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**Faculty of Veterinary Medicine
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The adverse effect profile of gabapentin in dogs

A retrospective questionnaire study

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The adverse effect profile of gabapentin in dogs – a retrospective questionnaire study

Gabapentins biverkningsprofil hos hund – en retrospektiv enkätstudie

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SUMMARY

Gabapentin, originally designed as an antiepileptic drug, has shown promising properties for treatment of neuropathic and chronic pain conditions in humans with diseases such as post herpetic neuralgia, amyotrophic lateral sclerosis (ALS) and diabetic neuropathy, but the evidence regarding analgesic effect, adverse reactions and dosing in animals remains sparse.

Recommendations in human medicine are to progressively increase, and taper, dosing of gabapentin to minimize the risk of adverse effects. The most common adverse effects in humans are dizziness, somnolence, peripheral edema and gait disturbance. No studies have been conducted on adverse effects of gabapentin in dogs. The pharmacokinetics of gabapentin, in both humans and dogs, also suggest dosing three times daily to maintain concentrations considered therapeutical in humans.

A retrospective study of dogs medicated with gabapentin at the University Animal Hospital in Uppsala was conducted between 1st of September 2017 and 1st of January 2018. The aim of this study was to evaluate the adverse effect profile of gabapentin in dogs. The main research hypothesis tested was if there is a dose relationship regarding the adverse effects seen in dogs, similar to that seen in humans. An additional hypothesis was if there are risk factors, such as not gradually increasing dosing, or peak serum concentrations, for developing adverse effects from gabapentin treatment.

The study was conducted through a questionnaire sent out to owners of dogs medicated with gabapentin within the past two years. The first page of the questionnaire included several questions with a combination of open- and closed questions. The second part listed adverse effects that the owner graded using a 5-grade scale from “not present”, “mild”, “moderate”, “severe” to “very severe”. The questionnaire was conducted in Swedish and was sent out by mail.

A total of 50% reported some type of adverse effect during treatment with gabapentin, but 12 of 16 dogs were, during the whole treatment, on multimodal treatment protocols. Neurological adverse effects, similar to those seen in humans on gabapentin treatment, were reported in five dogs. These adverse effects could not be related to other medications or disease symptoms. Four dogs underwent a period of monotherapy with gabapentin. No adverse effects were reported in these dogs.

Despite recommendations in human medicine to gradually increase the gabapentin dose, only 4 of 16 dogs were prescribed a dosing regimen following these recommendations. A total of 6 dogs were administered gabapentin twice daily, whereas the remaining 10 received gabapentin 3 times daily.

The study provided insight into dosing and effect of gabapentin in dogs. However, due to a small sample size and a relatively homogenous study group regarding dose range, and a large number of dogs on multimodal pain treatment, the study resulted in few conclusive findings regarding adverse effects of gabapentin in dogs.

Insufficient knowledge about gabapentin’s properties in dogs and other pets poses a risk that a drug that could potentially treat chronic pain conditions may be administered in a way that gives results in suboptimal, or not effective, blood concentrations. Therefore, more research is needed to determine the pharmacodynamics of gabapentin in dogs. For example, it is of paramount importance to further investigate if gabapentin provides the same analgesic effect for dogs as seen in studies of humans, as gabapentin may open possibilities of treating otherwise untreatable pain conditions.

SAMMANFATTNING

Gabapentin utvecklades ursprungligen som en antiepileptisk medicin, men visade sig senare ha effekt även vid behandling av neuropatiska och kroniska smärttillstånd hos människa. Läkemedlet har använts vid bland annat postherpetisk neuralgi, amyotropisk lateral skleros (ALS) och diabetesneuropati, men evidensen gällande analgetisk effekt, biverkningar och dosering till djur är i dagsläget begränsad.

Inom humanmedicinen rekommenderas upptrappning, och nedtrappning, av gabapentindosering för att minimera risken för biverkningar. De vanligaste biverkningarna på humansidan är yrsel, somnolens, perifera ödem och ataxi. Inga studier på biverkningar av gabapentin hos hund finns att tillgå. Gabapentins korta halveringstid talar även för att läkemedlet, hos både människa och hund, bör administreras tre gånger dagligen för att bibehålla de koncentrationer som visats vara terapeutiska hos människa.

En retrospektiv enkätstudie av hundar medicinerade med gabapentin vid Universitetsdjursjukhuset (UDS) i Uppsala gjordes mellan 1:a september 2017 och 1:a januari 2018. Målet med denna studie var att undersöka gabapentins biverkningsprofil hos hund och om riskfaktorer för att utveckla biverkningar, såsom att ej trappa upp dosen eller höga maximala koncentrationer i blod, kunde identifieras. Studiens primära hypotes var att ett dosrelaterat samband fanns gällande gabapentins biverkningar hos hund, liknande sambanden som setts på humansidan.

En enkät skickades ut till djurägare med hundar medicinerade med gabapentin inom de senaste två åren. Första sidan i enkäten inkluderade flertalet frågor, där en del var öppensvarsfrågor och en del flervalfrågor. Den andra delen i enkäten bestod av en tabell där djurägaren kunde gradera biverkningar från "ej förekommit", "lindrigt", "måttligt", "kraftigt" till "mycket kraftigt". Enkäten var skriven på svenska och skickades ut via post.

Hälften av hundarna rapporterade någon form av biverkning under behandling med gabapentin, men av dessa stod 12 av 16 hundar under hela behandlingperioden på multimodala behandlingsprotokoll. Totalt 5 hundar rapporterade neurologiska biverkningar, liknande de som setts vid gabapentinbehandling på humansidan, som inte kunde direkt relateras till individernas övriga medicinering eller sjukdomsbild. Totalt 4 hundar behandlades under en period med enbart gabapentin. Hos dessa hundar rapporterades inga biverkningar.

Trots doseringsrekommendationerna på humansidan trappades medicineringen upp hos endast 4 av 16 hundar. Totalt 6 hundar fick gabapentin två gånger dagligen, medan resterande 10 medicinerades tre gånger dagligen.

Studien gav insikt i dos- och effektförhållanden av gabapentin hos hund. Beroende på multimodala behandlingsprotokoll och ett begränsat antal svarande och därmed en relativt homogen urvalsgrupp avseende dosspann, kan dock få avgörande slutsatser dras från denna studie gällande gabapentinbiverkningar hos hund.

Otillräcklig kunskap om gabapentins egenskaper hos hund, och våra andra husdjur, medför en risk att ett läkemedel som skulle kunna behandla kroniska smärttillstånd administreras på ett sådant sätt att suboptimala, eller inadekvata, koncentrationer fås. Därför behövs mer forskning för att fastställa gabapentins farmakodynamiska profil hos hund. Det är av största vikt att vidare kartlägga om gabapentin ger upphov till samma analgetiska effekt hos hund som hos människa, då gabapentin potentiellt skulle kunna vara en effektiv behandling av smärttillstånd där andra alternativ saknas.

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INTRODUCTION

Gabapentin, originally designed as an antiepileptic drug, has, alongside treatment of epilepsy, shown promising properties for treatment of neuropathic and chronic pain conditions in humans with diseases such as post herpetic neuralgia, amyotrophic lateral sclerosis (ALS) and diabetic neuropathy. (FASS, 2017; Thomson/Micromedex, 2006). Several studies on adverse effects in humans have proven dizziness, somnolence and peripheral edema to be the most common adverse effects of gabapentin (Parsons et al., 2004; Moore et al., 2014). Gabapentin has been increasingly used within the veterinary field as an analgesic drug over the past decade. However, the evidence regarding analgesic effect, adverse reactions and dosing in animals remains sparse (Peck, 2015).

Although general knowledge regarding epilepsy is somewhat lacking, there are several treatment options for dogs, aside from gabapentin, such as phenobarbital, imepitoin, potassium bromide, levitiracetam and others (Charalambous et al., 2014). When it comes to chronic and neuropathic pain conditions there are limitations in the treatments available (Läkemedelsverket, 2005) and therefore drugs that can treat these conditions are needed.

Providing adequate analgesia to animals in pain is key in ensuring animal welfare (Sneddon et al., 2014). Opioids and non-steroidal-anti-inflammatory drugs (NSAIDs) both have limitations when it comes to chronic pain conditions (Läkemedelsverket, 2005). The development of alternative treatment for chronic pain is therefore essential to increase the possibility of treating otherwise untreatable pain conditions and thus strengthen the quality of life for pets suffering from neuropathic and chronic pain.

This study aims at serving as a building block in answering whether gabapentin can be classified as a safe drug for dogs and if the adverse effect profile in dogs is similar to that described in man. The main research hypothesis was if there is a dose relationship regarding the adverse effects seen in dogs, similar to that seen in humans, and if there are risk factors, such as not gradually increasing dosing or peak concentrations in blood, for developing adverse effects from gabapentin treatment. A retrospective, non-blinded pet owner-directed questionnaire with emphasis on adverse effects in dogs treated with gabapentin was created to collect information on the properties of the drug in dogs.

