Effect of PO Administered Gabapentin on Chronic Lameness in Horses

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Gabapentin has been used to treat chronic pain in people and small animals. To date, no study has reported its use in horses for the treatment of chronic painful conditions. The clinical effectiveness of gabapentin as an analgesic in horses with chronic lameness was evaluated in a double-blinded crossover study. Six horses with chronic lameness referable to musculoskeletal pathology were randomly assigned to one of three treatments: 5 and 10 mg/kg body weight of gabapentin, and placebo administered PO three times daily for 14 days. All horses received each treatment separated by a 2-week interval. Complete blood count and serum biochemistry were performed before and after each treatment. Lameness was evaluated subjectively by blinded observers before, during, and after each treatment period. The data were analyzed using the general linear model for repeated-measures analysis of variance. A P value of < .05 was considered significant. No significant reduction in lameness level was observed while receiving either gabapentin dose when compared with the placebo group. Further studies are necessary to determine effective plasma concentration and length of treatment period after PO administered gabapentin for analgesia in horses with chronic lameness.

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1. Introduction

Horses, similar to other species, can suffer from chronic pain with musculoskeletal pain being a common source [1]. It is the responsibility of veterinarians to ensure a good quality of life and minimize suffering of animals under his or her care. There are currently a limited number of drugs available to the veterinarian for long-term pain management in horses. Commonly used PO administered analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), flunixin meglumine, and phenylbutazone are effective in relieving pain in horses, but long-term administration has resulted in systemic adverse effects such as gastrointestinal ulceration and renal papillary necrosis [2]. Recently, a COX-2 selective NSAID, firocoxib, has become available and shown to be effective in inhibiting pain associated with osteoarthritis while having fewer side effects as compared with the traditional nonselective NSAIDs [2]. However, firocoxib has been shown to be considerably more costly to the client and has never been challenged against horses predisposed to gastrointestinal ulceration [3,4].

Gabapentin has been used successfully for pain management in veterinary species, particularly in the treatment of chronic and neuropathic pain in small animals, with minimal to no side effects [5–7]. Originally labeled as an antiepileptic in human medicine, gabapentin has been used recently for the treatment of neuropathic and postoperative pain [8,9]. Although the exact mechanism of action is not completely understood, gabapentin is believed to inhibit neurotransmitter release within the peripheral
and central nervous system through interaction with the \(\alpha_2\beta\) subunit of voltage-gated calcium channels [10,11]. In humans, gabapentin is reported to be relatively safe with side effects reported to include somnolence, dizziness, sedation, and ataxia [12,13]. In dogs, mild sedation and ataxia have been the primary side effects reported by their owners [14,15]. The pharmacokinetics and behavioral effects of gabapentin in horses has been previously evaluated [10,11]. The purpose of this study is to evaluate the clinical effectiveness of gabapentin in horses with chronic lameness.

2. Materials and Methods

Six apparently healthy adult horses with varying degrees of chronic forelimb lameness, as indicated by their caretakers and medical history, were identified and selected from the hospital teaching herd and used in this study. All procedures were approved by the Auburn University Institutional Animal Care and Use Committee. Experimental horses consisted of four American Quarter Horses, one Thoroughbred, and one Hanoverian. Horses' mean age was 17.7 years (range, 14–21 years), and mean weight was 562.5 kg (range, 475–691 kg). For all horses, the source of lameness was localized through use of regional anesthesia followed by radiographic examination to substantiate the clinical condition. Clinical sources of lameness included navicular syndrome (n = 2), carpal degenerative joint disease (DJD) (n = 2), proximal interphalangeal joint DJD (n = 1), and metacarpophalangeal joint DJD (n = 1). Horses were evaluated for lameness by trotting in hand on an asphalt surface daily for three separate observations to characterize the baseline lameness as consistent and unchanging. These observations were video recorded by trotting the horse in hand moving both toward and away from the camera as well as back and forth moving parallel to the camera for a set distance and number of passes. Only horses with a consistent, unchanging level of lameness were included in the study.

For each treatment period, two horses were randomly assigned to one of the following treatment groups. Group 1 was the control group and received a placebo, group 2 was administered 5 mg/kg body weight (bwt) of gabapentin (Amneal Pharmaceuticals, Hauppauge, NY) PO every 8 hours, and group 3 was administered 10 mg/kg bwt PO every 8 hours. The horses rotated randomly through all three treatment groups with a 2-week interval between each treatment.

