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Review

Gabapentin in Cattle: A Pharmacology Snapshot

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Abstract: Gabapentin (GBP) is an antiepileptic and analgesic drug that is derived from gamma-aminobutyric acid. It is used as an analgesic in multi-modal pain management, as well as an anticonvulsant and anxiolytic, off-label in animals. Particularly, oral GBP prescriptions for cattle are becoming increasingly popular. Since its introduction into cattle farm practices, several types of research on GBP in cattle have been published, covering pharmacokinetics and safety studies. Other studies concerning cattle dehorning and lameness have found synergism when GBP and meloxicam are co-administered. Because of the significant therapeutic effect of these medications when used together, practical veterinarians might be able to execute other surgical procedures on cattle without causing pain to the animals. This is important because pain management and the prevention of animal suffering are critical components of the animal well-being approach in veterinary medicine. Oral doses between 10 and 20 mg/kg were safe, and effective in dehorning and lameness, in combination with MEL. Such dose is preferable to be administered 8 h before any procedure, as part of the preemptive therapy. This review focuses on the clinical applications and therapeutic effects of GBP in cattle, both for farming practices and surgical interventions.

Keywords: Cattle, Gabapentin, Analgesia, Pharmacodynamics, Pharmacokinetics, Pain Management

Introduction

Gabapentin (GBP), an antiepileptic drug with analgesic effects, is an analog of Gamma-Aminobutyric Acid (GABA) (Maneuf *et al*., 2003). It was first approved by the United States Food and Drug Administration (FDA) in 1993 for the treatment of epilepsy, but it was later approved as an analgesic for postherpetic neuralgia in 2004 (Mack, 2003). GBP was approved by the European Medicines Agency (EMA) in 2006 for epilepsy and certain types of neuropathic pain and the National Institute for Clinical Excellence in the United Kingdom recommends it as a first-line treatment for all types of neuropathic pain (EMA, 2006; NICE, 2013).

Assumed to have no abuse potential and an efficient therapeutic effect, GBP is widely used off-label to treat a wide range of disorders in humans, including insomnia, drug and alcohol addiction, anxiety, bipolar disorder, borderline personality disorder, malignant pain, menopausal conditions, vertigo, pruritic disorders and migraines (Hamer *et al*., 2002; Radley *et al*., 2006).

As human medicine is for veterinary medicine, prescribing oral GBP for cattle, horses, cats, and dogs is becoming more popular among veterinarians. Being administered off-label in animals, it is prescribed as an analgesic in multi-modal pain management, including neuropathic, postoperative and chronic pain. It is also used off-label as an anticonvulsant, as well as an anxiety medication for cats to reduce stress during travel or veterinary visits (Lamont, 2008; Platt *et al*., 2006; Coetzee *et al*., 2011; Siao *et al*., 2010; Vettorato and Corletto, 2011; Van Haaften *et al*., 2017).

In most animal species, recognizing pain and/or stress, as well as their severity, is a crucial, yet challenging step. Their recognition in cattle is even more difficult, in chronic cases too (except for lameness), since they originated as prey species and may hide behavioral indicators of pain and/or stress so as not to appear weak to a possible predator (Bomzon, 2011).

Rising moral and ethical issues have resulted in public demands for better farming techniques and improved animal welfare all around the world. However, despite significant advances in pain management in companion animals over the last 30 years, bovine veterinarians and food producers have been slow to respond to demands for pain treatment and stress management in cattle from

animal welfare organizations, government regulations, corporate programs, and customers (Fraser, 2006). Pain causes behavioral, autonomic, and neuroendocrine changes. Chronic pain, particularly when associated to lameness, remains one of the most important welfare concerns in cattle to this day because hyperalgesia lasts for at least 28 days after the primary lesion has resolved (Ley *et al*., 1996; Whay *et al*., 1998; 2003). It has been demonstrated as well that chronic pain in cattle reduces food consumption and average daily weight growth, raises heart rate and blood pressure, and lowers body temperature (Stewart *et al*., 2010).

Several factors could explain this very low consideration of pain management and the use of analgesics in cattle. According to Coetzee *et al*. (2014), the lack of FDA-approved analgesic drugs for livestock in the US is due to the lack of validated methods for assessing pain in cattle. In other words, approval for the use of an analgesic drug in cattle necessitates proof that the drug does relieve pain, which calls for the need of more studies to be done. Time, cost, and lack of knowledge or skills are other reasons on the list too (Huxley and Whay, 2007).

Pain in cattle can be mild to severe and it is frequently caused by routine procedures like vaccinations, ear tagging, hoof trimming, branding, castration, and dehorning. The same holds for pathologies such as lameness, obstetrical procedures, and abdominal complaints such as bloat, intestinal obstructions, and volvulus (Bomzon, 2011).

GBP has numerous advantages that make it appealing for use as an analgesic in animals. GBP is not a controlled substance and it is widely available in oral form. In addition, GBP's toxic effects are minor in a variety of species when compared to the use of opioids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which can cause toxic effects in chronic treatments (Siao *et al*., 2010).

Lameness, alongside farm practices, can cause both inflammatory and neuropathic pain, suggesting that a concurrent administration of a neuropathic pain reliever such as GBP should provide superior analgesia (Glynn *et al*., 2013; Coetzee *et al*., 2014) and is worth including in multimodal treatment protocols in cattle, where there is still a lack of data. Most importantly, neuropathic pain occurring from nerve damage or neuronal dysfunction is considered refractory to the effects of NSAIDs and many opioid analgesics (Woolf and Mannion, 1999), and hence the increased interest in the use of GBP. Also, NSAIDs only have a modest effect on inflammatory pain associated with lameness (Whay *et al*., 2005; Flower *et al*., 2008). These findings encouraged the co-administration of GBP and NSAIDs, such as meloxicam (MEL), in the field.

This review provides an overview of the current knowledge on GBP pharmacology in cattle, with a focus on its Pharmacokinetics (PK), Pharmacodynamics (PD), interaction with other drugs, and medical applications.

Chemical Structure and Synthesis

The IUPAC name is 2-[1-(Aminomethyl) cyclohexyl] acetic acid. The neurotransmitter GABA does not penetrate the blood-brain barrier, therefore lipophilic groups were added to its carbon backbone to increase bioavailability. As a result, GBP was discovered as a potent anticonvulsant by chance in 1975 (Sneader, 2005). It was first approved under the brand name Neurontin® and a generic version first became available in the US in 2004 (Reed, 2012).

It is a derivative of GABA, thus a γ-amino acid, with a pentyl di-substitution at position three, hence the name GBP, forming a six-membered ring (Benzon *et al*., 2013). The amine and carboxylic groups are not in the same relative positions after the ring is formed as they are in GABA: They are more conformationally constrained (Levandovskiy *et al*., 2011). The similarities and differences between GBP and GABA are displayed in Fig. 1.