LITTERATURE REVIEW

Managing neuropathic pain

When it comes to neuropathic pain conditions there are limitations in the treatments available. The Swedish Medical Products Agency organized a workshop in year 2005 to develop recommendations for treatment of pain, including neuropathic pain, in small animals. Non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, acupuncture and heat treatment were recommended for chronic pain conditions in dogs. Alongside NSAIDs and acupuncture, corticosteroids were also put forward as an alternative treatment for cats (Läkemedelsverket, 2005). Pentosan polysulfate (Cartrophen) is also used in dogs for treatment of pain associated with osteoarthritis (Ghosh, 1999). Another alternative is tricyclic antidepressants, considered first-line agents for neuropathic pain in humans (Moore, 2016). Due to adverse effects and risk of cardiovascular mortality (Cohen et al., 2000), they are not used to any larger extent. During the previously mentioned workshop, it was stated that available analgesia for chronic pain is inadequate (Läkemedelsverket, 2005). Opioids seldom provide the pain relief needed for this type of patient and is not optimal for long term use (Läkemedelsverket, 2005).

Mechanism of action

Gabapentin is an amino acid originally developed as a structural analogue of the inhibitory transmitter substance gamma amino butyric acid (GABA). Because of its similar structure to this transmitter substance, gabapentin was thought to be useful in the treatment of epilepsy. Gabapentin showed additional properties when used in vivo due to gabapentinoids having an alternative mechanism of action (Gee et al., 1996; Field et al., 2004).

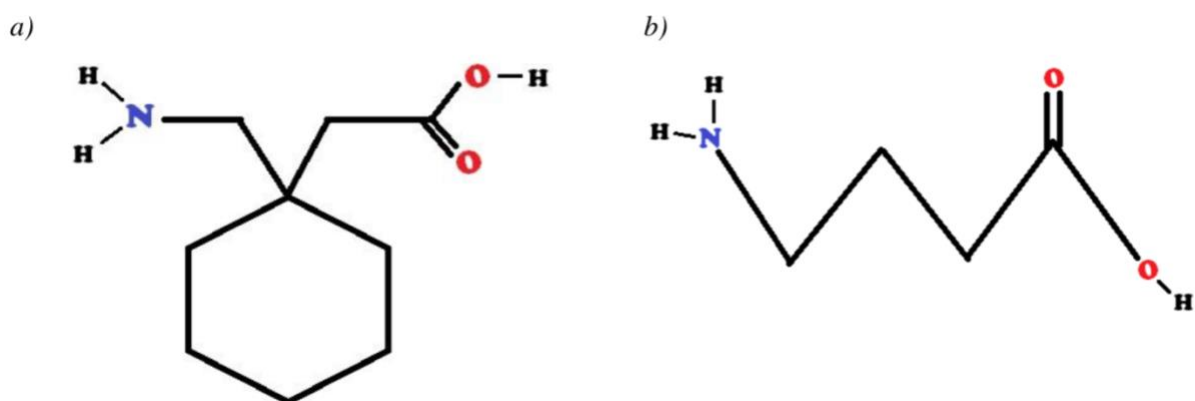


Figure 1. A 2D model of the molecular structure of a) gabapentin and b) the endogenous signal substance GABA, which gabapentin was constructed as an analogue of (Peck, 2015).

Research shows that gabapentin has no affinity to GABAA- or GABAB-receptors in rats, despite the molecules similarity to the GABA-molecule (Lanneau et al., 2001; Jensen, 2002). Gabapentin is not metabolised to GABA. Despite this, gabapentin does increase the concentration of GABA in the brain (Kuzniecky et al., 2002). It is not known whether this is through increased GABA synthesis, increased release in the vesicles or decreased GABA metabolism (KuKanich & Cohen, 2011).

The currently dominating theory on how gabapentin exerts its effect is that it binds to the $\alpha 2$ - δ -subunits of the voltage dependent calcium channels (VDCC) in the dorsal horn of the bone marrow. Several animal studies have strengthened this theory by confirming the significance of the $\alpha 2$ - δ -subunits role for gabapentins analgesic properties (Gee et al., 1996; Bryans et al., 1999; Field et al., 2000). There are several different types of voltage-gated calcium channels

and a large range of genes encoding their subunits. This, along with co-assembly with a wide range of ancillary calcium channel subunits and alternative splicing, give these channels the ability to play many different, and very specific, roles in neuronal subtypes. The $\alpha 2$ - δ -subunits of the VDCC, which gabapentin targets, are upregulated in chronic pain states. Inhibition of this passage way, and consequently relief from pain, is therefore achieved by targeting the subunit (Zamponi, 2015). The calcium channels are crucial for brain function. When they are dysfunctional, neurological disorders such as pain, epilepsy, migraine and ataxia may arise (Simms & Zamponi, 2014).

Gabapentin has been proven to interact with both the $\alpha 2$ - δ -1- and the $\alpha 2$ - δ -2-subunit of the VDCC, but the analgesic properties are linked to interaction with $\alpha 2$ - δ -1 (Liao et al., 2010). Binding to the VDCC and inhibiting influx of Ca^{2+} to the neuron decreases the release of excitatory neurotransmitters, inhibiting the signaling pathways in the nervous system (Taylor et al., 2004). Additionally, Field et al. (2004) has shown that mice with a mutation in the $\alpha 2$ - δ -1-subunit receive no, or very low, analgesic effect of gabapentin.

There are also studies on acute, inflammatory pain in rat models suggesting antinociceptive efficacy of gabapentinoids on pain response. No neuropathic pain component was present in the animals in these studies. This forwards the theory that, depending on the type of neuropathic pain present, gabapentin may exert its action through more mechanisms than those known to date (Liao et al., 2010; Rahman & Dickenson, 2013).

Indications and administration protocols

Humans

According to the Pharmaceutical Specialties in Sweden (FASS), gabapentin has multiple indications in human medicine, including treatment of epilepsy, ALS and peripheral neuropathic pain. Partial epileptic seizures, with or without generalization, can be treated with gabapentin as part of the medical protocol or as monotherapy. As for specific neuropathic pain conditions, gabapentin is used in treatment of diabetic neuropathy and post herpetic neuralgia (FASS, 2017). The drug is FDA approved in humans for postherpetic neuralgia (PHN) and the extended release gabapentin ester formula, Gabapentin Enacarbil, is approved for treatment of restless legs syndrome (Thomson/Micromedex, 2006).

Initial dosing for adults is recommended to start at 300 mg orally on day one, two doses of 300 mg on day two and three doses of 300 mg on day three. After three days, an increase in the separate rations can be done. Maximum dose in adult humans is 1800 mg a day (FASS, 2017). The therapeutic concentration of gabapentin in humans is over $2\mu\text{g/mL}$ (Thomson/Micromedex, 2006). Gabapentin is, in Sweden, available in capsules of 100, 300, 400, 600 and 800 mg (FASS, 2017). At the end of gabapentin treatment, it is recommended that the treatment is phased out during a minimum of seven days. This is recommended, regardless of indication, as seizures and withdrawal symptoms may occur otherwise (Barrueto et al., 2002; See et al., 2011; KuKanich, 2013; FASS, 2017).

Dogs

The oral dose needed in dogs to generate the therapeutic plasma concentration seen in man ($2\mu\text{g/mL}$) is 10-20 mg/kg every eight hours. Gabapentin is not approved for use in dogs but is frequently prescribed in clinics for a variety of pain related conditions (Vollmer et al., 1986; Radulovic et al., 1995; Rhee et al., 2008, KuKanich, 2013). The evidence regarding gabapentin as an anti-epileptic drug in dogs is insufficient and therefore it is mainly recommended as an alternative adjunctive therapy alongside phenobarbital and potassium bromide in cases of treatment failure (Charalambous et al., 2014).

Formulas

Several different formulas of gabapentin have been developed. These include Gabapentin, extended release gabapentin (Gabapentin ER) and the prodrug Gabapentin Enacarbil (GEN). The three formulations have, in humans, been proven to have different properties when it comes to half-life, adverse effects and recommended dose. A large review article has compiled several randomized control trials studying dosing of gabapentin for humans suffering from post-herpetic neuralgia (PHN). In total, the review article includes seven studies with a total of 4091 randomized individuals, where 2041 of these individuals were studied regarding efficacy and 2050 individuals were studied with focus on safety assessment of gabapentin. Several formulas were used in these studies, including gabapentin, gabapentin ER and GEN. The studies showed that single daily oral administration of Gabapentin ER improved pain scoring, but also resulted in a higher prevalence of adverse effects, such as dizziness, somnolence and peripheral edema. GEN 1200 mg/day and 2400 mg/day was proven to be more effective for treatment of PHN and gave rise to fewer adverse effects (Wang & Zhu, 2016). Gabapentin ER and GEN are not currently available in Sweden (Fass, 2017).

