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 Haafsen 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 penty1 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 (Levandovsky 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, implying 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 Cmax/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

<table>
<thead>
<tr>
<th>Appearance</th>
<th>White crystalline solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point</td>
<td>314.4°C</td>
</tr>
<tr>
<td>Brand name</td>
<td>Neurontin®, Aclonium®, Equipax®, Gantin®, Gabarone®, Gralise®, Neurostil®, Progress®</td>
</tr>
<tr>
<td>Density</td>
<td>1.058 g/cm³</td>
</tr>
<tr>
<td>IUPAC name</td>
<td>[1-(Aminomethyl) cyclohexyl]acetic acid</td>
</tr>
<tr>
<td>Melting point</td>
<td>162-166°C</td>
</tr>
<tr>
<td>Molar mass</td>
<td>171.237 g/mol</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C₈H₁₅NO₂</td>
</tr>
<tr>
<td>Dissociation constant</td>
<td>pKa= 3.7</td>
</tr>
<tr>
<td>Solubility</td>
<td>Freely soluble in water, alkaline and acidic solutions</td>
</tr>
<tr>
<td>Synonyms</td>
<td>1-(Aminomethyl) cyclohexaneacetic Acid; Apo-Gabapentin; ApoGabapentin; Convalis gabapentin; Gabapentin Hexal; Gabapentin Ratiorpharm; Gabapentin Stada; Gabapentin-ratiorpharm; Novo Gabapentin; Gabapentin; Gabapentin; Gabapetin; Cyclohexaneacetic acid; GOE 2450, 2-[1 (Aminomethyl)cyclohexyl]acetic Acid; Aclidinium; Serada; Fanatrex.</td>
</tr>
</tbody>
</table>
Table 2: Summary of the gabapentin analytical methods used in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Biological matrix</th>
<th>Clean-up</th>
<th>LOD μg/mL</th>
<th>LOQ μg/mL</th>
<th>Validated following FDA/EMA guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malreddy et al. (2013)</td>
<td>Cattle</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>NA</td>
<td>0.025</td>
<td>Yes</td>
</tr>
<tr>
<td>Glynn et al. (2013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraccaro et al. (2013)</td>
<td>Cattle</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Coetzee et al. (2011)</td>
<td>Cattle</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>0.05</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Coetzee et al. (2014)</td>
<td>Cattle</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>0.05</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Yaw et al. (2015)</td>
<td>Owls</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>NA</td>
<td>0.0625</td>
<td>Yes</td>
</tr>
<tr>
<td>Terry et al. (2010)</td>
<td>Horses</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>0.001</td>
<td>0.01</td>
<td>Yes</td>
</tr>
<tr>
<td>Park et al. (2007)</td>
<td>Humans</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>NA</td>
<td>0.02</td>
<td>Yes</td>
</tr>
<tr>
<td>Adrian et al. (2018)</td>
<td>Cats</td>
<td>Plasma</td>
<td>Protein precipitation</td>
<td>0.01</td>
<td>0.05</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Cmax, peak plasma concentration; Tmax, time of peak concentration; t1/2, terminal half-life; CI/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

<table>
<thead>
<tr>
<th>Reference</th>
<th>GBP+MEL</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynn et al. (2013)</td>
<td></td>
<td>Decreased substance P concentration, greater mechanical nociceptive threshold, and higher average daily weight gain after dehorning Compared to the control group, no decrease in haemoglobin and cortisol concentrations and no differences upon thermography. No a significant effect for GBP alone 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 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</td>
</tr>
<tr>
<td>Fraccaro et al. (2013)</td>
<td></td>
<td>Had no significant effect on prostaglandins PGE2 levels</td>
</tr>
<tr>
<td>Coetzee et al. (2014)</td>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>
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 (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 Ca2+ 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 pathways and pain propagation.
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 (PGE₂ 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, 2013). 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.

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