Starting with 1,1-diacetyl hexane anhydride, the chemical synthesis of GBP has been described, as shown in Fig. 2 (Kumar *et al*., 2008). The chemical characteristics of GBP are listed in Table 1.

Described Analytical Methods

In various species, several PK studies on GBP have been conducted. In all these researches, the analytical techniques for detecting GBP concentrations were held with High-Performance Liquid Chromatography (HPLC), coupled with mass spectrometry. The clean-up methods used in the studies, as well as the chosen PK model and the determined Limits of Detection (LoD) and Limits of Quantification (LoQ), are summarized in Table 2. It is important to note that there is no validated method yet in meat tissues.

Pharmacokinetics

The main PK parameters of GBP found in the literature on cattle are shown in Tables 3 and 4. Little is known about GBP's PK in cattle up to this point. This is because no commercially available injectable solution was present to perform an intravenous study. All available formulations of GBP are oral formulations, which makes true bioavailability, clearance, and volume of distribution difficult to establish. Instead, the apparent plasma clearance and volume of distribution, adjusted for the unknown absorbed fraction of GBP, are present. With a bioavailability of less than 100%, these values are overestimated (Coetzee *et al*., 2011).

Concerning the formulation, a significant difference in the t1/2 Kel was found between the encapsulated GBP (11.02 h) and its powder form (8.12 h), suggesting a slow dissolution of the capsules in the rumen and thus a slower release of GBP (Coetzee *et al*., 2011). In all cases, the t1/2 Kel values in cattle (5-15 h) were longer than in children (4.44 h, Haig *et al*., 2001), horses (3.4 h,

Dirikolu *et al*., 2008), dogs (3.25 h, Kukanich, and Cohen, 2011) and cats (3.78 h, Adrian *et al*., 2018), suggesting a decrease in the rate of absorption in cattle, associated with dilution and retention of the drug in the forestomach, compared to monogastric species (Coetzee *et al*., 2011). GBP studies in other ruminants such as goats and sheep are not present to support this theory. It is also worth mentioning that after administering 20 mg/kg of GBP, the digestive and mammary epithelial barriers were not saturated, since doubling the dose from 10 mg/kg in the first trial resulted in a dose-proportional increase in milk and plasma concentrations (Malreddy *et al*., 2013).

According to Table 4, the difference in t1/2 Kel amongst cattle is quite diverse. It could be attributed to age, lactation status (whether cattle are lactating or not), breed type, or the formulation. The Holstein-Friesian cows in Malreddy *et al.* (2013) study were in their first, second, or third lactation, and all of them had similar t1/2 Kel and other PK parameters values, implicating that GBP's PK is not influenced by the lactation cycle number. In both studies by Coetzee *et al.* (2013, 2014), the meat/beef calves had similar t1/2 Kel. Instead, in 6-month-old post-weaning dairy calves, in Glynn *et al*. (2013) and Fraccaro *et al.* (2013), the t1/2 Kel had the highest values. The observed t1/2 Kel values seem to be longer in non-lactating dairy cows and beef cattle than in lactating cows (Table 4).

Given the time to maximum plasma concentration Tmax, oral preemptive analgesia should be administered several hours (8 h) before surgeries so that surgery coincides with peak drug concentrations (Fraccaro *et al*., 2013; Malreddy *et al*., 2013; Glynn *et al*., 2013).

There was no information on GBP metabolism and excretion in cattle other than the fact that about 0.1% of the GBP supplied dose was eliminated through milk (whether at 10 or 20 mg/kg GBP) (Malreddy *et al*., 2013). No metabolites of GBP were identified in humans, horses, rats, and monkeys, in which the drug did not undergo liver metabolism and was almost entirely cleared by the kidneys in its unchanged form (Radulovic *et al*., 1995; Terry *et al*., 2010). In such cases, both the plasma clearance and renal clearance of GBP are directly proportional to the patient's creatinine clearance due to its primarily renal elimination. In dogs, despite that elimination is primarily via renal routes, a remarkable formation of N-methyl-gabapentin was found (34%) and it is unknown whether this metabolite is active or not (Vollmer *et al*., 1986). For these species, plasma protein binding is less than 3%. While specific studies in cattle are still lacking, they would be valuable in confirming GBP's excretion, metabolism, and plasma protein binding status.

Furthermore, it appears that when GBP and MEL are co-administrated, they do not seem to alter each other's PK (Malreddy *et al*., 2013; Coetzee *et al*., 2011; Coetzee *et al*., 2014). However, apart from other PK parameters, Cmax appears to have been altered in some situations. In Fraccaro *et al*. (2013), the Cmax of GBP co-administered with MEL (4.1 µg/mL) was higher than GBP alone (2.7 µg/mL) and the t1/2 Kel was shorter, but it seems to be due to individual variability. In Mzyk *et al*. (2019), the milk Cmax was higher in cows treated with MEL alone (1.48 µg/mL) than in cows treated with MEL and GBP (0.81 µg/mL).

Concerning milk penetration, the percentage in which GBP penetrates milk seems very low as mentioned before (0.1%). This was confirmed by the low GBP's milk clearance Cl_{Milk}/F (0.2-0.3 L/h) when compared to the total apparent body clearance (150 L/h) and the mammary tissue blood flow in the lactating cow (120 L/h) (Malreddy *et al*., 2013). Milk drug concentrations were below the detectable levels by 72 h in dairy cows, in Gehring *et al.* (2011) and by 48 and 60 h after the administration in post-partum and mid-lactation cows, respectively, in Mzyk *et al.* (2019). As a result, there is no delay in GBP appearance in milk and its rate of depletion from milk is comparable to that from plasma, concluding that GBP sequestration in milk is unlikely (Malreddy *et al*., 2013).

Table 1: Chemical characteristics of gabapentin

Appearance	White crystalline solid
Boiling point	314.4°C
Brand name	Neurontin®, Aclonium®, Equipax®, Gantin®, Gabarone®, Gralise®, Neurostil®, Progresse®
Density	1.058 g/cm^3
IUPAC name	[1-(Aminomethyl) cyclohexyl]acetic acid
Melting point	162-166°C
Molar mass	171.237 g/moL
Molecular formula	$C_9H_{17}NO_2$
Dissociation constant	pka= 3.7
Solubility	Freely soluble in water, alkaline and acidic solutions
Synonyms	1-(Aminomethyl) cyclohexaneacetic Acid; Apo-Gabapentin; ApoGabapentin; Convalis gabapentin; Gabapentin Hexal; Gabapentin Ratiopharm; Gabapentin Stada; Gabapentin-ratiopharm; Novo Gabapentin; Gabapentin; Gabapentin; Garbapentin; Gabapetine; Cyclohexaneacetic acid; GOE 2450, 2-[1 (Aminomethyl)cyclohexyl]acetic Acid; Aclidinium; Serada; Fanatrex.