Pharmacokinetics

Gabapentin is in humans distributed to practically all tissues and passes over the blood-brain-barrier to the central nervous system (Vollmer et al., 1986; Radulovic et al., 1995). The drug has been studied in several animal models to evaluate the effect in treatment of epilepsy. In these studies, gabapentin has been noted to be quickly absorbed and active after oral consumption (Vollmer et al., 1986; Gidal et al., 2000; Kammerer et al., 2011). The oral bioavailability in dogs is 80% when administering a dose of 50 mg/kg (Vollmer et al., 1986; Radulovic et al. 1995; KuKanich & Cohen, 2011). Radulovic et al. (1995) studied gabapentins pharmacokinetic profile in one female beagle dog. The dog was administered 50 mg/kg of gabapentin intravenously and this was compared to an oral dose of 50 mg/kg in the same dog. This study gave a clearance value of 0.1362 L/kg/h, $t_{1/2}$ of 2.9-4 h and a volume of distribution of 0.158 L/kg (Vollmer et al., 1986; Radulovic et al. 1995).

Gabapentin has a dose-limited absorption behavior and is absorbed from a short part of the duodenum. The dose-limited absorption has in man and rat been linked to saturable active transporters in the duodenum (Stewart et al., 1993; Larsen et al., 2014). It is not known which transporters are involved in absorption. These properties may increase risk for variable, unpredictable and suboptimal plasma concentrations (Vollmer et al., 1986; Gidal et al., 2000; Kammerer et al., 2011).

Terminal half-life in dogs after oral administration has been proven to be 3-4 hours. Because of this property, gabapentin needs to be administered three times daily to maintain target concentration. The target concentration is 2 µg/mL, a concentration which has been derived from human medicine due to lack of studies on gabapentins pharmacodynamics in veterinary medicine (Vollmer et al., 1986; Radulovic et al. 1995; KuKanich et al. 2011; Kukanich & Cohen, 2011).

Studies of the pharmacokinetics of gabapentin in dogs has showed great variation in plasma concentrations. In Aghighi et al. (2012) 63 dogs were given an oral dose twice daily. Blood samples were collected after 12 and 72 hours from the first dose. The plasma concentrations 12 hours after oral administration of 10 mg/kg of gabapentin, given twice daily, ranged from >1.0 µg/mL (detection limit) to 9.08 µg/mL at 24 hours. After 72 hours from the first dose, when 6 doses had been given, the plasma concentrations ranged from 1.0 µg/mL to 11.00 µg/mL. The median concentration was 2.45 µg/mL at 24 hours and 1.36 µg/mL at 72 hours. At 24 hours, 6

of 29 dogs given gabapentin fell below the detection limit in serum. The same was true for 7 of 28 dogs at 72 hours (Aghighi et al., 2012).

Gabapentin is excreted unmetabolized through the kidney in humans, but this is not the case for dogs. On the contrary, when Radulovic et al. (1995) studied the pharmacokinetic profile of gabapentin in dogs they reported that 34% of the plasma concentration of gabapentin was metabolized to N-methyl-gabapentin in the liver.

Previous research

Analgesic properties in dogs

The evidence base regarding gabapentin's pain-relieving properties in other species than humans is low. Aghighi et al. (2012) showed that 10 mg/kg of gabapentin 2 times daily did not increase analgesia, compared with solely opioid analgesia, after intervertebral disc surgery in dogs. This was a randomized, placebo-controlled clinical trial with the observer unaware of the treatment given. The number individuals included in the study were 63 and they were divided into two categories based on serum concentration above or below 3 µg/mL. It is important to note that the dogs in this study were administered methadone during the first 24 hours and that the dosing was lower than recommended (Thomson/Micromedex, 2006).

Antiepileptic properties in dogs

There are no unbiased, well-designed studies on the use of gabapentin in treatment of epilepsy in dogs. There are case studies which have shown that, when combined with phenobarbital and bromide in dogs, gabapentin has anticonvulsant properties (KuKanich, 2013). A review article on the topic mentions two minor studies, which both were considered biased to some extent. One of the studies recommend the use of gabapentin as a complementary treatment alongside other antiepileptic compounds. One of the studies recommended gabapentin with reservation. More studies are needed to conclude the efficacy and safety of gabapentin for treatment of epilepsy in dogs (Charalambous et al., 2014).

Evidence in other species

Gabapentin has been reported to relieve both traumatic and orthopedic pain in cats (KuKanich, 2013). However, this information is merely from case reports. Therefore, more studies are needed to confirm these results (KuKanich, 2013). No analgesic effect was seen when studying the pharmacodynamics of gabapentin in cats in an experimental thermal antinociceptive model (Pypendop et al., 2010).

Gabapentin has been proven to have an acute inhibitory effect on substance P release from small primary afferent neurons and effect in inhibiting facilitated pain states after formalin paw injections when administered intraperitoneally and spinally in rats (Takasusuki & Yaksh, 2011). No controlled clinical trials of gabapentin in animals have been conducted on the analgesic effects in chronic neuropathic pain. As a result, the appropriate dosing for analgesic effect in animals has not been established (KuKanich, 2013).

Adverse effects

Gabapentin does not induce CYP450, does not bind to plasma proteins to any larger extent and passes through most species bodies unmetabolized, with dogs being the exception. Therefore, the substance stands out amongst other anti-epileptic compounds (Radulovic et al., 1995).

In an article reviewing gabapentin as a potential medication for chronic pain and fibromyalgia in adult humans, multiple adverse effects were reported. A total of 62% of the 4125 participants

had some adverse effect related to their intake of gabapentin and 11% had to withdraw because of these adverse effects (Moore et al., 2014). Several studies on adverse effects in humans have proven dizziness, somnolence, peripheral edema and gait disturbance to be the most common adverse effects (Parsons et al., 2004; Moore et al., 2014) but a case report also reports a human patient presenting with neutropenia when treated with gabapentin (Derbyshire & Martin, 2004). The risk for peripheral edema was dose related and seen in individuals given 1800 mg or more of gabapentin daily. Dizziness and somnolence were not dose related adverse effects. Serious adverse effects did not occur to any higher extent in the gabapentin groups compared to placebo. All adverse effects reported in the reviewed articles were linked to a dosage of 1200 mg daily or more (Parsons et al., 2004; Moore et al., 2014). Adverse effects of gabapentin in humans have been classified as mild to moderate and generally subside within 10 days after day one of treatment (Backonja & Glanzman, 2003). Gabapentin is frequently prescribed as part of a multimodal pain protocol but there are no studies conducted within the human field on adverse effects occurring with multimodal pain treatment, such as paracetamol, NSAIDs or glucocorticoids in combination with gabapentinoids (Mathiesen, 2014).

Another gabapentinoid, pregabalin, has been reviewed in regard to adverse effects. Studies show adverse effects of visual disturbances, dizziness and lightheadedness. Despite pregabalin's similar mechanism of action, it has a slightly different adverse effects profile than gabapentin. It has been hypothesized that this may be due to their different pharmacokinetic characteristics or additional mechanisms of action on other receptors, such as NMDA-receptors, alpha-2-adrenergic receptors or adenosine A1 receptors that are not yet known (Mathiesen, 2014).

Gabapentin is, as noted previously, primarily excreted through the kidney in humans. This may give rise to higher serum concentrations of the drug in individuals with impaired kidney function, as a result of not excreting the drug to the same extent. This could lead to a higher risk of toxic effects on the central nervous system. There are several reports on gabapentin induced myoclonus (Zand et al., 2010; Kaufman et al., 2014). Recommendations have been made for dose adjustment of gabapentin in humans with renal impairment, where the maximum dose with a normal clearance (≥ 60) is 3600 mg, with clearance 30-60 1400 mg, clearance 15-30 700 mg and with a clearance of 15 the recommended maximum dose is 300 mg (Schmidt et al., 2014). The adjustment schedule of dose due to kidney problems may be less relevant in dogs as an alternative elimination pathway has been established.

In a study of 11 dogs with epilepsy treated with gabapentin, added to a dose regimen of previously prescribed phenobarbital and potassium bromide, 6 of 11 showed signs of adverse effects. The adverse effects reported were two cases of mild sedation, three cases of sedation and one case of ataxia. The serum concentrations varied greatly amongst the individuals with signs of adverse effects. Sedation was seen in a golden retriever with a serum concentration of 2,2 mg/L, where the sample was taken immediately before the next administered treatment (Platt et al., 2006). This serum concentration is just above the theoretically therapeutical limit (Thomson/Micromedex, 2006).

