Article

Effectiveness of tapentadol hydrochloride for treatment of orthopedic pain in dogs: A pilot study

Nina R. Kieves, James Howard, Phillip Lerche, Jeffrey Lakritz, Turi K. Aarnes

Abstract — This pilot study evaluated the short-term analgesic effect of oral tapentadol hydrochloride (tapentadol) in dogs with unilateral hind limb lameness secondary to naturally occurring cranial cruciate ligament rupture. Baseline data including pharmacodynamic parameters, sedation scores, lameness scores, and objective gait analyses were collected. Tapentadol was administered orally (30 mg/kg body weight). Four hours following administration of tapentadol all data were collected again. Plasma concentrations of tapentadol 4 hours after administration were assessed using high performance liquid chromatography tandem mass spectrometry. No significant side effects were noted. All dogs had measurable plasma concentrations of tapentadol (mean concentration: 18.9 ng/mL). There were no significant differences in pharmacodynamic parameters or sedation over time. Subjective lameness scores were significantly lower than baseline at 4 hours post-drug administration. No significant improvement was seen in objective gait analysis. Further studies are needed to assess dosing regimens which may lead to effective treatment of acute pain and long-term use.

Résumé — Efficacité de l'hydrochlorure de tapentadol pour le traitement de douleur orthopédique chez des chiens : une étude pilote. La présente étude pilote a évalué l'effet analgésique à court terme d'hydrochlorure de patentadol (tapentadol) chez des chiens avec une boiterie unilatérale d'un membre arrière secondaire à une rupture du ligament croisé antérieur se produisant naturellement. Les données de base obtenues incluaient des paramètres pharmacodynamiques, des pointages de sédation, des pointages de boiterie et des analyses objectives de la posture. Du tapentadol fut administré oralement (30 mg/kg de poids corporel). Quatre heures suivant l'administration de tapentadol toutes les données furent prises à nouveau. Les concentrations plasmatiques de tapentadol 4 heures après l'administration furent déterminées en utilisant la chromatographie à haute performance en phase liquide en tandem avec la spectrométrie de masse. Aucun effet secondaire significatif ne fut noté. Tous les chiens avaient des concentrations plasmatiques mesurables de tapentadol (concentration moyenne : 18,9 ng/mL). Il n'y avait pas de différence significative dans le temps pour les paramètres pharmacodynamiques ou la sédation. Les pointages subjectifs de boiterie 4 heures post-administration du médicament étaient significativement plus faibles que les valeurs de base. Aucune amélioration significative ne fut observée dans l'analyse objective de la posture. Des études supplémentaires sont requises pour évaluer les régimes de dosage qui pourraient mener à un traitement efficace de la douleur aiguë et de l'utilisation à long-terme.

(Traduit par Dr Serge Messier)

Can Vet J 2020;61:289–293

Introduction

Numerous pharmaceuticals are available as oral analgesics including nonsteroidal anti-inflammatory drugs (NSAIDs), central-acting synthetic opiate-like (μ-receptor) agonists (tramadol), gamma-aminobutyric acid (GABA) analogs (gabapentin, pregabalin), and *N*-methyl-D-aspartate (NMDA) receptor antagonists (amantadine) (1). The commercial availability and proven clinical efficacy of oral pain medications for dogs remain elusive outside the use of NSAIDs. The analgesic effect of oral opioids in dogs is limited by poor bioavailability (2,3). Recently, the use of tramadol was evaluated in dogs with chronic osteoarthritis and found to provide no improvement in objective gait analyses or pain scores compared with a placebo (4).

Gabapentin, an alterative neuropathic pain reliever, has unproven efficacy in small animal patients. Based on extrapolated data from clinically healthy dogs it is commonly prescribed at subtheraputic doses and frequencies. The current literature supports the need for increased plasma concentrations to achieve clinically effective analgesia for gabapentin (2,5,6). Adjunctive oral medications such as amantadine are available, but take 42 d to reach therapeutic levels in dogs and provide no immediate treatment for acute pain (7). Therefore, NSAIDs remain the cornerstone of clinically effective oral analgesics (8). This reliance

Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio, USA.

Address all correspondence to Dr. Turi K. Aarnes; e-mail: aarnes.1@osu.edu

on NSAIDs poses risks and concerns for patients with underlying systemic disease and severely limits appropriate analgesia in certain populations of patients such as those with concurrent renal disease, hepatopathy, endocrine disease, gastrointestinal disease, or concurrent corticosteroid use. Consequently, there is merit in exploring if there are safe and effective oral analgesic alternatives to NSAIDs available for use in veterinary medicine.

