme responsible for formation of M1. Unlike the parent tramadol compound, which displays weak μ opioid receptor activity, M1 exerts profound pharmacological effects as a high-affinity opiate μ-receptor agonist. This metabolite has demonstrated an affinity to μ-opioid receptors that is 200 times greater than that of the parent compound. This high affinity to μ-opioid receptors is highly correlated to its analgesic activity in humans.[3] Other metabolites including N-desmethyltramadol (M2) and N,O didesmethyltramadol (M5) are present in dogs, but are considered either inactive or unable to cross the blood brain barrier in several species.[3] The wide variability in the pharmacokinetic properties of tramadol can partly be attributed to genetic polymorphism within the CYP gene leading to the belief that there are different genotypes of the isoenzyme in humans. In a 1996 study by Poulsen et al, the phenotypes of the gene were described and included both extensive and poor metabolizers of tramadol based on M1 concentrations following oral administration of tramadol. In humans, the serum concentration of M1 after tramadol administration ranged from 10-100 ng/ml in extensive metabolizers, whereas in poor metabolizers serum concentrations of M1 were below or near the detection limit of 3 ng/ml.[13] Previous drug failure rates among humans labeled as poor

metabolizers of the drug are reported to be as high as 50%.[2] Most studies have identified very low concentrations of M1 in dogs after tramadol administration, except Kukanich and Papich in 2004, in which their laboratory identified much higher concentrations of M1.[15] That study was conducted prior to the commercial availability of reference standards for M2 and M5. It is likely that the high performance liquid chromatography assay used in that study was not specific for M1 and either M2 and/or M5 co-eluted with M1, which resulted in biased and reportedly high M1 concentrations.

The population pharmacokinetics of the parent tramadol compound in the current study suggests a range in variability of metabolism present in canine species as well. The C_{max} of tramadol in the current study after a second oral dose of 5-7 mg/kg ranged from 46.8 to 613.0 ng/mL. This 13-fold variation in tramadol drug concentration may be attributable to inter-individual differences in drug bioavailability or recent anesthesia. Underlying disease conditions influencing metabolic pathways could have been present, but no abnormalities were noted in the pre-surgical evaluation. It is also possible that dogs, like humans, display mutations in the enzyme responsible for tramadol metabolism with some dogs having a low oral bioavailability of tramadol and other dogs having a greater oral bioavailability. To the authors' knowledge, the cytochrome p450 enzymes responsible for tramadol's metabolism have not been fully investigated in the dog. Further investigations would be needed to determine the genotypic expression of the cytochrome p450 enzyme responsible for tramadol metabolism, in order to predict poor metabolizers of the drug in our canine population coupled with intravenous drug dosing to determine the actual variability in the oral bioavailability of tramadol.

Previous studies in dogs show very low M1 concentrations throughout the 8 hour time course.[4-6, 14] The concentrations of M1 following intravenous and rectal dosing at 4 mg/kg in healthy beagle dogs were 10-21 ng/mL and 7-28 ng/mL, respectively.[15] At a similar oral dose, by mouth administration showed a C_{Max} of M1 as high as 54 ng/mL.[4] Administration of tramadol near 10 mg/kg showed a C_{Max} of M1 to be as low as 5.7 ng/mL.[6] These previous reports are consistent with results of the current study in which the active metabolite M1 concentrations are exceptionally low and not likely contributing to analgesia. Similar metabolite profiling of the M2 and M5 inactive metabolites were identified in this study and consistent with previous pharmacokinetic results in healthy, fasted, unanesthetized dogs.[4-6,14,15]

Canine species, unlike most humans, must rely on the activity of the parent compound tramadol or other potential metabolites rather than from the M1 metabolite. If the antinociceptive effects in dogs are due to tramadol alone and not M1, then the effects may be independent of opioid receptor activity all together. Though the parent compound tramadol acts as a low affinity opiate μ-receptor agonist, it can also act as a serotonin and norepinephrine reuptake inhibitor based on the complementary action of its two enantiomers and those actions may play a big role to enhance inhibitory effects on pain transmission.[1,7]

Blood samples were collected at time of rescue drug therapy based on pain scoring with the modified Glasgow Composite Measure Pain Scale. This was done in order to assess the concentration of drug at the time of perceived drug failure. Based on the median drug concentrations at the time of failure, little can be said about the clinical efficacy of the drugs. Both tramadol and HC concentrations at the time of perceived treatment failure were well within the concentration range for dogs in this study that did not receive rescue analgesia and did not reflect an absence of drug. This discrepancy is likely due to the scoring system's lack of sensitivity in detecting pain, differences between how dogs interacted with the blinded assessor, differences between how the assessor interpreted the scoring criteria, true differences in the dogs sensitivity to the drug, true differences in the degree of pain that occurred between dogs, or that some dogs did not show signs of pain, or were truly not painful despite the pain scale indicating they were painful.