Carcinogenic properties

There is little data on the carcinogenic properties of gabapentin in humans. A cohort study of epidemiologic data over 15 years from the United States and United Kingdom showed no link between gabapentin and an increased risk for neoplasia, although high doses of gabapentin in rats have been related to pancreatic acinar cell tumours (Irizarry et al., 2011). No such research has been conducted in dogs.

Pregnancy

Studies in humans have investigated the teratogenic effects of gabapentin during the first trimester of pregnancy. A prospective study of 223 pregnant humans treated with gabapentin, and an equally sized control group, showed no increased risk for teratogenic effect on the fetus when the child bearer was treated with gabapentin. Studies of gabapentin's effect on pregnancy regarding low birth weight and preterm birth, which have not yet been studied, could give more information on the safety of gabapentin (Fujii et al., 2013).

Withdrawal

The most common adverse effects of gabapentin in humans are dose related, with a higher risk when simultaneously being treated with drugs that have a similar adverse effect profile (Kukanich, 2013). Several case reports in humans suggest an increased risk for seizures and other withdrawal symptoms when discontinuing gabapentin treatment without tapering the dosage (Barrueto et al., 2002; See et al., 2011; Kukanich, 2013).

Canine specific toxicity

Because of the metabolism of gabapentin in the canine liver, there is a potential theoretical risk for hepatotoxicity if the drug is administered with other liver-straining substances, such as phenobarbital (Radulovic et al., 1995; Platt et al., 2006). Some formulas of gabapentin contain small amounts of xylitol, which is toxic to dogs, but the amount is considered too small to give rise to toxic effects. The combination of these formulas of gabapentin and other xylitol containing agents is not recommended (Kukanich, 2013).

Insensitivity

Long term gabapentin use could give rise to gabapentin insensitivity. The $\alpha_2\delta$ -1 subunit is crucial for the anti-allodynic effects of gabapentin. In a rat model of central post-stroke pain hypersensitivity, it has been shown that the $\alpha_2\delta$ -1 protein is upregulated during the first two weeks after injury. After this time period, the protein is dramatically down regulated. This coincided with the emergence of gabapentin insensitivity in these rats (Yang et al., 2016).

Synergism

Selective serotonin reuptake inhibitors

5-HT₆ receptor antagonists have been proven to enhance the analgesic effect of gabapentin in rats. This, in theory, may provide an option for treatments with lower doses of gabapentin and therefore a reduction of the frequency of adverse events (Jayarajan et al., 2015).

Morphine

Morphine combined with gabapentin has in man been proven to give a partly superior pain elevating effect than the two substances alone. Higher serum concentrations of gabapentin have been noted when administered together with morphine. Morphine tolerance and the pain-relieving properties of this substance in rats has also been improved with co-administration of gabapentin. This mechanism has been linked to the increased expression of the anti-inflammatory cytokine IL-10, which morphine downregulates when gabapentin is not administered as part of the treatment. Gabapentin has also reduced early postoperative pain and the use of opioids after surgery in humans. The efficacy of the combination of these two substances is therefore superior to single therapy with gabapentin or morphine (Eckhardt et al., 2000; Gilron et al., 2005; Schmidt et al., 2014; Bao, 2014).

NSAIDs

The combination of NSAIDs and gabapentin in rats with inflammatory pain in peripheral nerves has given rise to a three times higher pain elevating effect than the sum of the two substances effect when administered as single therapy (Picazo *et al.*, 2006).

Acetylcholinesterase inhibitors

There is evidence indicating that an increased concentration of acetylcholine in the synapses in the CNS in combination with activation of α_2 -receptors may decrease hypersensitivity from neuropathic pain. The use of acetylcholinesterase inhibitors can be used to obtain a higher concentration of acetylcholine in synapses (Kimura *et al.*, 2012). Humans diagnosed with neuropathic, cancer induced pain have, in a non-blinded study, been treated with a combination of gabapentin and acetylcholinesterase inhibitors. The pain-relieving properties were significantly higher in these six patients than expected. It should be noted that no comparison with placebo was included in this study (Basnet *et al.*, 2014).

MATERIALS AND METHODS

Study design

A retrospective study of dogs medicated with gabapentin at the University Animal Hospital in Uppsala was conducted between 1st of September 2017 and 1st of January 2018. Data was collected through a questionnaire sent out to pet owners with dogs medicated with gabapentin and from electronic records at the Animal Hospital.

A questionnaire was designed using the Toronto side effects scale and the UKU Side effects rating scale (Lingjærde *et al.*, 1987). Symptoms not seen previously which emerged during the two first weeks of treatment with gabapentin were reported. The first page of the questionnaire had several questions with a combination of open and closed questions and was followed by a second part with a table with a list of adverse effects. Adverse effects were graded based on severity, with a scale from 1-5 where 1 was “not present”, 2 was “mild”, 3 was “moderate”, 4 was “severe” and 5 was “very severe”. The questionnaire was conducted in Swedish. The last page included an option to take part of the study when it was complete. The full questionnaire is enclosed as an attachment (*Appendix 1*).

Study population

The questionnaire was sent out by mail to households with dogs currently, or previously, on gabapentin. The first page of the questionnaire was an introduction that explained the study, why the respondent’s answers were important and how long time it would take to finish. It was also explained that information the respondents submitted would be presented on group level and no personal information would be disclosed. Included in the envelope was a pre-stamped envelope with the institution address. An e-mail address for responding by e-mail was also provided to improve the respondent rate.

Inclusion criteria were that the dog had started gabapentin treatment within two years before the day they received the questionnaire. All breeds and all indications for use of the drug were included. Dogs on multimodal treatment protocols were also included. Dogs who received gabapentin within the past 2 years were included in the study. After 3 weeks, a reminder was sent out to all non-responders.

Data collection

Individuals were identified through the journal system “Trofast” used at the University Animal Hospital in Uppsala. The journal system featured no way to search for individuals who were prescribed a particular substance or search for a specific diagnosis. Therefore, the search was conducted by going through bookings and posting a list for veterinarians, veterinary technicians and students to write down cases if they encountered a dog currently on gabapentin, or one who they prescribed gabapentin to. Articles for the literature review were searched for in Pubmed, Web of science, Google scholar and Primo. The search words used were: “gabapentin”, “neurontin”, “neuropathic pain”, “evidence”, “effect”, “adverse effects”, “side effects”, “adverse reactions”, “dog”, “pharmacokinetic”, “pharmacodynamic” and “monte carlo”.

Information regarding weight, age, dose, reported adverse effects during use and possible multimodal therapy was collected from the electronic clinical record. The onset time of adverse effects in relation to first day of medication was also noted, as was the consequence on regimen of medication after adverse effects were noted. This was done to minimize the risk of compliance related misinformation. No veterinary evaluations were conducted, nor any blood samples taken, of the animals included in the study.

Additionally, the Swedish Medical Products Agency was contacted for access to their database on adverse effect reports on gabapentin in dogs. The findings from this database are included in the results section.

Data analysis

The questionnaires were descriptively evaluated with regard to effect seen when on gabapentin, consequences of adverse effects and types of adverse effects seen. Simultaneous treatment with medications with a well-documented adverse effects profile and underlying diseases were taken into account when evaluating presence of adverse effects.

A Monte Carlo simulation was designed with data of clearance, volume of distribution and bioavailability obtained from Radulovic *et al.* (1995) and oral dose obtained from the mean dose of the dogs included in this study. The Monte Carlo simulation is a stochastic simulation model which offers variation in possible outcomes over time (Bonate, 2001). In this study 200 possible outcomes of the obtained pharmacokinetic data were simulated to show the theoretical variance of a single dose of gabapentin. This analysis was performed using Microsoft Excel.

To test the hypothesis that the risk for adverse effects is lower when gradually increasing initial doses were prescribed, two separate groups were created: one where the dogs had progressively increased dosing and one where the dogs did not increase dosing. These groups were further sub-categorised based on presence of adverse effects. With this table relative risk (RR) for adverse effects when not progressively increasing dose could be computed. This was done by dividing the dogs in groups: one group with dogs who had not progressively increased dosing and one where they had progressively increased dosing. They were also separated based on prevalence of suspected gabapentin related adverse effects (see *Table 3*). The 4 dogs on a period of single therapy with gabapentin were also evaluated as a separate group. Dosing regimens prescribed by veterinarians was compared to recommendations on dosing regimens of gabapentin in humans. All RR calculations were done manually by the author of this paper. No conflict of interest or biased evaluators partook in this study.

RESULTS

Out of the 43 questionnaires sent out, 17 households answered the questionnaire. One of the questionnaires sent back contained no information and was excluded from the study. The final count of dogs included in the study was 16, which gave a response rate of 39.5%.