Table 2: Summary of the gabapentin analytical methods used in the literature

Reference	Specie	Biological matrix	Clean-up	LOD µg/mL	LOQ µg/mL	Validated following FDA/EMA guidelines
Malreddy *et al*. (2013)	Cattle	Plasma	Protein precipitation	NA	0.025	Yes
		Milk	Solid phase extraction	NA	0.01	Yes
Glynn *et al*. (2013); Fraccaro *et al*. (2013)	Cattle	Plasma	Protein precipitation	NA	NA	Yes
Coetzee *et al*. (2011)	Cattle	Plasma	Protein precipitation	0.05	NA	Yes
Coetzee *et al*. (2014)	Cattle	Plasma	Protein precipitation	0.05	NA	Yes
Yaw *et al*. (2015)	Owls	Plasma	Protein precipitation	NA	0.0625	Yes
Terry *et al*. (2010)	Horses	Plasma	Protein precipitation	0.001	0.01	Yes
Park *et al*. (2007)	Humans	Plasma	Protein precipitation	NA	0.02	Yes
Adrian *et al*. (2018)	Cats	Plasma	Protein precipitation	0.01	0.05	Yes

NA: Not Available, LOD: Limit of Detection, LOQ: Limit of Quantification, FDA: Food and Drug Administration, EMA: European Medicines Agency

Table 3: Summary of the gabapentin experimental protocols in cattle and safety studies published in the literature

Reference	*n*	Species	Health status	Feed status	ROA and formulation	Dosage schedule	Dose mg/kg	Safety data
Malreddy *et al*. (2013)	12	Holstein-Friesian	Healthy	Fed	PO capsules (Actavis Elizabeth)	Single dose (Parallel study)	Group 1 (n = 6) 10 mg/kg GBP + 1 mg/kg MEL Group 2 (n = 6) 20 mg/kg GPB + 1 mg/kg MEL	No side effects noted
Coetzee *et al*. (2011)	6	Male beef calves (castrated)	Healthy	Fed	PO capsules/powder administered by stomach tube(Actavis Elizabeth)	Single dose (2 phases separated by a 3 week washout period)	Phase 1 10 mg/kg GBP Phase 2 15 mg/kg GBP + 0.5 mg/kg MEL	No side effects noted
Glynn *et al*. (2013); Fraccaro *et al*. (2013)	40	Holstein	Healthy	Fed	PO capsules administered using a balling gun (Amneal pharmaceuticals)	Single dose (Parallel study)	Group 1 (n = 8) 15 mg/kg GBP Group 2 (n = 8) 15 mg/kg GBP + 1 mg/kg MEL	No side effects noted
Coetzee *et al*. (2014)	18	Male British/ Continental beef calves	Healthy (4 h prior to the study, a chemical synovitis/arthritis was induced)	Fed	PO capsules (Actavis Elizabeth)	Single dose daily for 4 days (Parallel study)	Group 1 (n = 6) 15 mg/kg GBP + 0.5 mg/kg MEL Group 2 (n = 6) 0.5 mg/kg MEL	No side effects noted

PO, orally; n, number of individuals; ROA, Route Of Administration

Table 4: Main pharmacokinetic parameters of gabapentin found in the literature in cattle

	Dose GBP (mg/kg)	Cmax (µg/mL)	Tmax (h)	t1/2 Kel (h)	Cl/F (mL/min/kg)	AUC Last µg*h/mL	Vz/F (L/kg)	MRT (h)
Malreddy *et al*. (2013)	10(+1 mg/kg MEL)	2.87	8	5.50	NA	65.35	NA	10.44
	20(+1 mg/kg MEL)	5.42	9.33	5.26	NA	132.00	NA	12.38
Coetzee *et al*. (2011)	10	2.97	NA	11.02	3.42	59.73	NA	NA
	15 (+0.5 mg/kg MEL)	3.57	NA	8.12	3.88	70.29	NA	NA
Glynn *et al*. (2013);	15	2.7	8	15.30	2.87	87.20	4.45	26.6
Fraccaro *et al*. (2013)	15(+1 mg/kg MEL)	4.1	8	13.20	2.06	122.80	3.4	23.7
Coetzee *et al*. (2014)	15 (+0.5 mg/kg MEL)	3.97	84	9.45	NA	94.70	NA	NA

Cmax, peak plasma concentration; Tmax, time of peak concentration; t1/2 Kel, terminal half-life; Cl/F, plasma clearance corrected for unknown bioavailability; Vz/F, volume of distribution per fraction of dose absorbed; MRT, mean residence time; AUC Last, area under the concentration-time curve from dosing (time 0) to the time of the last measured concentration; NA, not assessed.

Table 5: Therapeutic effects of gabapentin combined with meloxicam

Reference	GBP+MEL	Notes
Glynn *et al*. (2013)	Decreased substance P concentration, greater mechanical the nociceptive threshold, and higher average daily weight gain after dehorning	Compared to the control group, no decrease in haptoglobin and cortisol concentrations and no differences upon thermography. No a significant effect for GBP alone
Fraccaro *et al*. (2013)	Had no significant effect on prostaglandins PGE2 levels	GBP has shown an analgesic effect alone, and more effectively in combination with MEL MEL and GBP alone also did not significantly decrease PGE2 levels, however, flunixin did
Coetzee *et al*. (2014)	Induced lameness resolved after 96 h in 83% of the individuals. Positive effect on the impulse of calves and greater force distribution to the lateral claw	No decrease in cortisol levels. No increase in the step count compared to the control group. When GBP was used alone, a positive effect on impulse was also observed

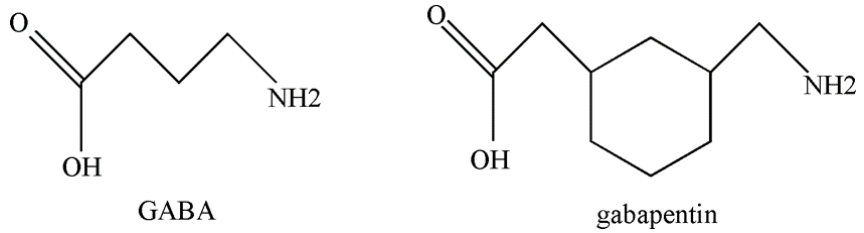

Fig. 1: Molecular structures of Gamma-Aminobutyric Acid (GABA) and gabapentin

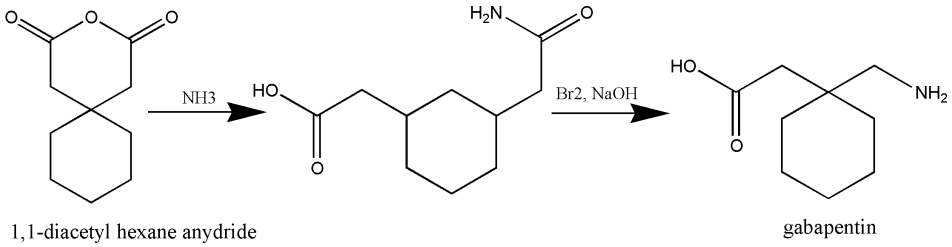

Fig. 2: Synthesis of gabapentin

Furthermore, when the dose was doubled from 10 to 20 mg/kg, the milk GBP concentration increased proportionally, in the late time points, while the milk clearance remained constant, implying that the drug's movement across the mammary epithelium was not saturated at doses up to 20 mg/kg (Malreddy *et al*., 2013). However, at higher doses, the percentage of the GBP dose excreted in milk may not increase linearly with the dose and the transporter-mediated movement of GBP may become saturated (Gehring *et al*., 2011).