Tapentadol hydrochloride (tapentadol) is a novel analgesic with widespread use in humans for treatment of chronic nociceptive and neuropathic pain and is approved for use in humans with diabetic neuropathies in the United States. In Canada, tapentadol is approved for use and is classified as a schedule 1 drug similar to other opioids. Tapentadol has a unique dual mechanism of action; it is a μ-opioid receptor agonist with norepinephrine reuptake inhibition (9). It lacks any clinically significant serotonergic activity. Additionally, the parent molecule (tapentadol) is the only active constituent with each known metabolite providing no analgesic potential in humans (10). Although the affinity of tapentadol for the μ-opioid receptor is 50× less compared with morphine, its analgesic potency is nearly identical and exhibits only a 2- to 3-fold decrease in efficacy (9,11). Moreover, in a recent study in dogs it was shown that tapentadol demonstrated a similar pharmacokinetic profile after oral administration in dogs compared to that in humans with a rapid first pass effect and oral absorption, minimal physiologic side effects, a comparable elimination half-life, and plasma concentrations within the established range of minimum effective plasma concentration in humans at all tested dosages [10, 20, and 30 mg/kg body weight (BW)] (12). This pharmacologic profile coupled with its lack of clinically significant side effects makes tapentadol an attractive oral analgesic for use in clinical canine patients.

The purpose of this study was to determine if a 30 mg/kg BW dosage of oral tapentadol would provide a clinically significant improvement in lameness in dogs with unilateral hind limb lameness caused by cranial cruciate ligament (CCL) rupture. This dosage was selected based on previous pharmacokinetic profiles (12). We hypothesized that oral tapentadol would provide pain relief evident as improvement in subjective and objective gait analyses.

Materials and methods

Study design

Dogs presented to The Ohio State University Veterinary Medical Center for unilateral hind limb lameness secondary to suspected naturally occurring CCL disease were enrolled prospectively in the study between February 2, 2017 and April 24, 2018. Owners were informed verbally of the study details and provided written consent before enrollment. The study was approved by the University Institutional Animal Care and Use Committee of The Ohio State University and Clinical Research Advisory Committee.

Participants

Client-owned animals examined for unilateral hind limb lameness attributable to CCL rupture diagnosed by physical examination were enrolled prospectively in the study. All dogs were fasted the morning the study was performed. Dogs were excluded if they had concurrent orthopedic disease resulting in lameness or neurologic disease identified by physical examination. Each dog underwent a full general physical, orthopedic, and neurologic examination by a Board-certified surgeon (NRK) to determine eligibility for enrollment. Prior to admission into the study a complete blood (cell) count (CBC) and serum chemistry profile were completed. Dogs were excluded if there were significant abnormalities noted on blood analysis or physical examination other than evidence of CCL rupture. Dogs were allowed to be on an NSAID during enrollment in the study, but other oral medications were withdrawn for a minimum of 1 wk before participating in the study.

Table 1. Sedation scoring system (14).

Score	Description
0	No sign of sedation.
1	Signs of sedation, but reactive to auditory stimulus.
2	Signs of sedation with no reaction to auditory stimulus, but reactive to physical handling.
3	Sedated, and unresponsive to handling and to auditory stimulus.

Experimental design

Following enrollment in the study, baseline temperature, heart rate, body condition score (scale of 1–9) (13), thoracic auscultation, and sedation score were recorded. Sedation was evaluated using a validated 4-point scale (0 to 3), as previously reported (14), at baseline and 4 h after oral administration of tapentadol (Table 1). In addition, the lameness grade was evaluated and objective gait evaluation was performed using a previously validated pressure sensitive walkway (HRV Walkway 6 VersaTek System; Tekscan Animal Walkway System, South Boston, Massachusetts, USA) before administration of oral tapentadol (Nucynta; Janssen Pharmaceuticals, Titusville, New Jersey, USA). Lameness was graded on a scale of 0–5 (15), by a Board-certified surgeon (NRK) at baseline and 4 h after drug administration (Table 2).

An oral dosage of 30 mg/kg BW of tapentadol was calculated based on the current weight of the dog; the nearest dose based on available tablet size with reasonable splitting of tablets (quartering or halving with a pill cutter) was given orally with 85 g of Hills a/d wet food (Hills a/d; Hill's Pet Nutrition, Topeka, Kansas, USA). Dogs were monitored to confirm that all food and tablets were swallowed.