All but one of the dogs included in the study were treated with gabapentin because of pain related pathology. One dog came to the clinic because of unprovoked aggression. The main theory for this dogs' behavior was pain or epilepsy.

Four dogs experienced a period of monotherapy with gabapentin, apart from one dog being administered a previous single dose of Nexgard. Twelve dogs received multimodal treatment protocols. The most common drugs prescribed alongside gabapentin included NSAIDs, corticosteroids and opioid analgesics. One dog was given gastroprotective medication and one dog was on allergen specific immunotherapy (Artuvetrin).

Doses of gabapentin ranged between 15.2 mg/kg to 45.4 mg/kg every 24 hours. No correlation was seen between single therapy and higher doses of gabapentin. The doses of gabapentin were divided into three rations daily in ten dogs, and six dogs were prescribed administration twice daily. A total of four dogs were prescribed a dosing regimen of gabapentin which was initially progressively increased, and twelve dogs did not progressively increase the dosage when starting gabapentin. The mean oral dose was 11.2 mg/kg every 8-12 hours. As noted previously, an oral dose of 10 mg/kg every 8 hours is needed in most dogs to obtain the recommended serum concentration of over 2 µg/mL (Radulovic et al., 1995). The relevance of this recommendation is delineated in the Monte Carlo simulation of gabapentins pharmacokinetic profile in Figure 2 below as it shows that all dogs had a serum concentration >2 µg/mL after 8 hours, whereas most had < 2µg/mL at 12 hours after last dose, and all after 12.8 hours.

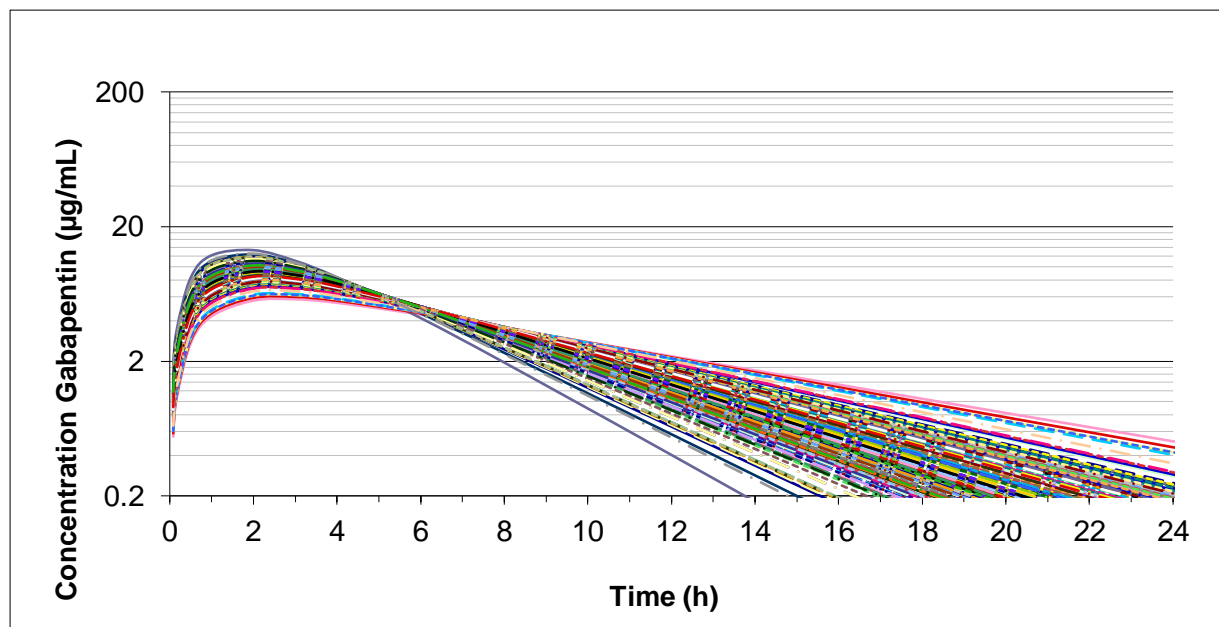


Figure 2. Monte Carlo simulation of the kinetic profile of orally administered gabapentin in 200 dogs. Clearance: 0.1362 L/kg/h, Volume of distribution: 0.158 L/kg, Bioavailability: 80% extrapolated from Radulovic et al. (1995). The variation of these parameters was set to 0%. Variation in absorption was set to an estimated 20% based on gabapentins dose limited absorption (Stewart et al., 1993; Larsen et al., 2014). The oral dose was obtained from the mean dose of the dogs included in this study and therefore set to 11.2 mg/kg. C_{max} in this simulation was around 10 µg/mL. All dogs were below the theoretical terapeutical limit 2 µg/mL (Thomson/Micromedex, 2006) between 8 and 12.8 hours after administration.

A total of 50% (8/16) reported any type of adverse effect during treatment with gabapentin. Many of these dogs had adverse effects that could be related to other substances included in their therapy, such as polyuria/polydipsia and weight gain seen when on gabapentin combined with corticosteroids. Neurological adverse effects were reported in five dogs. These adverse effects were similar to those seen in humans on gabapentin treatment (KuKanich, 2013) and could not be related to other medications or disease symptoms.

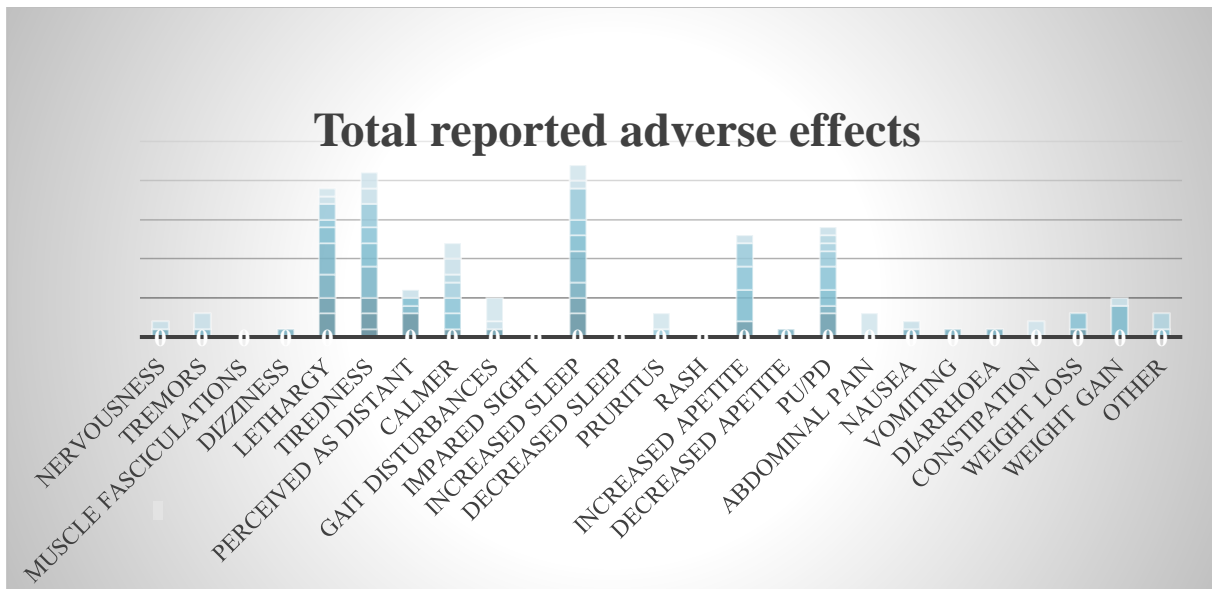


Figure 3. All reported adverse effects in the submitted questionnaires with staging of severity included. Symptoms translated from Swedish questionnaire to English. Dogs on multimodal treatment protocols included.

Of the 16 households who answered the study, 15 had a dog who, at some point, received multimodal treatment. Of these 14 dogs two only received multimodal treatment during a short period of time and could be classified as “single therapy” cases. One of the dogs was given one tablet of Nexgard before gabapentin treatment. This dog was also classified as “monotherapy”. This resulted in a total of four dogs who could be evaluated in regard to gabapentin as single therapy. In the group of four dogs on a period of single therapy with gabapentin no adverse effects were seen.

Dose regimens varied between two and three doses per day, where six dogs were administered gabapentin two times daily and ten dogs three times daily. Five of six households with dogs prescribed gabapentin two times daily reported no adverse effects and one household answered this question inconclusively. Three of these dogs were on a period of single therapy with gabapentin and five of six reported improvement of gabapentin therapy. One household did not answer this question.