Previous pharmacokinetic studies include the use of only a small number of unanesthetized, fasted, healthy dogs that were homogenous including research bred hounds, beagles, or greyhounds. Despite this limitation, the breeds in this study accurately represent the population of dogs presenting for cruciate rupture at our hospital that are in need for postoperative analgesics. Other limitations include the enrollment of only 50 dogs (25 per treatment group), but if larger numbers of dogs were used some individual characteristics may have been able to be identified better predicting treatment success or failure (e.g. breed, age, gender, etc). Based on the IACUC protocol, each patient was only allotted 5 blood samples in the postoperative period to minimize handling. Despite the limited number of samples obtained, naïve pooled pharmacokinetic models were still able to fit the data for all of the analytes and a population pharmacokinetic was able to be fit to the tramadol data. However, population pharmacokinetic models were not able to be fit to HC or the other tramadol metabolites. Further

studies increasing the total sample numbers may be able to have better model fits for HC and tramadol metabolites.

CONCLUSIONS

This study represents the first clinical investigation on the pharmacokinetics of hydrocodone and tramadol for postoperative analgesia in clinical dogs. Our hypothesis was accepted that tramadol was metabolized with low concentrations of the active M1 metabolite similar to previous reports. Wide variations do exist in drug tramadol concentrations and clinical effects are likely to be variable and independent of the μ-opioid. Results indicate poor metabolism of hydrocodone to its active metabolite, hydromorphone. The hypothesis was rejected that hydromorphone would be present at levels anticipated for clinical analgesia, however, efficacy of the drug may still be achieved through its parent compound, hydrocodone.

ABBREVIATIONS

TPLO, tibial plateau leveling osteotomy

HC, hydrocodone

HM, hydromorphone

KSU VHC, Kansas State University Veterinary Health Center

IACUC, Institutional Animal Care and Use Committee

CBC, complete blood count

ASA, American Society of Anesthesiologist

ACVS, American College of Veterinary Surgeons

mGCMPS, modified Glasgow Composite Measure Pain Scale

ACVS, American College of Veterinary Surgeons

C_{max}, maximum serum drug concentration

T_{max}, time to maximal serum drug concentration

FOOTNOTES

[a] Hydrocodone bitartrate 5 mg and 10 mg/Acetaminophen 325 mg, Qualitest Pharmaceuticals, Huntsville, AL, 35811, USA.

[b] Tramadol hydrochloride 50 mg, Amneal Pharmaceuticals LLC, Paterson, NJ, 07504, USA.

FIGURES

Figure 2—1 Mean serum concentrations of tramadol metabolite in dogs after a mean ± SE dose of 5.91 ± 0.61 mg/kg of tramadol administrated by mouth postoperatively.

