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Research Article

Retrospective Study of 240 Dogs Receiving Gabapentin for Chronic Pain Relief

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Abstract

Our goal was to assess gabapentin dosage and tolerability in dogs taking it for chronic pain. We retrospectively analyzed the medical records of 240 dogs taking gabapentin for chronic pain and systematically assessed: patient signalment, definitive diagnosis, location and description of pain, VAS scores immediately preceding and following the patient's maximum gabapentin dose, maximum gabapentin dosage, presence or absence of side effects related to gabapentin use, use of NSAID/immunomodulator drugs and nutraceuticals, presence or absence of levothyroxine supplementation, surgical procedures, and physical medicine. The range of tolerated gabapentin doses was 6.9 - 500 mg/kg/day [3.1- 227.3 mg/lb], PO, q12 hr (every 12 hrs) and only 10% of patients experienced the most common side effect of sedation. The data support the hypothesis that gabapentin is a well-tolerated and safe analgesic over a wide range of doses. Gabapentin appears to be tolerated at much higher doses than has been previously described.

ABBREVIATIONS

VAS: Visual Analogue Scale; NSAID: Non-Steroidal Anti-inflammatory Drug; GABA: Gamma-amino butyric acid; SD: Standard Deviation

INTRODUCTION

Current data on gabapentin largely has been derived from human medical research. Gabapentinoids have been proven useful for treating pain following spinal cord injuries [1]. Studies in humans have also shown gabapentin to be a safe analgesic for post-herpetic neuralgia [2]. Given the promising scientific and clinical data, further study of this drug, particularly its efficacy in dogs for neuropathic and chronic pain appears warranted.

Gabapentin, an amino acid molecule, was initially developed to mimic GABA, an inhibitory neurotransmitter. It is thought to work centrally by binding to the alpha-2-delta subunit of voltage-gated calcium channels within the dorsal horn of the spinal cord to reduce calcium currents [3]. This in turn prevents release of glutamate, an excitatory neurotransmitter, in the nociceptive pathways [4]. It is likely that multiple other pathways, not well described at this time, are also involved with mechanism of action [4]. Initially designed as a human antiepileptic drug, gabapentin has been used in numerous other capacities including analgesic management of neuropathic pain conditions, such as post herpetic neuralgia, diabetic neuropathy and amyotrophic lateral sclerosis [5].

In humans, there appears to be an inverse relationship between gabapentin dosage and bioavailability [3]. Gabapentin is absorbed intestinally via facilitated transport, which can become saturated as the gabapentin dose increases. It is theorized that the saturation of the transport mechanism necessitates a steady progression of dose increases to achieve the same level of analgesia [3]. There is also evidence of extensive pharmacokinetic variability among human patients; one study found up to a 22-fold pharmacokinetic variability in concentration to dose ratios [6]. A meta-analysis of five randomized human trials found that most patients require an increase of doses from 900 mg/day to 1800 mg/day to 3600 mg/day to achieve maximum efficacy. Importantly, however, they also found that the most effective dose for each patient required individualization according to patient response and tolerability [7]. In humans, gabapentin's most common side effects are sedation, somnolence, fatigue and dizziness [4]. Human use of gabapentin is thought to be relatively safe, evidenced by the fact that case reports of massive overdoses do not appear to lead to any clinically significant toxicity [3].

Despite the positive results on the use of gabapentin reported by numerous human medical reports, there remains limited data supporting gabapentin's efficacy in animals. One of the few studies done found that gabapentin, administered intraperitoneally and spinally, had inhibitory effects on substance P release in small primary afferent neurons and therefore decreasing facilitated pain states in rats [8]. There have been a handful of other studies that have explored gabapentin's efficacy for pre-

and post-operative animal pain management. One canine study did not find a perceivable difference in perioperative analgesia following forelimb amputations. These dogs received one 10 mg/kg [4.5 mg/lb] dose, followed by 3 days of 10 mg/kg/day [9]. The current dose protocol derived from pharmacokinetic data in six Greyhound dogs for gabapentin in dogs is 10-20 mg/kg [4.5 - 9.1 mg/lb] every 8 hours [10]. Plumb's recommends gabapentin at 5-10 mg/kg [2.3 - 4.5 mg/lb] every 12 hours for chronic pain [11].

Although the bioavailability data of gabapentin comes from human research, it is possible that a similar inverse relationship between dosage and bioavailability exists in dogs. However, one study of gabapentin in cats did not show an inverse relationship between bioavailability and dose received over two weeks [12]. It is possible that two weeks was not enough time to see the inverse relationship between bioavailability and dosage in cats. It may also be that cats do not experience the same overload of intestinal receptors as humans, therefore their bioavailability is less inversely affected by dosage.