The adverse effects reported generally occurred at the beginning of gabapentin treatment. The definition of “beginning of gabapentin treatment” was not stated (see Appendix 1). One owner reported withdrawal symptoms, adverse effects at the end of gabapentin treatment, which has also been identified as a risk in humans (Barrueto et al., 2002; See et al., 2011; KuKanich, 2013; FASS, 2017). A total of two of 16 dogs (12.5%) had to withdraw from gabapentin treatment because of adverse effects. Both of these dogs had adverse effects that occurred at the start of gabapentin treatment and reportedly became depressed when on gabapentin.

Table 1. Table presenting the progressive increase in dose, prevalence of adverse effects, pet owners' perception of efficacy, additional medication administered, and which dogs presented with adverse effects that could not be directly related to other medication or pathology of disease. Information obtained from questionnaire answers and journals including 16 dogs treated with gabapentin.

Case	Progressive increase	Adverse effects	Perceived as helped	Additional medication	Adverse effects most likely due to gabapentin
1	No	No	Yes	NSAID + gastroprotective medication	No
2	No	No	Yes, mildly	Tramadol, cortisone, then switched to NSAID	No
3	Yes	Yes	First time yes, second time no	Initially NSAID, then switched to cortisone	Yes
4	No	Inconclusive	Yes	Cortisone + allergen treatment	No
5	No	No	Yes	Cortisone	No
6	No	Yes	No, depressed from gabapentin	NSAID	Yes
7	No	Yes	No, depressed from gabapentin	NSAID	Yes
8	No	Yes	Yes	NSAID + opioid	No
9	No	Inconclusive	Yes	Opioid + cortisone	No
10	Yes	Yes	Yes, markedly	Cortisone	Yes
11	No	No	Yes, partly	A few days on NSAID, then just gabapentin.	No
12	No	No	-	One tablet of Nexgard previously	No
13	Yes	No	Yes	A few days on NSAID, then just gabapentin.	No
14	No	Yes	Yes	Initial opioid + Cortisone	Yes
15	Yes	No	Yes	NSAID	No
16	No	No	Yes	No	No

A total of ten dogs were reportedly markedly improved by their treatment, three reported being partially improved and one respondent did not answer this question. Two dogs were not

perceived as helped by their owners. One of these dogs was on a dose of 9.1 mg/kg three times daily and the other dog on 13.2 mg/kg three times daily. They were both, as previously mentioned, reportedly depressed from gabapentin and had to withdraw from treatment. These two dogs had not progressively increased their dosage. In the group of four dogs who had a period of single therapy with gabapentin two pet owners reported their dogs' conditions as improved, one partly improved, and one pet owner did not answer this question.

Of the dogs included five weighed <10 kg and eleven dogs weighed >10 kg. Of the dogs <10 kg one of five were administered gabapentin two times daily and four of five three times daily. The mean total dose for dogs <10 kg was 37.9 mg/kg per 24 hours. Of the dogs >10 kg five of eleven were administered gabapentin two times daily and six of eleven three times daily. The mean dose for this group was 25,1 mg/kg every 24 hours. In the group of dogs <10 kg two of five had adverse effects that were classified as being most likely related to gabapentin. The same was true for three of five dogs in the >10 kg group. The relative risk (RR) for adverse effects in dogs <10 kg was calculated to 1.47 and the P-value was 0.60.

Table 2. Table over dogs divided into groups based on weight (over/under 10 kg), daily dosing intervals and separate rations, total dose per kilo every 24 hours and if the dog at some point received single therapy of gabapentin.

Case	Dog over/ under 10 kg	Dose/kg	Total dose/ kg q24 hours	Single therapy at some point
1	Over	12.05 mg x2	24.1 mg/kg	No
2	Over	8.55 mg x3	25.65 mg/kg	No
3	Over	9.84 mg x3	29.52 mg/kg	No
4	Under	22.7 mg x2	45.4 mg/kg	No
5	Under	12.66 mg x3	37.98 mg/kg	No
6	Under	13.16 mg x3	39.48 mg/kg	No
7	Over	9.09 mg x3	27.27 mg/kg	No
8	Under	10.53 mg x3	31.59 mg/kg	No
9	Over	11.3 mg x3	33.9 mg/kg	No
10	Over	9.43 mg x3	28.29 mg/kg	No
11	Over	10 mg x3	30 mg/kg	Yes
12	Over	13.45 mg x2	26.9 mg/kg	Yes
13	Over	9.09 mg x2	18.18 mg/kg	Yes
14	Under	11.76 mg x3	35.28 mg/kg	No
15	Over	8.47 mg x2	16.94 mg/kg	No
16	Over	7.58 mg x2	15.16 mg/kg	Yes

As previously noted, there were five questionnaire answers which indicated adverse effects that could not be related to underlying disease or other medication given. A separate calculation, only including these adverse effects when studying the risk factors for adverse effects, was conducted. This was done to rule out bias related to additional drugs. The RR for adverse effects when not progressively increasing initial dosage of gabapentin was 0.5 (P-value: P = 0.33), see table 3.

Table 3. *Presence of adverse effects related to progressive increase of initial dosing of gabapentin. Individuals with adverse effects most likely related to other medication or symptoms of disease marked as “no adverse effect”.*

	Adverse effect	No adverse effect	Total
No progressive increase in dose	3	9	12
Progressive increase in dose	2	2	4
Total	5	11	16

RR: 0,5

The Swedish Medical Products Agency reported a total of three adverse effect reports on gabapentin use in dogs between January 2010 to November 2017. The reports included two Cavalier King Charles Spaniels and one Rottweiler. One of the Cavalier King Charles Spaniel’s reportedly had tongue disorder and tiredness during gabapentin use, one suffered from pancreatitis and was euthanized, and the Rottweiler presented with aggression.

DISCUSSION

This study was conducted to increase the knowledge about gabapentin in our pets. A large amount of the information on gabapentin's pharmacodynamics and adverse effects in animals is to date comprised of case reports.

It is important to note that the overall number of dogs treated with gabapentin, and thus included in the study, is relatively small. The information obtained is solely based on pet owner observation and several of the individuals in the study have been on multimodal pain relief protocols. Inclusion of animals on multimodal treatment protocols is not optimal and makes interpretation of results more difficult, but because of the low number of cases treated with solely gabapentin the sample size of these animals would have been minimal.

Questionnaire

Questionnaire design

The questionnaire sent out to pet owners was, as mentioned in "Materials and Methods", conducted with inspiration from the UKU- and Toronto side effects scales. These two scales are used within human medicine, mainly when studying the adverse effects related to psychotropic drugs (Lingjærde et al, 1987; Vanderkooy et al., 2002). The final questionnaire included parts of these scales but was modified to include a broader spectrum of adverse effects and become more suited for evaluations of animals. Options that were defined by a certain sensation or feeling were modified to describe a sign or symptom a practitioner or pet owner could observe in the animal studied.

The questionnaire design provided postal service or e-mail as the two options for responding. The strengths of these methods, compared to face-to-face or telephone-interviews, lie in the opportunity for pet owners to reflect over their answers during several days before responding and the researchers not having to book a specific time to connect with the respondents. There is no risk for the interviewer to influence answers or for the interviewer to avoid sensitive questions. Negative aspects of this type of design could be that the respondents have no opportunity to ask follow-up questions, misconceptions cannot be explained and nuances in answers may be overlooked (Lina Hedman, 20171).

Study Design

Questionnaires are efficient in retrieving data for studies and have additional advantages including standardization of questions and that they are easy to use. However, the questionnaire gives rise to several potential sources of bias, especially because of the answer frequency being low. A questionnaire study based solely on pet owner observation may lead to observational bias such as false reports of adverse effects and inconspicuous adverse effects being overseen. The people who decide to answer the questionnaire may of some reason be more prone to answering, and therefore a low response rate affects the degree of how representative the findings are. For example, pet owners who saw adverse effects in their dogs, may be more invested in the subject matter and therefore these dogs may be overrepresented in the study.

The base for inclusion criteria was broad due to the small number of individuals treated as well as dogs on gabapentin as single therapy strenuous to find. A retrospective design would have benefitted from a shorter time span of inclusion to limit recall bias for events further back in time, but this would have resulted in a smaller sample size. A broad inclusion criterion, in this

¹ Lina Hedman, Institutet for Bostads-och Urbanforskning, 2017-12-05

case, limits the number of conclusions that can be drawn from the study and requires a more descriptive approach.

Results

The respondent rate was 39.5%, which is classified as an acceptable respondent rate (Lina Hedman, 2017²). The recommended minimum number of cases to include in a randomized selection questionnaire study for representative results is 30 (Lina Hedman, 2017³). This questionnaire was, as previously noted, not randomized as all individuals identified to meet the inclusion criteria were included.