Gait analysis

A previously validated pressure-sensitive walkway system was used to collect objective gait data. Ten video-recorded trials per dog were acquired before oral administration of tapentadol, and 4 h following dosing. Dogs were led over the walkway at a comfortable walk, with a velocity between 0.8 and 1.3 m/s and acceleration of ± 0.1 m/s^2. Five valid trials were averaged for statistical analysis. To be considered valid the dog must have been walking at a relaxed, steady walk without any overt

Table 2. Lameness scoring system (15).

Lameness score	Description
0	No lameness.
1	Lameness difficult to observe and not consistently apparent with any gait.
2	Lameness difficult to discern at walk or trot, more apparent with circling or stairs.
3	Lameness consistently present at a trot.
4	Lameness obvious at a walk; intermittent non-weight-bearing lameness.
5	Non-weight-bearing lameness.

turning of the head from midline. Data were collected using commercially available software (Tekscan Walkway Research ver. 7.66-03, Tekscan) associated with the walkway system. Data collected included velocity, acceleration, maximum force (kg and %BW), impulse (%BW × s and kg × s), maximum peak pressure (PSI), and symmetry index.

Pharmacokinetic analytic method

Prior to enrollment blood samples were collected *via* puncture of the jugular vein with a 20-gauge needle for CBC and serum chemistry profiles to ensure the systemic health of the animal. A second blood sample was collected 4 h following drug administration. This was acquired *via* puncture of the saphenous vein in the clinically unaffected limb with a 22-gauge needle, or the jugular vein if blood could not be obtained from the lateral saphenous vein. This was saved for further analysis to determine plasma concentrations of tapentadol.

Immediately following collection whole blood samples were centrifuged at 2000 × *g* for 20 min at 4°C. Plasma supernatant was aspirated from the collection tubes and placed into duplicate microcentrifuge tubes for storage. Plasma samples were frozen at −70°C until they were assayed by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) (12).

Statistical analysis

Data for heart rate, rectal temperature, velocity, maximum force, impulse, maximum peak pressure, and symmetry were tested for normality using a Kolmogorov-Smirnoff test. Normally distributed data were analyzed using a 2-tailed paired *t*-test. Data that were not normally distributed were analyzed using a Wilcoxon matched pairs test. Sedation and lameness scoring were analyzed using a Wilcoxon matched pairs test. $P < 0.05$ was considered significant.

Results

Descriptive analyses

Eighteen dogs were enrolled in the study. The mean age of dogs was 75.3 mo ± 37.0 mo [standard deviation (SD)] (range: 19 to 149 mo), with a mean weight of 38.1 kg ± 7.9 kg (range: 27.0 to 52.0 kg) and median body condition score of 6 (range: 5 to 9). Seven dogs had right hind limb lameness and 11 had left hind limb lameness attributable to CCL rupture based on physical examination findings. Radiographs in some dogs demonstrated variable degrees of stifle osteoarthritis and cranial displacement of the infrapatellar fat pad consistent with CCL rupture; others were diagnosed based solely on physical examination consisting of generalized muscle atrophy of the affected limb, medial buttress, joint effusion, pain with range of motion of the stifle, and instability consisting of positive cranial drawer and positive tibial thrust. Mean duration of lameness was 4 mo ± 2.8 mo (range: 2 to 12 mo, with 2 dogs having unknown duration of lameness). Three dogs had a previous CCL injury surgically stabilized on the contralateral limb; this limb was non-painful with no lameness in all 3 dogs. Ten dogs were not on any oral medication at the time of enrollment, 6 received carprofen orally at a dose of approximately 2.2 mg/kg BW, q12h, and 1 dog received grapiprant (Galliprant; Aratana Therapeutics, Leawood, Kansas, USA), unknown dose. Of the 18 dogs enrolled, 10 underwent surgery to stabilize the CCL rupture with a tibial plateau leveling osteotomy (TPLO) after completion of the study. In all dogs undergoing surgery, a CCL tear was confirmed, with 7 dogs having a complete rupture of the CCL, 3 dogs having a partial rupture of the CCL, and 6 having a concurrent medial meniscal tear.

Table 3. Temperature, heart rate, lameness, and sedation scores in 18 dogs before and after oral administration of tapentadol hydrochloride, 30 mg/kg body weight.