With the paucity of studies on gabapentin in animals, data regarding dosing and side effects remains limited. In one study of 11 epileptic dogs receiving gabapentin as an antiepileptic, 6 dogs experienced side effects. Two dogs experienced mild sedation, 3 experienced sedation, and 1 became ataxic. The serum concentrations among these patients experiencing side effects were highly varied [13]. According to the ASPCA Animal Poison Control Center, there were 462 canine gabapentin exposure reports from 2009-2013. Ninety of these patients were symptomatic, with the most commons signs being ataxia, lethargy, and vomiting. To the knowledge of the authors, this is the first study of this magnitude to examine the use of gabapentin for canine chronic, pain management. The goal of this study was to analyze the medical records of canine patients diagnosed with chronic pain to better understand the efficacy and tolerability of gabapentin and its pattern of side effects.

MATERIALS AND METHODS

Subjects

Subjects included 240 dogs, treated by one practitioner (RD, one of the authors) between 2007-2018 at two different veterinary practices in Colorado, US. All the dogs were receiving gabapentin, in addition to other analgesics, to manage their chronic pain. For this study, chronic pain is defined as persistent pain lasting at least three months. All subjects are now deceased (either by euthanasia or natural causes).

Methods

This retrospective study focused on two sources of data. The first were results of each dog's VAS, used to assess degree of pain (conducted by RD during each office visit exam). The second sources of data were the systematic review of the subjects' medical records (Table 1). Data were entered into a commercially available software program and descriptive statistics are reported.

RESULTS

A total of 240 dogs were included in this study. Their ages ranged from 3 to 19 years, with a mean of 12.6 years (SD = 2.52). Their weights ranged from 2.5 [5.5 lb] to 59 kilograms [129.8 lb], with a mean weight of 23.8 kgs (SD =11.35). There were 126 spayed females, 107 neutered males, 4 intact females, and 3 intact males.

Table 1: Systematic review of the subjects' medical records.

Overall assessment:
Signalment
Definitive diagnosis (if applicable)
Pain:
Description of pain
Location of pain
VAS score immediately preceding and following the patient's maximum gabapentin dose
Gabapentin specific:
Maximum gabapentin dosage
Presence or absence of side effects related to gabapentin use
Drugs and other interventions:
NSAID/immunomodulator drugs
Other pain medications
Nutraceuticals
Presence or absence of levothyroxine supplementation
Surgical procedures (if performed)
Physical medicine (if performed)

All dogs suffered from chronic pain. The majority (217 patients; 90.42%) had pain localized to their back. The other anatomic locations of pain included stifle (33; 13.8%), elbow/shoulder (21; 8.8%) and hip (11; 4.6%). Some patients' pain was localized to multiple areas and is counted in all categories. The most common diagnosis of pain was osteoarthritis (203; 84.6%), followed by generalized, nonspecific back pain (22; 9.2%), intervertebral disk disease (18; 7.5%), and degenerative myelopathy (11; 4.6%). Some patients experienced two different kinds of pain and are embodied in both categories. One hundred and thirty-six (56.67%) patients did not have definitive anatomic cause for their pain, such as cruciate tears or intervertebral disc disease, as seen in Table 2.

Table 2: Through physical exam and diagnostics, we attempted to diagnose the cause of pain. Some patients received multiple diagnoses and are represented in multiple categories.

	Number of patients
No definitive diagnosis	136
Cruciate tear(s)	44
Intervertebral disc disease	18
Spondylosis	16
Luxating patella(s)	16
Osteosarcoma	8
Elbow or hip dysplasia	8
Disc protrusion	1

Treatment for the dogs' pain included gabapentin doses ranging between 6.9 mg/kg/day [3.1 mg/lb/day] to 500 mg/kg/day [227.3 mg/lb/day] with a mean dose of 80.6 mg/kg/day [36.6 mg/lb/day] (SD = 53.76). Dosages were calculated on an mg/kg/day basis. Twenty-six of the dogs (10.8%) experienced dose-limiting side effects including sedation, agitation, or ataxia. Of the dogs that experienced dose-limiting side effects, their dosages ranged from 9.5 mg/kg/day [4.3 mg/lb/day] to 362.3 mg/kg/day [164.7 mg/lb/day] with a mean dose of 64 mg/kg/day [29 mg/lb/day] (SD = 77.8). Their body weights ranged from 6 kg [13.2 lb] to 56 kg [123 lb] with a mean body weight of 26.2 kg [57.6 lb] (SD =11.12). Their ages ranged from 3 to 16 years with a mean age of 12.9 years (SD = 2.59).