Milk concentrations below the Maximum Residue Limit (MRL) that are safe for human consumption have not been established for GBP yet and an appropriate withdrawal time following GBP's extra-label usage in dairy cattle is required. The provisional withdrawal time, which was based on the time after which GBP was no longer detectable in milk, will typically be at least 72 h for doses up to 20 mg/kg and would be longer depending on the dose (Malreddy *et al*., 2013).

It's also worth noting that tissue concentrations following GBP administration are not available and thus MRL for meat tissues from beef cattle has not been established yet. Such findings are needed before the widespread use of GBP in cattle intended for human consumption. Until then, without tissue elimination data, one alternative for calculation of withdrawal intervals in food animal species is to multiply the terminal plasma t1/2 Kel by 10. Thus, a conservative meat withdrawal interval of 21 days is recommended (Riviere and Papich, 2018; Smith, 2013). Coetzee *et al*. (2014) found that the GBP plasma accumulation index ratio, which is the ratio of GBP accumulation under steady-state conditions compared to a single dosage, was 1.21. Assuming there would be a drug equilibrium between plasma and tissues, such a low value might suggest that the risk of GBP accumulation is minimal.

It is also unlikely that GBP would be given to cattle without co-administration of an NSAID, so the withdrawal interval of that drug must also be taken into consideration (Smith, 2013). For example, if MEL is the co-administered drug and based on the plasma t1/2 Kel of 40 h reported in calves (Mosher *et al*., 2012), a conservative meat withdrawal interval of 21 days is recommended (Smith, 2013), for the MEL-GBP combination.

Mechanism of Action, Clinical Application, and Therapeutic Effects

The mechanism of action is still unclear despite GBP's widespread use. It has been partially demonstrated, mainly in mice, rats, and humans. As a result, this review will briefly describe the findings on GBP's PD, followed by findings on therapeutic effects in cattle.

Despite their structural resemblance, GBP does not bind to GABA receptors but has a high affinity for the α2δ-1 subunit of voltage-gated calcium channels (Gee *et al*., 1996). α2δ-1 subunits play a role in nociception because their level increases after injury and can take months to decrease. Therefore GBP's analgesic effects were thought to be related to their direct binding to the α2δ-1 subunit, which inhibits calcium currents and reduces post-synaptic excitability. However, GBP has not been found to consistently inhibit Ca^{2+} currents, hence this assumption is not completely correct (Uchitel *et al*., 2010). Despite this, it is effective in neuropathic pain and can influence nociceptive responses in animal models by stimulating glutamate uptake and inhibiting its release (Ryu *et al*., 2012), inhibiting the formation of new excitatory

synapses by blocking the binding of thrombospondin derived from astrocytes to α2δ-1 (Park *et al*., 2016), inhibiting descending serotonergic and adrenergic pathways (Lin *et al*., 2014), inhibiting the accumulation of α2δ-1 in the pre-synaptic terminals in the dorsal horn (Bauer *et al*., 2010) and by inhibiting the α2δ-1- mediated enhanced neurotransmitter release (Zhou and Luo, 2014).

Thanks to LAT-1, L-type amino acid transporter 1, GBP is actively transported across the blood-brain barrier (Takahashi *et al*., 2018). Figure 3 below shows the proposed mechanism of action of GBP.

Concerning the therapeutic approach for pain management, the medicines chosen should be tailored to the expected pain, its severity, and duration. Ideally, a pharmacological strategy should include the provision of analgesia as early as possible and preferably preemptively, the use of more than one class of analgesic agent acting at different sites of action within the pain pathways (multimodal analgesia), and finally to be practical in terms of frequency and route of administration (Bomzon, 2011). In the context of anti-nociception, experimental evidence from human research suggests that GBP works synergistically with NSAIDs like naproxen (Hurley *et al*., 2002) and diclofenac (Picazo *et al*., 2006) to produce anti-hyperalgesic effects. All of the reasons above encouraged veterinarians to administer GBP alongside MEL as part of the multimodal analgesia in cattle (Glynn *et al*., 2013).

Furthermore, given that treating neuropathic pain alone is insufficient for farm practices and illnesses (to not use GBP alone for pain management in cattle) and that NSAIDs have only a small impact on inflammatory pain associated with lameness (PGE_2 levels did not significantly decrease in Fraccaro *et al*. (2013) when treated with MEL), they are more efficacious together (Glynn *et al*., 2013). The important peripheral site of action for NSAIDs and the central action of GBP potentiate each other (Hurley *et al*., 2002).

This synergism between MEL and GBP has also been evidenced in the past literature on cattle, to varying degrees, as seen in Table 5. The co-administration gave a better outcome in the treatment of cattle than MEL alone. Although the clinical response to MEL-GBP alone was only slightly better than MEL alone in Coetzee *et al*. (2014) and given that more severe lameness scores are commonly recorded in the field than the induced lameness in this experiment, an effect of GBP in cattle with established central sensitization was not ruled out based on these findings.

Flunixin was more efficacious than MEL (Fraccaro *et al*., 2013; Glynn *et al*., 2013) and it's possible that flunixin and GBP would have a comparable or possibly a better synergism.