Variable	Baseline	4 hours after drug administration	*P*-value
Temperature (°C)	39 ± 0.6	38.8 ± 0.4	0.1782
Heart rate (beats/min)	126 ± 26	115 ± 23	0.1461
Sedation score	0	0 (0 to 1)	1.000
Lameness score	3 (1 to 4)	2 (1 to 4)	0.0147

Temperature and heart rate are presented as mean ± standard deviation. Sedation score and lameness score are presented as median (range).

Pharmacodynamic analysis

The median calculated oral tapentadol dose was 1107.0 mg (range: 810 to 1560 mg) and the median nominal dose was 1112.5 mg (range: 800 to 1562 mg) or 30.04 mg/kg BW (range: 29.63 to 30.35 mg/kg BW).

Rectal temperature and heart rate were normally distributed. There was no significant difference in temperature ($P = 0.1782$) or heart rate ($P = 0.1461$) between the 2 time points (Table 3). Sedation scoring between baseline and 4 h post-drug administration was not significantly different ($P = 1.000$). All dogs received a sedation score of 0 at baseline; at 4 h after drug administration 1/18 dogs (5.6%) was scored at 1 for sedation with all others having a sedation score of 0. One dog vomited approximately 1 h after receiving oral tapentadol with no evidence of tapentadol tablets in the vomitus and this dog did have measurable plasma levels of tapentadol; no other side effects were noted during the study. Respiratory rate was not statistically evaluated, as over 50% of the dogs were panting both at baseline and at 4 h after drug administration with no numerical value being recorded.

Table 4. Objective gait analysis of 18 dogs before and after oral administration of tapentadol hydrochloride, 30 mg/kg body weight.

Variable	Baseline	4 hours after drug administration	*P*-value
Velocity (m/s)	1.11 ± 0.13	1.09 ± 0.16	0.5466
Maximum force (%BW)[a]	21.3 (10.2 to 51.5)	22.4 (7.8 to 52.2)	0.5135
Maximum force (kg/m/s^2)[a]	8.15 ± 3.13	8.34 ± 3.24	0.5266
Impulse (%BW × s)[a]	5.9 ± 2.52	6.28 ± 2.90	0.1941
Impulse (kg × s)[a]	5.2 (2.5 to 13.3)	6.35 (1.9 to 13.0)	0.4458
Maximum peak pressure (PSI)[a]	38.94 ± 8.36	39.56 ± 7.41	0.5132
Symmetry score	0.765 (0.29 to 3.49)	0.795 (0.43 to 3.1)	0.9434

Data are presented as mean ± standard deviation or median (range).
[a] Value is for the affected hind limb.

Subjective lameness scores were significantly lower than baseline at 4 h post-drug administration, indicating an improvement in lameness score (P = 0.0147). The median lameness score decreased from 3 to 2 over the course of the study (range: 1 to 4 at both time points).

Gait analysis

Velocity, maximum force (kg/m/s^2), impulse (%BW × s), and maximum peak pressure (PSI) were normally distributed, while maximum force (%BW), impulse (kg × s), and symmetry were not. Gait velocity was not different between baseline and 4 h post-drug administration. No differences were seen between baseline gait analysis variables and 4 h post-drug administration analysis (Table 4).

Pharmacokinetic analysis

All samples were found to have measurable plasma tapentadol levels at 4 h after drug administration when assessed with HPLC-MS/MS; mean: 18.9 ng/mL ± 9.1 ng/mL (range: 9 to 49 ng/mL). The relative SD values (an indication of the precision of the assay) were 4.7%, 3.7%, and 3.8% at 5, 25, and 100 ng/mL, respectively within days. Overall, values for the closeness of the found concentration to the amount added (accuracy) were 102.5%, 97.0%, and 94.9% at 5, 25, and 100 ng/mL, respectively within days. The mean recoveries from extracted plasma at 5, 25, and 100 ng/mL were 98.9%, 90.8%, and 91.9%, respectively.

Discussion

Our study demonstrated that a dosage of 30 mg/kg BW tapentadol administered orally lowered subjective lameness scores significantly in dogs with unilateral hind limb lameness attributable to CCL rupture 4 h after administration. There was, however, no corresponding statistically significant improvement in objective gait analysis as assessed by a pressure sensitive walkway system. Therefore, we reject our hypothesis that both subjective and objective lameness would improve with oral tapentadol administration in dogs with unilateral hind limb lameness secondary to CCL disease.