In addition to gabapentin, 235 (97.9%) patients were on additional analgesics (often multiple types per patient). The most common analgesics were NSAIDs with 210 (87.5%) patients taking some form of a NSAID. The additional ancillary analgesics can be found in Table 3. Some patients also received corticosteroids for non-pain related issues such as atopy. Other interventions used for these dogs' pain included some form of physical medicine (138; 57.5%) or surgical orthopedic procedure (41; 17%). Of the 240 patients, 185 (77.1%) were also found to be hypothyroid or "grey-zone" hypothyroid as part of their overall health screening and were supplemented with levothyroxine.

Throughout the patients' care, their VAS scores were measured during each office visit. For the purpose of this study, we analyzed the VAS scores immediately preceding and following the maximum gabapentin dosage as noted from the medical records. Although we acknowledge that there are too many factors in the patients' medical management to attribute any change in VAS to any specific drug or analgesia modality, we still feel it is of value to note the VAS scores specifically before and after their maximum gabapentin dose. The maximum pain score was 3.71±1.88 (Mean ± standard deviation) with a median score of 3. The pain score after the maximum gabapentin dose was 1.51±1.21 (Mean ± standard deviation) with a median score of 1. Twelve patients did not have two VAS scores due to limited time spent with the practitioner. Of the remaining 228 patients, 20 had a net zero change in VAS score across the point of maximum gabapentin dose. Two hundred and eight patients showed a change in VAS. The maximum decline in VAS was -8, and the maximum incline in VAS was +4. The mean change in VAS was a decline by -2.25.

Table 3: These data describe how many patients were receiving various analgesics. Most patients were taking multiple medications and are represented in multiple categories.

	Number of patients
NSAID	210
Nutraceutical	187
Adequan	74
Tramadol	59
Amantidine	51
Steroids	29
Immunomodulators	3
Methocarbamol	1
CBD oil	1

DISCUSSION

This is the first study to the authors' knowledge to document the dose range and dose limiting side effects in a population of dogs actively managed for chronic pain. All patients in this study were on gabapentin due to an inability to fully control their pain with NSAIDs or nutraceuticals alone. This is evidenced by the fact that 97.9% of the patients were also receiving some form of other analgesic modalities including analgesics, nutraceuticals, and physical medicine - all in an attempt to alleviate their chronic pain.

Results of this study found gabapentin to be a well-tolerated analgesic, as evidenced by the low rate of dose-limiting side effects. In this group of patients, we found gabapentin to have a large effective dosage range, from 6.9 to 500 mg/kg/day. Only 26 dogs (10.8%) of dogs experienced sedation or other side effects and none of the side effects was life threatening. According to human medical studies, in the face of chronic, maladaptive, neuropathic pain, gabapentin typically requires dose elevations over time to maintain efficacy. It has been suggested that this is due to the facilitated transport mechanism being overwhelmed and a decrease in bioavailability of the drug as dosage is increased.[3]Our results suggest the same to be true for dogs experiencing chronic pain; that gabapentin should be dosed to effect and pain should be monitored at every office visit. Results also support the use of higher doses of gabapentin to achieve better analgesia and pain management with minimal risk of side effects.

There are two aspects of the subjects' medical records that deserve future study. The first is that 8 of the dogs in our study experienced paresis at some time in their medical history. Their gabapentin dose was not changed due to this. We cannot rule out gabapentin as a cause or contributing factor to their paresis, but the clinical impression at the time was that it was a progression of the neuropathic disease.

The second is the fact that 77.1% of the subjects were taking levothyroxine, a fact that is difficult to interpret without the ability to compare this figure against the general population of hypothyroid dogs. Although national or worldwide incidence of canine hypothyroidism is unknown, it has been noted that hypothyroidism is the most common endocrinopathy in dogs [14]. The unexpected finding that 185 (77%) patients were hypothyroid warrants a follow up study to explore the possible connection between chronic pain and hypothyroidism. Perhaps chronic pain, and therefore chronic bodily stress, leads to an accelerated depletion of thyroid hormone.

Limitations of this study include a smaller sample size and the fact that all patients were from the same geographical area and seen by the same practitioner. We cannot rule out variations related to different geographic regions. Additionally, side effects seen with gabapentin are often behavioral and therefore analysis of side effects is inherently subjective. Moreover, in this study, we relied on clients' awareness of behavioral side effects/changes at home and their willingness to be forthcoming with that information in order to decrease or discontinue gabapentin. There are also inherent limitations with any retrospective study

and therefore the need for controlled, prospective studies of gabapentin use in dogs.

The results from this case series suggest that gabapentin is well-tolerated at much higher doses than what is typically prescribed. Side effects were uncommon, with no clear pattern based on dose, or dog size or age. Therefore, like many other analgesic medications, the efficacy of gabapentin appears patient-specific and should be dosed to effect until side effects are noted or analgesia is achieved.

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