If all questionnaires had been answered the total number of individuals with a period of solely gabapentin treatment would have been eleven and the span of doses broader. This could have contributed to more information on the specific adverse effect profile of gabapentin. Only four respondents were included who at some point were prescribed gabapentin as single treatment and the study group was relatively homogenous in respect to dose variation. These factors significantly impact the bearing of the results as they may not be representative for the population at large. Therefore, caution should be taken in drawing conclusions from the results to a wider population, in particular since the statistical test for the RR was non-significant. Even if the RR for adverse effects was higher in the small dog group and in the group who progressively increased dosing thus opposing the expectations, these results do not conclude these factors as risk factors for adverse events.

In the group of dogs on a period of single therapy with gabapentin, including four dogs, no adverse effects were seen. Even if this sample is too small to calculate RR on, it is an interesting finding that none of the dogs on single therapy with gabapentin presented with adverse effects. This could be a coincidental finding, or an indication that gabapentin is in fact a relatively safe drug in dogs. It leaves to question how many of the reported adverse effects in this study are in fact true adverse effects of gabapentin.

The improvement on gabapentin treatment reported by pet owners may be due to gabapentin treatment, but could also be an effect of other medications, rest, a physical therapist, placebo effect or a spontaneous improvement. Out of the four pet owners with dogs on single therapy with gabapentin three reported improvement with treatment. This rules out other medications as the reason for improvement and may indicate that the dose prescribed to these dogs was therapeutic, but the other bias factors mentioned above still may be the reason for improvement in these dogs. Five of six dogs who were prescribed gabapentin twice daily also reported improvement on gabapentin treatment. Three of these dogs were on a period of single therapy with gabapentin. This gives rise to a possibility that gabapentin treatment twice daily may be sufficient for controlling neuropathic pain conditions in dogs. Because of these findings, and the lack of previous research, controlled clinical trials of the pharmacodynamics of gabapentin are needed to establish a therapeutic dose and dose interval. It is also important to note that pet owners, and no trained professionals with evaluation protocols, have subjectively evaluated these dogs' improvement. In future studies, ideally trained staff would evaluate the dogs in a blinded study design although changes at home over time might need additional technical solutions such as activity necklace, filming, etcetera to capture any changes in the dogs' status.

Many of the dogs with reported adverse effects had adverse effects that could be related to other substances included in their therapy, such as polyuria/polydipsia and weight gain seen when on gabapentin and corticosteroids. These adverse effects are well known and confirmed adverse

² Lina Hedman, Institutet for Bostads-och Urbanforskning, 2017-12-05

³ Lina Hedman, Institutet for Bostads-och Urbanforskning, 2017-12-05

effects of corticosteroids. Because of this, five cases with reported adverse effects were selected into a separate group. This was done because of the character of these adverse being similar to those seen in humans, such as somnolence and other signs of central nervous impact. These dogs were not on other medication with known side effects of this character or affected by disease that would be expected to give rise to these signs. It was done to rule out false positive reports of adverse effects. Despite this, it cannot be certainly established that these adverse effects were from gabapentin, and in some cases true adverse effects might have been overseen, and therefore result in an overrepresentation of false negative results.

The two dogs who were reportedly depressed and did not improve from gabapentin treatment had not progressively increased dosing, but they were on dosing three times daily and on the lower dose interval (9.09-13.16 mg/kg). Due to the limited scope of this study no blood samples were taken of the animals included. This could theoretically have been a way to correlate blood concentrations of gabapentin to adverse effects, as gabapentin has been proven to give rise to a broad spectrum of serum concentrations at similar oral doses. Fluctuations in gabapentin concentrations could also be evaluated with blood concentrations measured. This could be used to investigate if different adverse effects were dose dependent in dogs, and if fluctuations impacted on the risk for developing adverse effects. Because of the lack of blood samples, it cannot be known if these two dogs had higher serum concentrations. The reason for adverse effects in these dogs could therefore not be thoroughly investigated and are consequently not established. Future studies within this field should aim at correlating serum concentrations with adverse effects and include veterinary evaluations of the animals.

The information on adverse effects obtained from the Swedish Medical Products agency is scarce. Only three reports on adverse effects from gabapentin have been sent in since 2010. This may be due to a low frequency of adverse effects, but more likely it reflects a low report rate of adverse effects within the veterinary field in Sweden. The three reports sent in included tongue disorder, tiredness, pancreatitis and aggression. Similar to the reasoning above, it is not known whether these reports reflect true adverse effects of gabapentin. They may be related to underlying disease, other medication or a coincidentally occurring pathology. Hence, no conclusions of the side effects in gabapentin treated dogs in Sweden can be drawn from this information.

Despite the recommendation in human medicine to progressively increase, and taper, the dose of gabapentin, only four of 16 dogs were prescribed a dosing regimen including progressive increase of gabapentin by their veterinarians. In addition, not all dogs received the recommended dosing regimen of three times daily but six dogs also received dosing twice daily. All but one of these dogs weighed over 10 kg and the separate doses were not significantly higher than doses for dogs who received three rations a day, which excludes tablet sizes being too large for small dogs as the reason for twice daily dosing. As the adverse effects and optimal therapeutic dose of gabapentin in dogs has not been investigated previously broader knowledge amongst veterinarians on how to optimally administer this drug should be a goal within the field. This could potentially contribute to a reduction of adverse effects and, in cases with suboptimal plasma concentrations, prohibit gabapentin from being ruled out on the basis of default of treatment response.

Pharmacokinetics

All available formulations of gabapentin are oral formulations, which makes true bioavailability and volume of distribution impossible to establish. All studies, but one, on bioavailability in animals are to date conducted with oral administration of gabapentin. These pharmacokinetic properties can only be studied with an intravenous formulation. Vollmer et al. (1986) study,

with intravenous gabapentin, does not present any figures on clearance or volume of distribution.

Terminal half-life in dogs after oral administration has been proven to be 3-4 hours and the theoretical therapeutic concentration is 2µg/ml. To obtain concentrations over this limit for >12 hours with a half-life of 3 hours (four half-lives) a Cmax of 32 µg/ml is needed. This would require large single doses, which consequently would result in large fluctuations of the gabapentin concentration in blood. Because of this property, gabapentin needs to be administered three times daily to maintain target concentration. Dosing three times daily could give rise to non-compliance in our pets. In epilepsy patients, this could be a substantial risk. A sustained release formula for our pets could therefore be an alternative to bypass this risk. There are no studies on extended release gabapentin in dog, and therefore the plasma concentration and half-life following administration of gabapentin enacarbil is not known (KuKanich & Cohen, 2011). Future research on the pharmacokinetics of an extended release formulation could, in theory, improve pet owner compliance and reduce the risk of peak drug levels, or fluctuations, inducing adverse effects.

Previous studies have seen an ample difference in dogs, compared to other species, regarding the metabolism of gabapentin. In dogs, approximately 34% of the compound is metabolized to N-methyl-gabapentin. The properties of this metabolite have not been studied to date, but metabolism has not been seen in any other species studied. Gabapentin is considered a relatively safe drug in humans because of not binding to plasma proteins and not being metabolized in the liver, but with these variations in metabolism, humans are not an optimal model for studying gabapentin in dogs. Further, there is no information to be found on the metabolites protein-binding properties and risks related to this factor. The results Radulovic et al. (1995) presented show that species variations exist. This is one additional reason why extrapolation from human medicine regarding dosing, efficacy and safety may pose a risk for dogs when medicating with gabapentin. Investigation of the role of this metabolite could give more information on the dimension of the risks, or potential benefits, gained from the metabolization.

Previous research

In Aghighi et al. (2012), where 63 dogs were administered 10 mg/kg of gabapentin twice daily no difference was seen between the gabapentin group and placebo. The dose given in this study was slightly lower than recommended (Thomson/Micromedex, 2006; Aghighi et al., 2012), which could be a possible explanation for the outcome, but whether this was related to the low dosing used in the study or gabapentins analgesic profile, which does not include acute inflammatory pain, is not known (Aghighi et al., 2012).

Several studies included have administered relatively low doses of gabapentin and taken blood samples from the dogs 12 hours after administration (Platt et al., 2006; Aghighi et al., 2012). Despite this the serum concentrations at these points have been higher than seen in other studies where administered doses were higher and blood samples taken closer to the point of administration (Vollmer et al., 1986; Radulovic et al., 1995; Rhee et al., 2008). One reason for this could be that gabapentins dose-limited absorption gives rise to lower oral bioavailability at the higher doses administered (Stewart et al., 1993; Larsen et al., 2014). Variations may also exist in the way of measuring blood concentrations of gabapentin. Further, it is not known if the metabolite, N-methyl-gabapentin, is included in the measurements made in the separate studies. In Aghighi et al. (2012) study one dog reaches a confounding 11.00 µg/mL at 72 hours, 12 hours after oral administration of 10 mg/kg of gabapentin. This serum concentration is higher than the expected Cmax obtained from that dose, which, according to KuKanich (2013), is approximately 10 µg/mL.