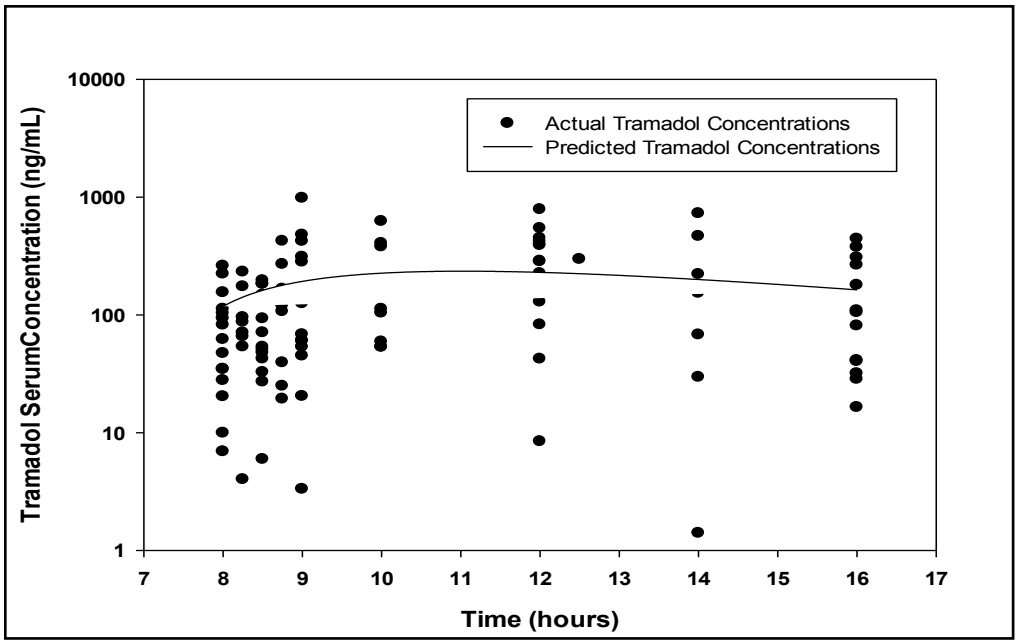


Figure 2—2 Mean serum concentrations of M1 metabolite in dogs after a mean ± SE dose of 5.91 ± 0.61 mg/kg of tramadol administrated by mouth postoperatively.

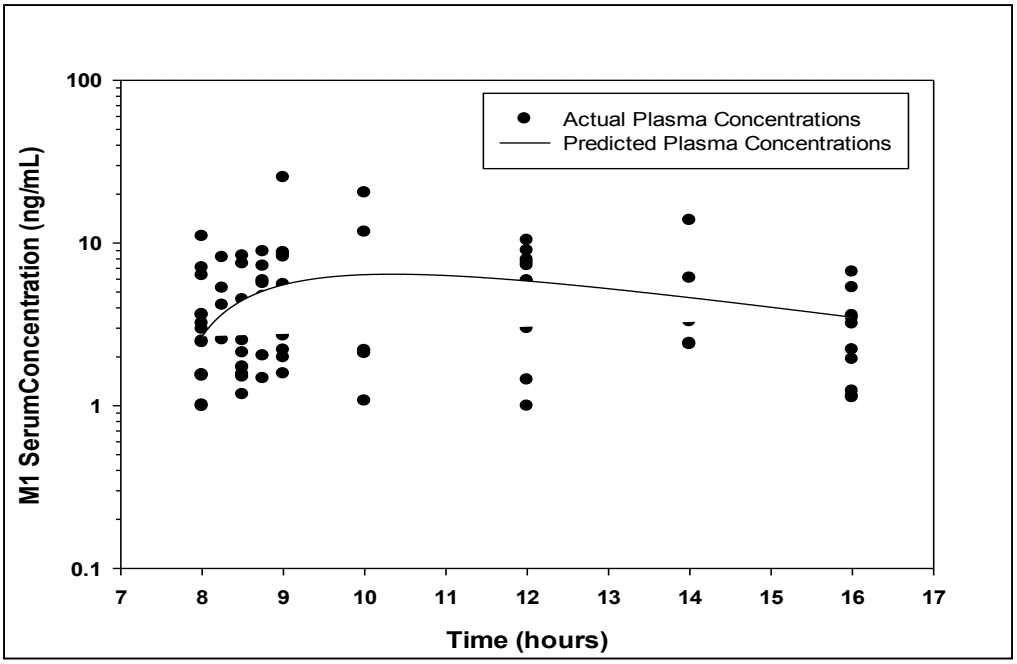


Figure 2—3 Mean serum concentrations of tramadol, M1 (O-desmethyltramadol – active metabolite), M2 (N-desmethyltramadol – inactive metabolite), and M5 (N,O di-desmethyltramadol – inactive metabolite) in dogs after oral tramadol administration.