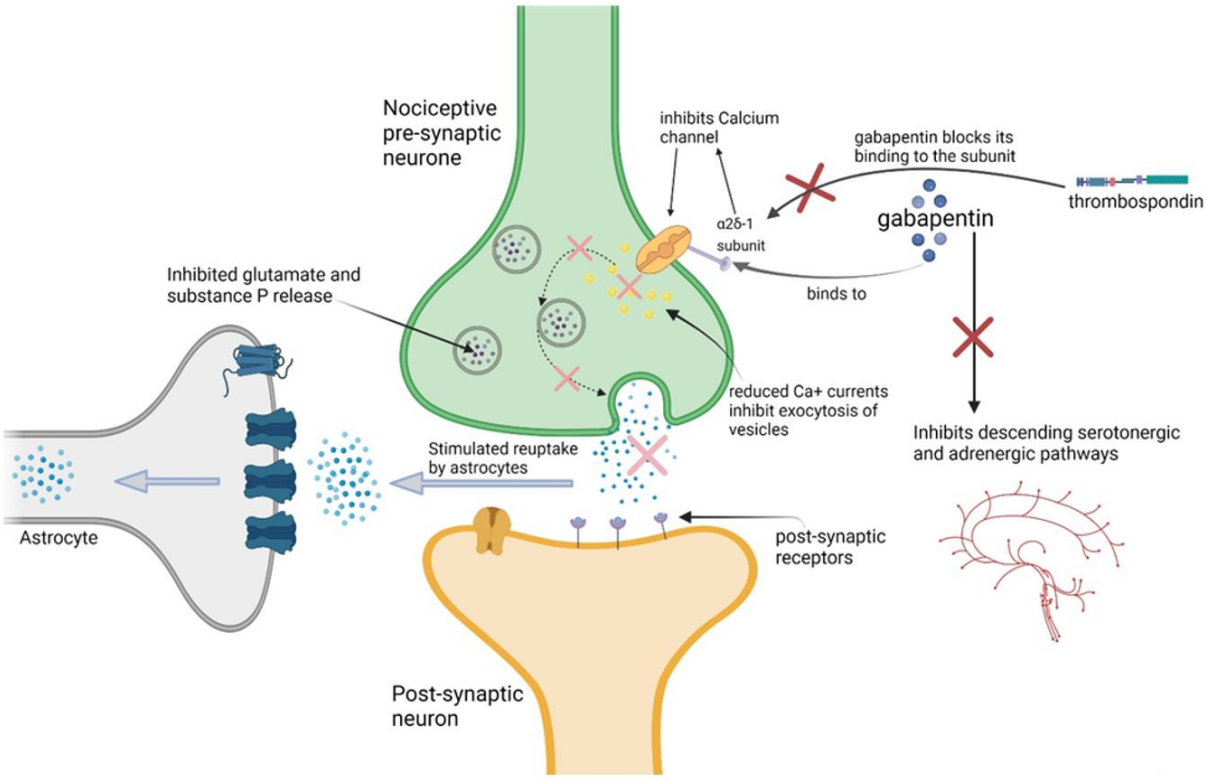

Fig. 3: Proposed mechanism of action of gabapentin

In humans, plasma GBP concentrations above 2 μg/mL are linked to a lower frequency of seizures (Sivenius *et al*., 1991). Epilepsy and neuropathic pain are both treated with similar levels, implying that comparable concentrations will be useful for analgesia as well (Sivenius *et al*., 1991). If it is assumed that cattle and humans have the same minimal effective concentration, plasma concentrations of GBP greater than 2 μg/mL will have an anti-nociceptive effect and the treatment regimens mentioned in Table 3 were adequate to meet the trial's objectives. Based on the PK parameters values and throughout the preceding experiments, in Table 4, GBP concentrations in cattle were kept above this threshold for at least 10 h, with administered oral doses ranging from 10 to 20 mg/kg. A 15 mg/kg dose was associated with plasma concentrations of >2 μg/mL for up to 15 h (Coetzee *et al*., 2021) and up to 20 h with a dose of 20 mg/kg (Malreddy *et al*., 2013). These findings indicate that this compound might be very useful in mitigating chronic neuropathic and inflammatory pain in cattle.

Safety Profile, Side Effects, and Interaction with other Drugs

Previous studies found no side effects for GBP doses up to 20 mg/kg, even after repeated daily administration for four days (Coetzee *et al*., 2014; Cain *et al*., 2014). However, in Coetzee *et al*. (2014), the MEL-GBP treated calves had fewer step counts (recorded using pedometers) compared to the MEL treated calves. Therefore, it was hypothesized that GBP may have a sedative effect on cattle, adding to the decrease in mobility.

In humans, for instance, sedation, dizziness, somnolence, peripheral edema, and gait disturbance are the most common side effects (Parsons *et al*., 2004; Moore *et al*., 2014). In dogs, GBP is generally well tolerated. The most prevalent side effects include moderate sedation, ataxia, and weariness (Peck, 2018). These side effects could also be expected in cattle.

Generally, GBP is very safe, with therapeutic doses that are much lower than toxic doses. However, it should be noted that, like opiates, GBP overdose can be lethal. There is no specific antidote for GBP in the event of overdose and the long half-life necessitates prolonged, intensive hospitalization and care (Reinert and Dunn, 2019). In humans, overdoses involving 49 grams or more of GBP have been reported by the FDA, while in animals it is not documented.

The GBP/MEL combination is also well-known for its use in lame bulls, which frequently exhibit a decline in fertility after lameness, as well as for artificial insemination protocols. This prompted Cain *et al*. (2014) to investigate whether this administration affects the quality of bull sperm, as sperm motility and morphology were examined using light microscopy. All bulls had at least 70% morphologically normal sperm (the minimum for obtaining satisfactory potential breeder status according to Society for Theriogenology standards). Furthermore, for the duration of the study, all bulls maintained acceptable motility (>30% progressively motile), thus GBP/MEL administration did not adversely affect bull semen quality.

In terms of drug-drug interactions, studies have revealed that GBP has a low profile of interaction with other pharmaceuticals. This is due to GBP's lack of interaction with CYP 450 and other hepatic enzymes, insignificant binding to plasma proteins, and unmetabolized passage across organisms (except dogs) (Quintero, 2017; Johannessen and Patsalos, 2010). However, it is not exempt from interactions with other drugs (Díaz *et al*., 2008). GBP has a synergistic effect with a variety of drugs, including selective serotonin reuptake inhibitors or 5-HT6 receptor antagonists (Jayarajan *et al*., 2015), opioids such as morphine (Schmidt *et al*., 2013; Bao *et al*., 2014), and tramadol (Granados-Soto and Arguelles, 2005), NSAIDs (Picazo *et al*., 2006), acetylcholinesterase inhibitors (Basnet *et al*., 2014), other antiepileptic drugs such as phenytoin and mefloquine (Sanchez-Romero *et al*., 2002) and antacids such as magnesium oxide and cimetidine (Yagi *et al*., 2012).

Up to a certain point, GBP's drug-drug interactions in cattle could be analogous to past discoveries; nevertheless, the metabolic pattern should be explored first to see if it is similar to the rest of the animal species.

Conclusion

Although cattle are stoic creatures, bovine veterinarians should be worried about the level of pain and/or stress that cattle encounter and endure from "routine" treatments and pain following "non-routine" treatments such as surgery. Recognizing the benefits of pain management should be embedded in the culture of bovine veterinary practice. For this to happen, there is an urgent need to distribute up-to-date knowledge to ensure that pain and stress therapy in cattle is effective. When it comes to neuropathic pain conditions, there are limitations in the treatments available. Therefore, incorporating GBP in bovine medicine was a promising step. It is increasingly being prescribed in cattle as a complementary drug in multimodal pain protocols, particularly in conjunction with NSAIDs, in which a synergism with MEL was observed. Oral doses between 10 and 20 mg/kg were safe, and effective in dehorning and lameness, in combination with MEL. Such dose is preferable to be administered 8 h before any procedure, as part of the preemptive therapy. A provisional withdrawal time, for milk, should be at least 72 h for doses up to 20 mg/kg and 21 days for meat tissues. Future steps would necessitate the development of an intravenous PK study, as well as anti-nociceptive assays.