Although there was no statistically significant improvement in gait analysis values for maximum force, impulse, and maximum peak pressure of the affected limb, these did improve with time. It is possible that with a larger number of dogs enrolled in the study, a significant improvement in these objective assessments might be seen with oral administration of tapentadol. However, a blinded cross-over study with a control group would be best to elucidate any true effect oral tapentadol may have on acute pain relief in dogs. While dogs did not appear sedate from the drug, it is possible that they may have had some degree of sedation that was minor, experienced muscle relaxation, or cognitive dysfunction, which is seen in humans taking tapentadol (9); this change in demeanor could have hidden an improvement in lameness in the dogs. Furthermore, the validated sedation scoring system used in this study may not have provided the sensitivity necessary to discern a level of subclinical sedation that would still affect the gait analysis data. Alternatively, a single dose of oral tapentadol may not be an effective analgesic for dogs with CCL disease or osteoarthritis secondary to CCL disease.

Only 1 dosage of 30 mg/kg BW was given with assessment occurring 4 h after drug administration. This dosage and timepoint for plasma collection were selected based on a previous study of pharmacokinetics of oral tapentadol in dogs (12). In that study, the authors found that for a dose of 30 mg/kg BW, the plasma concentrations were highest at 4 h post-administration; therefore, this dosing and sampling point were chosen for this study (12). To ensure as uniform an absorption of drug as possible, all dogs were fasted the morning of the study. Additionally, all dogs were fed a high fat meal at the time of oral dosing as it is shown in humans that the AUC and C_{max} of tapentadol increase 25% and 16%, respectively, following a high-fat and calorie dense meal (16). It is possible that more than 4 h and repeated dosing are needed to see improvement in pain status. Importantly, pharmacokinetic assessment showed measurable levels of tapentadol in plasma concentrations for all dogs in the study 4 h after dosing. Mean plasma concentration was 18.9 ng/mL, with a range of 9 to 49 ng/mL, which is within the known range of the minimum effective plasma concentration validated in humans to provide sufficient analgesia (17,18). It is unknown what plasma level is required to achieve effective analgesia in dogs. It is possible that plasma concentrations need to be higher for demonstrable analgesia to occur. In a previous canine study, antinociception was demonstrated based on a tail flick test, but plasma concentrations of tapentadol were not evaluated (19).

Limitations of this study include the small number of dogs enrolled. An additional and substantial limitation to this study

was the unblinded nature of the assessment. It was known to the observer assessing subjective lameness scores that all dogs were given oral tapentadol. This may have biased the observer to give an improved lameness score to the dogs at the post-drug administration assessment that was not seen with objective gait analysis. The caregiver placebo effect could account for the improvement in the subjective lameness scores seen, as there was no corresponding significant improvement seen in the objective gait analysis performed. Ideally, the observer should have been blinded to whether dogs received the drug or not. Additionally, a blinded crossover study design would have enabled us to better determine if an effect was present. Venipuncture at the 4 h post-oral dosing timepoint was most commonly performed in the non-lame hind limb. This may have affected gait analysis results if the venipuncture caused significant discomfort to the dog. This, however, would likely have improved the symmetry index, thereby making the dog seem more sound, and this was not seen. Therefore, it is unlikely that this affected the interpretation of the data.

Although no significant improvement was seen in objective gait analysis, there was a subjective benefit in the lameness assessment. This study only assessed the short-term effect of a single 30 mg/kg BW dosage of tapentadol. Therefore, it is possible that long-term dosing may show a significant objective improvement in dogs for chronic pain management, or possibly acute post-operative pain. If proven to be efficacious, tapentadol could be a valuable addition to pain management for chronic pain states such as osteoarthritis, and post-operative analgesia as an adjunct to, or instead of, an NSAID. Additional studies are warranted to assess if long-term dosing with tapentadol can provide analgesia for chronic pain management. These studies should include objective assessment as well as evaluation with a validated client questionnaire such as the Canine Brief Pain Inventory (20).

Importantly, no significant side effects were noted in the short-term with a single oral dose of tapentadol. One dog vomited at the time of administration, but this was unlikely due to the drug itself as it was immediately following ingestion. There were no changes in temperature or heart rate with any of the dogs enrolled, which supports the findings of Howard et al (12), but differs from Giorgi et al (18), in which dogs were noted to have increased panting when given IV tapentadol. Furthermore, a minor sedative side effect was seen in only 1 dog in this study. An analgesic that causes significant sedation is not desirable in dogs undergoing orthopedic or neurologic surgery, as sedation can be interpreted by owners as adequate pain management since dogs are not moving much or whining, when in fact the dog is simply too sedate to demonstrate clinical signs of pain.