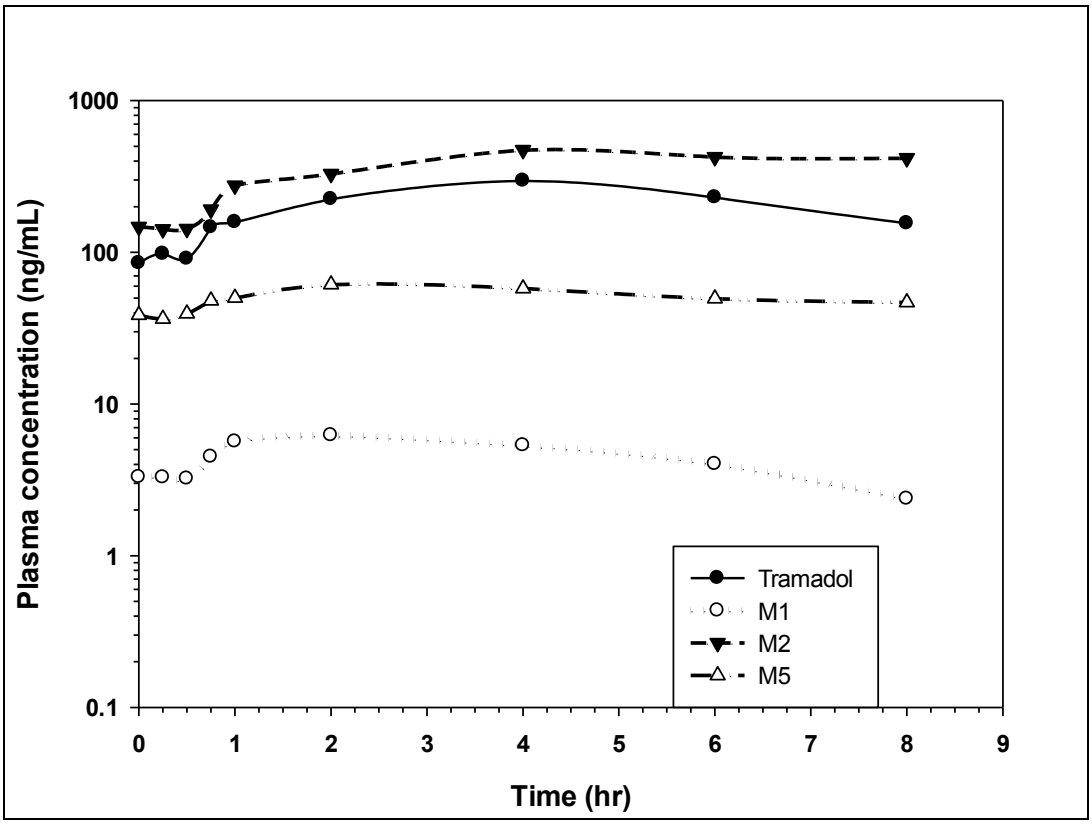
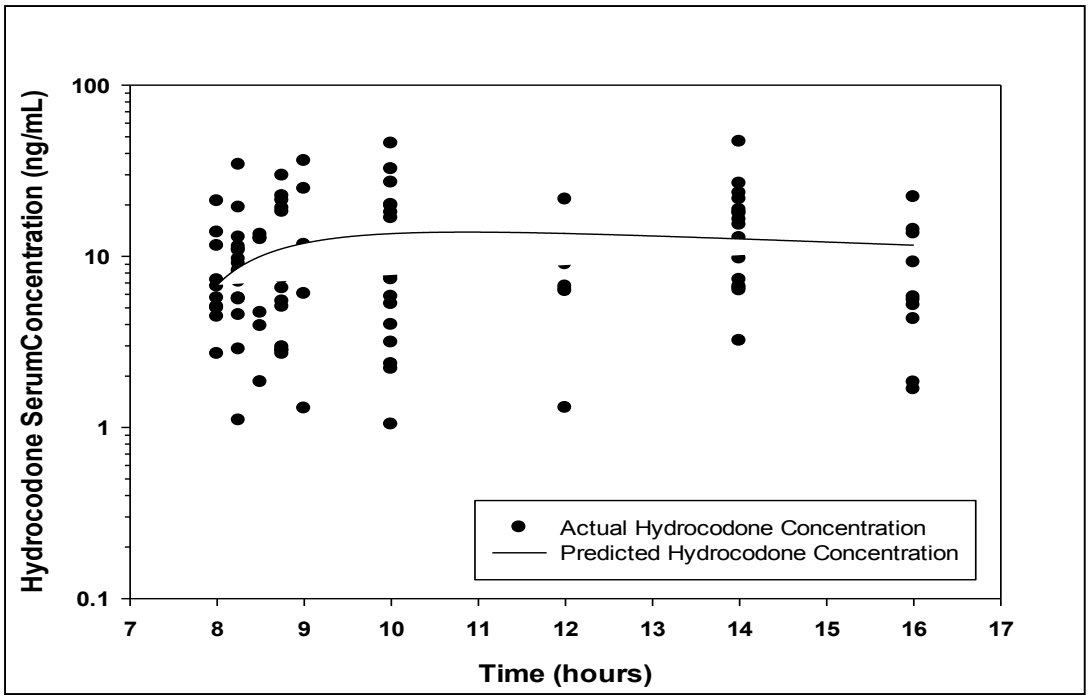