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Authors Contributions

Charbel Fadel: Developed the literature search and wrote the draft version of the review. Reviewed and approved the final version of the paper.

Irene Sartini: Contributed to the literature search, planned tables, and plots. Verified the consistency of the information. Reviewed and approved the final version of the paper.

Mario Giorgi: Conceived the presented idea and supervised the project. Provided critical feedback and helped shape the manuscript. Reviewed and approved the final version of the paper.

Ethics

None of the authors has any financial or personal relationships that would unreasonably influence or distort the paper's content or its integrity. No conflict of interest is present.

References

Adrian, D., Papich, M. G., Baynes, R., Stafford, E., & Lascelles, B. D. X. (2018). The pharmacokinetics of gabapentin in cats. *Journal of Veterinary Internal Medicine*, 32(6), 1996-2002. doi.org/10.1111/jvim.15313

Bao, Y. H., Zhou, Q. H., Chen, R., Xu, H., Zeng, L. L., Zhang, X., & Du, D. P. (2014). Gabapentin enhances the morphine anti-nociceptive effect in neuropathic pain via the interleukin-10-heme oxygenase-1 signaling pathway in rats. *Journal of Molecular Neuroscience*, 54(1), 137-146. doi.org/10.1007/s12031-014-0262-2

Basnet, A., Butler, S., Honoré, P. H., Butler, M., Gordh, T. E., Kristensen, K., & Bjerrum, O. J. (2014). Donepezil provides positive effects to patients treated with gabapentin for neuropathic pain: An exploratory study. *Acta Anaesthesiologica Scandinavica*, 58(1), 61-73. doi.org/10.1111/aas.12218.

Bauer, C. S., Rahman, W., Tran-Van-Minh, A., Lujan, R., Dickenson, A. H., & Dolphin, A. C. (2010). The anti-allodynic α2δ ligand pregabalin inhibits the trafficking of the calcium channel α2δ-1 subunit to presynaptic terminals in vivo. *Biochemical Society Transactions*, 38(2), 525-528. doi.org/10.1523/jneurosci.0356-09.2009

Benzon, H., Rathmell, J. P., Wu, C. L., Turk, D. C., Argof, C. E., & Hurley, R. W. (2013). Practical Management of Pain. *Elsevier Health Sciences*. ISBN 978-0-323-17080-2, pp: 1006.

Bomzon, A. (2011). Pain and stress in cattle: A personal perspective. *Israel Journal of Veterinary Medicine*, 66(2), 12-20.

Cain, A. J., Comstock, J. F., King, E. H., & Hopper, R. M. (2014, September). Co-administration of meloxicam and gabapentin does not compromise beef bull semen quality. *In American Association of Bovine Practitioners Proceedings of the Annual Conference* (pp. 163-164).

Coetzee, J. F. (2021, February). Practical pain management in cows and calves. *In American Association of Bovine Practitioners Proceedings of the Annual Conference* (pp. 77-83).

Coetzee, J. F., Mosher, R. A. anderson, D. E., Robert, B., Kohake, L. E., Gehring, R., & Wang, C. (2014). Impact of oral meloxicam administered alone or in combination with gabapentin on experimentally induced lameness in beef calves. *Journal of Animal Science*, 92(2), 816-829. doi.org/10.2527/jas.2013-6999

Coetzee, J. F., Mosher, R. A., Kohake, L. E., Cull, C. A., Kelly, L. L., Mueting, S. L., & KuKanich, B. (2011). Pharmacokinetics of oral gabapentin alone or co-administered with meloxicam in ruminant beef calves. *The Veterinary Journal*, 190(1), 98-102. doi.org/10.1016/j.tvjl.2010.08.008

Díaz, R. A. S., Sancho, J., & Serratosa, J. (2008). Antiepileptic drug interactions. *The Neurologist*, 14(6), S55-S65. doi.org/10.1097/01.nrl.0000340792.61037.40

Dirikolu, L., Dafalla, A., Ely, K. J., Connerly, A. L., Jones, C. N., ElkHoly, H., & Tobin, T. (2008). Pharmacokinetics of gabapentin in horses. *Journal of Veterinary Pharmacology and Therapeutics*, 31(2), 175-177. doi.org/10.1111/j.1365-2885.2008.00943

EMA. (2006). Summary information on referral opinion under Article 30 of Council Directive 2001/83/EC for Neurontin and associated names (Annex I), International Non-Proprietary Name (INN): Gabapentin: Background information. London, UK. *European Medicines Agency*.

Flower, F. C., Sedlbauer, M., Carter, E., Von Keyserlingk, M. A. G., Sanderson, D. J., & Weary, D. M. (2008). Analgesics improve the gait of lame dairy cattle. *Journal of Dairy Science*, 91(8), 3010-3014. doi.org/10.3168/jds.2007-0968

Fraccaro, E., Coetzee, J. F., Odore, R., Edwards-Callaway, L. N., Kukanich, B., Badino, P., & Bergamasco, L. (2013). A study to compare circulating flunixin, meloxicam and gabapentin concentrations with prostaglandin E2 levels in calves undergoing dehorning. *Research in Veterinary Science*, 95(1), 204-211. doi.org/10.1016/j.rvsc.2013.01.018

Fraser, D. (2006). Animal welfare assurance programs in food production: A framework for assessing the options.

Gee, N. S., Brown, J. P., Dissanayake, V. U., Offord, J., Thurlow, R., & Woodruff, G. N. (1996). The Novel Anticonvulsant Drug, Gabapentin (Neurontin), Binds to the α2δ Subunit of a Calcium Channel (∗). *Journal of Biological Chemistry*, 271(10), 5768-5776. doi.org/10.1074/jbc.271.10.5768

Gehring, R., Malreddy, P., Coetzee, J. F., & KuKanich, B. (2011, September). Pharmacokinetics and milk depletion of meloxicam and gabapentin in lactating holsteins. *In American Association of Bovine Practitioners Proceedings of the Annual Conference* (pp. 142-142).

Glynn, H. D., Coetzee, J. F., Edwards-Callaway, L. N., Dockweiler, J. C., Allen, K. A., Lubbers, B., & KuKanich, B. (2013). The pharmacokinetics and effects of meloxicam, gabapentin and flunixin in postweaning dairy calves following dehorning with local anesthesia. *Journal of Veterinary Pharmacology and Therapeutics*, 36(6), 550-561. doi.org/10.1111/jvp.12042

Granados-Soto, V., & Argüelles, C. F. (2005). Synergic antinociceptive interaction between tramadol and gabapentin after local, spinal and systemic administration. *Pharmacology*, 74(4), 200-208. doi.org/10.1159/000085700

Hamer, A. M., Haxby, D. G., McFarland, B. H., & Ketchum, K. (2002). Gabapentin uses in a managed Medicaid population. *Journal of Managed Care Pharmacy*, 8(4), 266-271. doi.org/10.18553/jmcp.2002.8.4.266

Hurley, R. W., Chatterjea, D., Rose Feng, M., Taylor, C. P., & Hammond, D. L. (2002). Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesic. *The Journal of the American Society of Anesthesiologists*, 97(5), 1263-1273. doi.org/10.1097/00000542-200211000-00033

Huxley, J. N., & Whay, H. R. (2007). Attitudes of UK veterinary surgeons and cattle farmers to pain and the use of analgesics in cattle. *Cattle Practice*, 189-193.