Sedation has been reported in a golden retriever with a serum concentration just above the theoretical therapeutic limit (Platt et al., 2006; Thomson/Micromedex, 2006), which could be an indication that some adverse effects are not dose related in dogs. However, it is important to note how long after administration blood samples are collected. In this case the sample was taken immediately before the next administered treatment (Platt et al., 2006) and the C_{max} in this dog is not known. It can therefore not be concluded if this dog had a high gabapentin concentration in blood before the blood sample was taken. Conclusively no conclusions can be drawn regarding the dose relationship of the adverse effect seen in this dog.

Set apart from the known mechanisms of action that gabapentin has there is evidence pointing towards the fact that gabapentin has several other mechanisms of action that are unknown (Liao et al., 2010). They suggest that gabapentin could exert its effect in several different ways depending on the type of neuropathic pain present. More research is needed to establish the alternative mechanisms of action for gabapentin and the pharmacodynamic properties these mechanisms may have.

Studying gabapentin

As noted, the substance is often used as a complementary drug in a multimodal protocol for controlling pain or epilepsy, which complicates distinguishing any adverse effects from gabapentin, from other drugs or the combination of them. Despite gabapentin being frequently used in multimodal pain protocols there are no controlled clinical trials in humans on the adverse effects occurring in combination with the most common pain medications, such as opioids or NSAIDs (Mathiesen, 2014). With metabolism occurring in dogs, the significance of the combination of drugs could be higher in this species. A combination of several liver straining drugs, such as the combination with phenobarbital, could theoretically impact negatively on the liver as the combination of drugs with adverse effects affecting the same organ, or enzyme, could contribute to accumulation of adverse effects.

Studies found in the literature search for this thesis also conclude that no effect was seen between gabapentin and placebo (Aghighi et al., 2012). It is important to note that all studies on pharmacodynamics and efficacy of gabapentin in dogs are conducted on acute or inflammatory pain. Studies such as these are easier to control, evaluate and find cases for, but the indication for gabapentin in humans is neuropathic pain. It has been proven that gabapentin requires an upregulation of the VDCC-subunit to exert its main action, a mechanism which does not modulate acute, inflammatory pain. Therefore, gabapentin may well have effect for neuropathic pain in dogs, but the evidence to strengthen this is low to non-existent. The studies merely confirm that gabapentin does not relieve acute, inflammatory pain. The drug is being used empirically for neuropathic pain without proper studies based on evidence of the effect seen on these conditions in humans. Furthermore, in Aghighi et al. (2012) a low dose gabapentin and methadone were compared to solely methadone as analgesic protocols after intervertebral disc surgery. One alternative theory for the lack of apparent allodynia in the gabapentin groups in this study is that methadone has an inhibitory action on the NMDA receptor. This action results in an inhibitory effect on central sensitization (Gorman et al. 1997), which could influence these results.

Future prospects

Gabapentin has been established as an alternative for treatment of neuropathic pain conditions, but there are chronic conditions involving pain, such as cancer, where the origin is of both inflammatory and neuropathic character. There are also chronic pain conditions mainly characterized by inflammatory pain where a progression in severity may lead to a neuropathic

component. Treatment of these mixed pain conditions could, in theory, benefit from a drug such as gabapentin (Rahman & Dickenson, 2013).

Although gabapentin is being increasingly prescribed to our pets the pharmacodynamics and efficacy have not been studied in these species. It has not been established whether the recommended therapeutic plasma concentration in humans can be extrapolated to dogs or other pets. This gives rise to a risk that a drug that could potentially treat chronic pain conditions, a field of medicine which lacks sufficient alternatives today, may be administered in a way that gives rise to suboptimal plasma concentrations in our pets. Therefore, more research is needed to determine the pharmacodynamics of gabapentin in various species. It should be recognized that gabapentin is a challenging drug to study adverse effects on in a clinical environment in our pets because of the scarce number of animals using the drug and the fact that it is most commonly used as a complementary drug incorporated in multimodal pain protocols. Because of the potential benefits in treating otherwise untreatable pain conditions, it is of paramount importance to further investigate if gabapentin provides the same analgesic effect for dogs as seen in studies of humans.

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APPENDIX

Appendix 1. Questionnaire

Hej!

Mitt namn är Charlie Peck och jag skriver mitt examensarbete i veterinärmedicin vid Sveriges

Lantbruksuniversitet (SLU), Uppsala.

Du har fått den här enkäten för att du har/har haft en hund som behandlats med substansen

gabapentin. Mitt examensarbete kretsar kring att öka kunskapen kring läkemedlets effekt och

vilka eventuella biverkningar som kan ses hos hundar som behandlas med medicinen, samt om

dessa biverkningar kan relateras till vilken dos hunden har fått.

Eftersom dagens forskning på hur gabapentin påverkar hundar är relativt begränsad behöver

jag din hjälp för att få en överblick över hur gabapentin upplevs fungera i praktiken hos våra

hundar. Jag är oerhört tacksam om du/ni tar er tid att svara på enkäten nedan och återsänder

den i bifogat frankerat kuvert innan den 15/10 2017.

Resultaten kommer att redovisas på gruppnivå och publiceras som ett examensarbete på

Epsilon, SLU:s litteraturlösningsdatabas. Möjlighet finns att få läsa det slutgiltiga arbetet från och med

januari 2018.

Ingen utöver jag och min handledare Lena Olsén kommer gå igenom ditt djurs journaler och

ingen övrig journalinformation kommer att användas utan ert godkännande.

Enkäten tar cirka 15 minuter att slutföra.

Stort tack på förhand!

Med vänlig hälsning,

Charlie Peck

Veterinärstudent år 6

Sveriges Lantbruksuniversitet

Handledare: Lena Olsén

Docent i Farmakologi

Kontakt: lena.olsen@slu.se

Ditt namn: _____ Hundens namn: _____

Datum: _____

1. Varför skrevs Gabapentin ut till just din hund?

2. Vilken dos Gabapentin startade din hund på?

3. Trappades medicineringen upp succesivt?

Ja

Nej

4. A) Hade din hund några tecken på biverkningar av Gabapentin?

Ja

Nej

B) Om din hund hade biverkningar: Vad resulterade detta i?

Vi fortsatte ge Gabapentin i samma dos.

Vi sänkte dosen.

Vi slutade ge Gabapentin och bytte ej till annat läkemedel.

Vi slutade ge Gabapentin och bytte till ett annat läkemedel. Specificera vilket:

Biverkningarna upphörde.

Annat. Specificera:

C) Om din hund hade biverkningar: När förekom dessa?

När läkemedlet började ges.

När dosen höjdes. Om ja, vid vilken dos?:

Efter en längre tids behandling med samma dos. Om ja, efter hur lång tid?:

Annat. Specificera:

5. Fick din hund några andra läkemedel under tiden som Gabapentin gavs?

Ja. Specificera vilka:

Nej

Vet ej

6. Hade Gabapentin önskad effekt för din hunds sjukdomssymtom?

Ja. På vilket sätt sågs förbättring?:

Nej. Eventuell kommentar:

7. Övriga kommentarer. Om kommentaren rör en specifik fråga, skriv frågans nummer

nedan.:

Tabellen nedan fylls i oavsett om biverkningar setts hos din hund eller ej.

Under de två första veckorna av gabapentingiva, noterade du något av symtomen listade nedan?

Markera även till vilken allvarlighetsgrad (1-5) biverkningen förekom. För varje symptom väljs

en gradering enligt skalan nedan.

Symptom

Gradering

	Ej förekommit (1)	Lindrigt (2)	Måttligt (3)	Kraftigt (4)	Mycket kraftigt (5)
Nervositet					
Skakningar					
Muskelryckningar/kramper					
Yrsel					
Nedstämdhet					

Trötthet/utmattning					
Nedsatt kontaktbarhet/Distanserad					
Lugnare/Mindre orolig					
Rörelsestörningar (t.ex. snubblande gång eller sämre koordination)					
Upplevts ha nedsatt syn					
Ökad sömn					
Minskad sömn					
Klåda					
Hudförändringar/Utslag					

Ökad aptit					
Nedsatt Aptit					
Ökat drickande/kissande					
Tecken på buksmärta (tittar sig/slickar sig mot buken, står i "bugande" ställning, krummande rygg etc.)					
Tecken på illamående (slickar sig om munnen, mindre intresserad av mat etc.)					
Kräkningar					

Diarré					
Förstoppning					
Viktnedgång					
Viktuppgång					
Övriga (specificera och gradera från 1-5):					

Jag vill ta del av arbetet när det är färdigställt:

Ja

Nej

Tack för att du tagit dig tid att fylla i enkäten och därmed bidragit

till ökad kunskap om läkemedlet gabapentin!