This study showed a significant improvement in subjective, but not objective lameness evaluation over a short time frame with administration of a single dose of oral tapentadol at a 30 mg/kg BW dosage. No significant adverse effects were noted with this single dose administration. Further studies are indicated to determine if a cumulative effect on pain relief may be seen with multiple daily dosing.

Acknowledgments

The authors thank RVTs Kayci Deakyne, Michelle Gilliam, Jimmy Quang, and Mary Ross, and Dr. Elizabeth Hoffman for their assistance in data collection. This study was supported by a grant from the ACVS Foundation and a grant from the Canine Research Funds of The Ohio State University. CVJ

References

1. Harper TAM. Conservative management of hip dysplasia. Vet Clin North Am Small Anim Pract 2017;47:807–821.
2. KuKanich B, Lascelles BDX, Papich MG. Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs. J Vet Pharmacol Therap 2005;28: 371–376.
3. Kukanich B, Spade J. Pharmacokinetics of hydrocodone and hydromorphone after oral hydrocodone in healthy Greyhound dogs. Vet J 2013;196:266–268.
4. Budsberg SC, Torres BT, Kleine SA, Sandberg GS, Berjeski AK. Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis. J Am Vet Med Assoc 2018;252:427–432.
5. Aghighi SA, Tipold A, Piechotta M, Lewczuk P, Kästner SB. Assessment of the effects of adjunctive gabapentin on postoperative pain after intervertebral disc surgery in dogs. Vet Anaesth Analg 2012;29:636–646.
6. Wagner AE, Mich PM, Uhrig SR, Hellyer PW. Clinical evaluation of perioperative administration of gabapentin as an adjunct for postoperative analgesia in dogs undergoing amputation of a forelimb. J Am Vet Med Assoc 2010;236:751–756.
7. Lascelles BD, Gaynor JS, Smith ES, et al. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. J Vet Intern Med 2008;22:53–59.
8. KuKanich B, Bidgood T, Knesl O. Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs. Vet Anaesth Analg 2012;39:69–90.
9. Tzschentke TM, De Vry J, Terlinden R, et al. Tapentadol hydrochloride. Drugs Future 2006;31:1053–1061.
10. Vadivelu N, Timchenko A, Huang Y, Sinatra R. Tapentadol extended-release for treatment of chronic pain: A review. J Pain Res 2011;4: 211–218.
11. Schröder W, Tzschentke TM, Terlinden R, et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. J Pharmacol Exp Ther 2011;337:312–320.
12. Howard J, Aarnes TK, Dyce J, et al. Pharmacokinetics and pharmacodynamics after oral administration of tapentadol hydrochloride in dogs. Am J Vet Res 2018;79:367–375.
13. Brooks D, Churchill J, Fein K, et al. 2014 AAHA weight management guidelines for dogs and cats. J Am Anim Hosp Assoc 2014;50:1–11.
14. Vettorato E, Bacco S. A comparison of the sedative and analgesic properties of pethidine (meperidine) and butorphanol in dogs. J Small Anim Pract 2011;52:426–432.
15. Wendlund TM, Martin KW, Duncan CG, Marolf AJ, Duerr FM. Evaluation of pacing as an indicator of musculoskeletal pathology in dogs. J Vet Med Anim Health 2016;8:207–213.
16. Fidman B, Nogid A. Role of tapentadol immediate release (Nucynta) in the management of moderate-to-severe pain. Pharm Thera 2010;35: 330–357.
17. Tzschentke TM, Christoph T, Kögel B, et al. (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): A novel m-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther 2007;323:265–276.
18. Giorgi M, Meizler A, Mills PC. Pharmacokinetics of the novel atypical opioid tapentadol following oral and intravenous administration in dogs. Vet J 2012;194:309–313.
19. Kögel B, Terlinden R, Schneider J. Characterisation of tramadol, morphine and tapentadol in an acute pain model in Beagle dogs. Vet Anaesth Analg 2014;41:297–304.
20. Brown DC, Boston RC, Coyne JC, Farrar JT. Ability of the Canine Brief Pain Inventory to detect response to treatment in dogs with osteoarthritis. J Am Vet Med Assoc 2008;233:1278–1283.