Haig, G. M., Bockbrader, H. N., Wesche, D. L., Boellner, S. W., Ouellet, D., Brown, R. R., & Posvar, E. L. (2001). Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. *The Journal of Clinical Pharmacology*, 41(5), 507-514. doi.org/10.1177/00912700122010384

Jayarajan, P., Nirogi, R., Shinde, A., Goura, V., Babu, V. A., Yathavakilla, S., & Bhyrapuneni, G. (2015). 5-HT6 receptor antagonist attenuates the memory deficits associated with neuropathic pain and improves the efficacy of gabapentinoids. *Pharmacological Reports*, 67(5), 934-942. doi.org/10.1016/j.pharep.2015.03.013

Johannessen-Landmark, C., & Patsalos, P. N. (2010). Drug interactions involving the new second-and third-generation antiepileptic drugs. *Expert Review of Neurotherapeutics*, 10(1), 119-140. doi.org/doi.org/10.1586/ern.09.136

KuKanich, B., & Cohen, R. L. (2011). Pharmacokinetics of oral gabapentin in greyhound dogs. *The Veterinary Journal*, 187(1), 133-135. doi.org/10.1016/j.tvjl.2009.09.022

Kumar, A., Soudagar, S. R., Nijasure, A. M., Panda, N. B., Gautam, P., & Thakur, G. R. (2008). Process for the synthesis of gabapentin. Ipca Laboratories, U.S. *Patent Application*, 11, 923.

Lamont, L. A. (2008). Adjunctive analgesic therapy in veterinary medicine. *Veterinary Clinics of North America: Small Animal Practice*, 38(6), 1187-1203. doi.org/10.1016/s0195-5616(08)70008-1

Levandovskiy, I. A., Sharapa, D. I., Shamota, T. V., Rodionov, V. N., & Shubina, T. E. (2011). Conformationally restricted GABA analogs: From rigid carbocycles to cage hydrocarbons. *Future Medicinal Chemistry*, 3(2), 223-241. doi.org/10.4155/fmc.10.287

Ley, S. J., Waterman, A. E., & Livingston, A. (1996). Measurement of mechanical thresholds, plasma cortisol and catecholamines in control and lame cattle: A preliminary study. *Research in Veterinary Science*, 61(2), 172-173. doi.org/10.1016/s0034-5288(96)90096-x

Lin, H. C., Huang, Y. H., Chao, T. H. H., Lin, W. Y., Sun, W. Z., & Yen, C. T. (2014). Gabapentin reverses central hypersensitivity and suppresses medial prefrontal cortical glucose metabolism in rats with neuropathic pain. *Molecular Pain*, 10, 1744-8069. doi.org/10.1186/1744-8069-10-63

Mack, A. (2003). Examination of the evidence for off-label use of gabapentin. *Journal of Managed Care Pharmacy*, 9(6), 559-568. doi.org/10.18553/jmcp.2003.9.6.559

Malreddy, P. R., Coetzee, J. F., KuKanich, B., & Gehring, R. (2013). Pharmacokinetics and milk secretion of gabapentin and meloxicam co-administered orally in Holstein-Friesian cows. *Journal of Veterinary Pharmacology and Therapeutics*, 36(1), 14-20. doi.org/10.1111/j.1365-2885.2012.01384.x

Maneuf, Y. P., Gonzalez, M. I., Sutton, K. S., Chung, F. Z., Pinnock, R. D., & Lee, K. (2003). Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cellular and Molecular Life Sciences CMLS*, 60(4), 742-750. doi.org/10.1007/s00018-003-2108-x

Moore, A., Wiffen, P., & Kalso, E. (2014). Antiepileptic drugs for neuropathic pain and fibromyalgia. *Jama*, 312(2), 182-183. doi.org/10.1001/jama.2014.6336.

Mosher, R. A., Coetzee, J. F., Cull, C. A., Gehring, R., & KuKanich, B. (2012). Pharmacokinetics of oral meloxicam in ruminant and preruminant calves. *Journal of Veterinary Pharmacology and Therapeutics*, 35(4), 373-381. doi.org/10.1111/j.1365-2885.2011.01331.x

Mzyk, D. A., Bublitz, C. M., Baynes, R. E., & Smith, G. W. (2019, September). Milk residues following multiple doses of meloxicam and gabapentin in postpartum and mid-lactation dairy cows. *In American Association of Bovine Practitioners Proceedings of the Annual Conference* (pp. 355-355).

NICE. (2013). Neuropathic Pain in Adults: Pharmacological Management in Non-Specialist Settings. NICE, London, UK. *National Institute for Health and Clinical Excellence.*

Park, J. H., Jhee, O. H., Park, S. H., Lee, J. S., Lee, M. H., Shaw, L. M., & Kang, J. S. (2007). Validated LC-MS/MS method for quantification of gabapentin in human plasma: Application to pharmacokinetic and bioequivalence studies in Korean volunteers. *Biomedical Chromatography*, 21(8), 829-835. doi.org/10.1002/bmc.826

Park, J., Yu, Y. P., Zhou, C. Y., Li, K. W., Wang, D., Chang, E., & Luo, Z. D. (2016). Central mechanisms mediating thrombospondin-4-induced pain states. *Journal of Biological Chemistry*, 291(25), 13335-13348. doi.org/10.1074/jbc.M116.723478

Parsons, B., Tive, L., & Huang, S. (2004). Gabapentin: A pooled analysis of adverse events from three clinical trials in patients with postherpetic neuralgia. *The American Journal of Geriatric Pharmacotherapy*, 2(3), 157-162. doi.org/10.1016/j.amjopharm.2004.09.004

Peck, C. (2018). The adverse effect profile of gabapentin in dogs. https://stud.epsilon.slu.se/13297/7/Peck_C_180424.pdf

Picazo, A., Castañeda-Hernández, G., & Ortiz, M. I. (2006). Examination of the interaction between peripheral diclofenac and gabapentin on the 5% formalin test in rats. *Life Sciences*, 79(24), 2283-2287. doi.org/10.1016/j.lfs.2006.07.025

Platt, S. R., Adams, V., Garosi, L. S., Abramson, C. J., Penderis, J., De Stefani, A., & Matiasek, L. (2006). Treatment with gabapentin of 11 dogs with refractory idiopathic epilepsy. *Veterinary Record*, 159(26), 881-884.