Figure 2—4 Mean serum concentrations of hydrocodone in dogs after a mean ± SE dose of 0.51 ± 0.04 mg/kg of HC administrated by mouth postoperatively.



TABLES

Table 2—1 Predicted values for pharmacokinetic variables after population pharmacokinetic and naïve pooled modeling for parent compound

		Population Pharmacokinetics				Naïve Pooled Pharmacokinetics
Parameter	Units	Mean	Minimum	Median	Maximum	
V/F	L/kg	5.4	5.4	5.4	5.4	5.90
K_a	1/hr	0.2046	0.0548	0.1145	0.7611	0.131
K_{el}	1/hr	0.5579	0.1762	0.5657	0.8866	0.444
AUC	hr*ng/mL	2115	943	1926	4811	1983
$T_{1/2}K_a$	hr	6.11	0.91	6.05	12.65	5.30
$T_{1/2}K_{el}$	hr	1.58	0.78	1.23	3.93	1.56
CL/F	mL/min/kg	30	9	31	48	43.6
T_{max}	hr	3.54	1.77	3.27	6.96	3.90
C_{max}	ng/mL	195.0	46.8	151.0	613.0	155.6

V/F = Apparent volume of distribution per bioavailability. K_a = Absorption rate constant. K_{el} = Elimination rate constant. AUC = area under the concentration vs time curve. $T_{1/2}K_a$ = Absorption half-life. $T_{1/2}K_{el}$ = Terminal half-life. Cl/F = Total body clearance per bioavailability. T_{max} = Time to maximal serum concentration. C_{max} = Maximal serum concentration.

Table 2—2 Predicted values for pharmacokinetic variables after naïve pooled modeling for tramadol metabolites M1 and M5.

Parameter	Units	M1	M5
V/F	L/kg	742.51	53.00
K_{ap}	1/hr	0.696	0.238
K_{el}	1/hr	0.148	0.192
AUC	hr*ng/mL	47	510
$T_{1/2}K_{ap}$	hr	1.00	2.91
$T_{1/2}K_{el}$	hr	4.67	3.61
CL/F	mL/min/kg	1835.8	169.7
T_{max}	hr	2.82	4.67
C_{max}	ng/mL	4.6	39.9

V/F = Apparent volume of distribution per bioavailability. Ka = Absorption rate constant. Kel = Elimination rate constant. AUC = area under the concentration vs time curve. $T_{1/2}$ K_a = Absorption half-life. $T_{1/2}$ K_{el} = Terminal half-life. Cl/F = Total body clearance per bioavailability. T_{max} = Time to maximal serum concentration. C_{max} = Maximal serum concentration

Table 2—3 Predicted values for pharmacokinetic variables after naïve pooled modeling for hydrocodone.

Parameter	Units	Hydrocodone
V/F	L/kg	33.82
K_a	1/hr	0.921
K_{el}	1/hr	0.0437
AUC	hr*ng/mL	211
$T_{1/2}K_a$	hr	0.75
$T_{1/2}K_{el}$	hr	15.85
CL/F	mL/min/kg	24.7
T_{max}	hr	3.47
C_{max}	ng/mL	7.9

V/F = Apparent volume of distribution per bioavailability. K_a = Absorption rate constant. K_{el} = Elimination rate constant. AUC = area under the concentration vs time curve. $T_{1/2}$ K_a = Absorption half-life. $T_{1/2}$ K_{el} = Terminal half-life. Cl/F = Total body clearance per bioavailability. T_{max} = Time to maximal serum concentration. C_{max} = Maximal serum concentration.

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