Quintero, G. C. (2017). Review about gabapentin misuse, interactions, contraindications and side effects. *Journal of Experimental Pharmacology*, 9, 13. doi.org/10.2147/JEP.S124391

Radley, D. C., Finkelstein, S. N., & Stafford, R. S. (2006). Off-label prescribing among office-based physicians. *Archives of Internal Medicine*, 166(9), 1021-1026. doi.org/10.1001/archinte.166.9.1021

Radulovic, L. L., Türck, D., von Hodenberg, A. L. B. R. E. C. H. T., Vollmer, K. O., McNally, W. P., Dehart, P. D., & Chang, T. (1995). Disposition of gabapentin (Neurontin) in mice, rats, dogs and monkeys. *Drug Metabolism and Disposition*, 23(4), 441-448.

Reed, D. (2012). The other end of the stethoscope: The Physician's Perspective on the Health Care Crisis. *Author House*. ISBN: 146854411X, pp: 63.

Reinert, J. P., & Dunn, R. L. (2019). Management of overdoses of loperamide, gabapentin and modafinil: A literature review. *Expert Review of Clinical Pharmacology*, 12(9), 901-908. doi.org/10.1080/17512433.2019.1657830

Riviere, J. E., & Papich, M. G. (Eds.). (2018). *Veterinary pharmacology and therapeutics*. John Wiley & Sons.

Ryu, J. H., Lee, P. B., Kim, J. H., Do, S. H., & Kim, C. S. (2012). Effects of pregabalin on the activity of glutamate transporter type 3. *British journal of anesthesia*, 109(2), 234-239. doi.org/10.1093/bja/aes120

Sanchez-Romero, A., Duran-Quintana, J. A., Garcia-Delgado, R., Margarito-Rangel, C., & Poveda-Andres, J. L. (2002). Possible gabapentin phenytoin interaction. Revista de Neurologia, 34(10), 952-953.

Schmidt, P. C., Ruchelli, G., Mackey, S. C., & Carroll, I. R. (2013). Perioperative gabapentinoids: Choice of agent, dose, timing and effects on chronic postsurgical pain. *Anesthesiology*, 119(5), 1215-1221. doi.org/10.1097/ALN.0b013e3182a9a896

Siao, K. T., Pypendop, B. H., & Ilkiw, J. E. (2010). Pharmacokinetics of gabapentin in cats. *American Journal of Veterinary Research*, 71(7), 817-821. doi.org/10.2460/ajvr.71.7.817

Sivenius, J., Kälviäinen, R., Ylinen, A., & Riekkinen, P. (1991). A double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia*, 32(4), 539-542. doi.org/10.1111/j.1528-1157.1991.tb04689.x

Smith, G. (2013). Extra label use of anesthetic and analgesic compounds in cattle. *Veterinary Clinics*: *Food Animal Practice*, 29(1), 29-45. doi.org/doi.org/10.1016/j.cvfa.2012.11.003

Sneader, W. (2005). Drug discovery: A history. John Wiley and Sons.

Stewart, M., Verkerk, G. A., Stafford, K. J., Schaefer, A. L., & Webster, J. R. (2010). Noninvasive assessment of autonomic activity for evaluation of pain in calves, using surgical castration as a model. *Journal of Dairy Science*, 93(8), 3602-3609.

Takahashi, Y., Nishimura, T., Higuchi, K., Noguchi, S., Tega, Y., Kurosawa, T., & Tomi, M. (2018). Transport of pregabalin via L-type amino acid transporter 1 (SLC7A5) in human brain capillary endothelial cell line. *Pharmaceutical Research*, 35(12), 1-9. doi.org/10.1007/s11095-018-2532-0

Terry, R. L., McDonnell, S. M., Van Eps, A. W., Soma, L. R., Liu, Y., Uboh, C. E., & Driessen, B. (2010). The pharmacokinetic profile and behavioral effects of gabapentin in the horse. *Journal of Veterinary Pharmacology and Therapeutics*, 33(5), 485-494. doi.org/10.1111/j.1365-2885.2010.01161.x

Uchitel, O. D., Di Guilmi, M. N., Urbano, F. J., & Gonzalez-Inchauspe, C. (2010). Acute modulation of calcium currents and synaptic transmission by gabapentinoids. *Channels*, 4(6), 490-496. doi.org/10.4161/chan.4.6.12864

Van Haaften, K. A., Forsythe, L. R. E., Stelow, E. A., & Bain, M. J. (2017). Effects of a single pre-appointment dose of gabapentin on signs of stress in cats during transportation and veterinary examination. *Journal of the American Veterinary Medical Association*, 251(10), 1175-1181. doi.org/10.2460/javma.251.10.1175

Vettorato, E., & Corletto, F. (2011). Gabapentin as part of multimodal analgesia in two cats suffering multiple injuries. *Veterinary Anaesthesia and Analgesia*, 38(5), 518-520. doi.org/10.1111/j.1467-2995.2011.00638.x

Vollmer, K. O., Von Hodenberg, A., & Kölle, E. U. (1986). Pharmacokinetics and metabolism of gabapentin in rats, dogs and man. *Arzneimittel-Forschung*, 36(5), 830-839.

Whay, H. R., Main, D. C. J., Green, L. E., & Webster, A. J. F. (2003). Assessment of the welfare of dairy cattle using animal-based measurements: Direct observations and investigation of farm records. *Veterinary Record*, 153(7), 197-202. doi.org/10.1136/vr.153.7.197

Whay, H. R., Waterman, A. E., Webster, A. J. F., & O'brien, J. K. (1998). The influence of lesion type on the duration of hyperalgesia associated with hindlimb lameness in dairy cattle. *The Veterinary Journal*, 156(1), 23-29. doi.org/10.1016/s1090-0233(97)80053-6

Whay, H. R., Webster, A. J. F., & Waterman-Pearson, A. E. (2005). Role of ketoprofen in the modulation of hyperalgesia associated with lameness in dairy cattle. *Veterinary Recor*d, 157(23), 729-733. doi.org/10.1136/vr.157.23.729

Woolf, C. J., & Mannion, R. J. (1999). Neuropathic pain: Aetiology, symptoms, mechanisms and management. *The Lanc*et, 353(9168), 1959-1964.

Yagi, T., Naito, T., Mino, Y., Umemura, K., & Kawakami, J. (2012). Impact of concomitant antacid administration on gabapentin plasma exposure and oral bioavailability in healthy adult subjects. *Drug Metabolism and Pharmacokinetics*, 1201060336-1201060336. doi.org/10.2133/dmpk.dmpk-11-rg-108

Yaw, T. J., Zaffarano, B. A., Gall, A., Olds, J. E., Wulf, L., Papastavros, E., & Coetzee, J. F. (2015). Pharmacokinetic properties of a single administration of oral gabapentin in the great horned owl (Bubo virginianus). *Journal of Zoo and Wildlife Medicine*, 547-552. doi.org/10.1638/2015-0018.1

Zhou, C., & Luo, Z. D. (2014). Electrophysiological characterization of spinal neuron sensitization by elevated calcium channel alpha-2-delta-1 subunit protein. *European Journal of Pain*, 18(5), 649-658. doi.org/10.1002/j.1532-2149.2013.00416.x