The day before drug administration (day 0), blood was collected for complete blood count and serum chemistry profile to ensure the animal had no underlying systemic disease. The horses were video recorded using the same system previously described. Gabapentin was administered PO every 8 hours beginning on day 1 and continued for 14 days. Treatment doses of gabapentin selected (5 and 10 mg/kg bwt) were based on previous doses safely used in various veterinary species as well as practitioner experience in clinical cases [9–15]. Horses were monitored on a daily basis for evidence of common side effects observed in other species such as sedation, ataxia, and fatigue [9,10,14,15]. The horses were video recorded at days 1, 2, 4, 7, and 14 after drug administration. On the days the horses were video recorded, it was performed approximately 1 hour posttreatment administration. Two equine clinicians unassociated with the project but experienced in the evaluation of lameness and blinded to the treatment groups, subjectively reviewed the 108 (six observations per horse per treatment dose) randomly arranged video segments. The clinicians assigned a numeric lameness score based on a visual analog grading scale of 0–10, where 0 indicates no lameness, 1 indicates a barely discernable lameness, and 10 indicates a nonweight-bearing lameness [16]. After each treatment, lameness was evaluated for return to baseline and blood was collected for complete blood count and serum chemistry profile analysis. Data were analyzed with a Statistical Analysis System software (SAS version 9.2, Cary, NC). For each daily lameness evaluation, scores were ranked and treatment was analyzed using the general linear model for repeated-measures analysis of variance.

3. Results

All horses tolerated the PO administration of gabapentin, and no evidence of side effect (e.g. somnolence, depression, sedation, or ataxia) of the drug at either dose (5 or 10 mg/kg bwt) was observed. The results of complete blood count analysis and serum chemistry profile were within reference range for all horses during the study period.

At the beginning of the third trial, the lameness level of horse #4 on day 0 was noticeably higher than during the two previous trials. After statistical analysis, the lameness level of this horse on day 0 was significantly higher than during previous trials. This horse was subsequently removed from the study due to a change in its baseline level of lameness during trial #3. No statistically significant change in the baseline level of lameness (day 0) was observed in the remaining horses.

When compared with placebo, no statistical differences in lameness score were detected in horses receiving either 5 or 10 mg/kg bwt of gabapentin during any time points throughout the duration of the trial (Figs. 1 and 2).

4. Discussion

Gabapentin, [1-(aminomethyl)cyclohexane acetic acid], was originally developed as a gamma-aminobutyric acid—mimetic compound to treat spasticity. The drug has been shown to have potent anticonvulsive effects [17,18] and was approved initially for the treatment of partial seizures in humans. During its use as an anticonvulsant, it was found to relieve chronic pain syndromes, especially neuropathic pain associated with primary nerve compression, diabetes, or neoplasia [19]. Studies have shown that gabapentin produces antihyperalgesic effects by its blockade on the \(\alpha_2\beta\) subunit of the voltage-dependent calcium channels resulting in relief of chronic neuropathic pain [20–24]. In rat neocortex, gabapentin inhibits neuronal calcium influx in a concentration-dependent manner [25]. The decreased calcium influx reduces excitatory amino acid (e.g. glutamate) release...
Fig. 1. Mean lameness scores for all horses (1–3, 5, 6) during the trial period. Horses received 5 mg/kg (■) or 10 mg/kg (▲) gabapentin or placebo (●).

Fig. 2. Individual lameness scores for each horse (1–3, 5, 6) during the trial period. Horses received 5 mg/kg (■) or 10 mg/kg (▲) gabapentin or placebo (●).
leading to decreased \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation and noradrenaline release in the brain. These observations suggest that the antihyperalgesic/antialloodynic effects of the drug are acting through a central mechanism. In dogs and cats suffering from neuropathic pain secondary to cervical or thoracolumbar intervertebral disk disease or pelvic trauma, Mathews and Dyson [26] reported that gabapentin appeared to be an effective analgesic. However, complete relief of pain took weeks to months. In rats, gabapentin is effective in relieving hyperalgesia and allodynia induced by thermal injury [27], substance P [22], or diabetic neuropathy [28]. Gabapentin was believed to be superior to morphine and amitriptyline in blocking both static and dynamic components of allodynia in rats when administered PO or intrathecally but ineffective when administered locally into the site of allodynia [19].

After PO administration, transport of gabapentin from the small intestinal lumen is facilitated by its binding to an unidentified receptor linked to a saturable \(\alpha\)-amino acid transport mechanism [29]. Because this carrier-dependent transporter is saturable, the bioavailability of a 300-mg dose per adult human patient is approximately 60% [30], whereas that of a 600-mg dose is about 40% and this decreases to around 35% at steady state with dose of 1,600 mg three times daily [31]. Similarly, in lactating Holstein cows, PO gabapentin at doses of 10 mg/kg bwt and 20 mg/kg bwt was transported across the mammary epithelium through a saturable mechanism as evidenced by a nonlinear increase in milk concentration in the presence of higher gabapentin dose [32]. In people, gabapentin does not undergo hepatic metabolism, and the drug is excreted unchanged in the urine [31,33]. Peak plasma concentration is reached between 3 and 3.3 hours with elimination half-lives of 4.8–8.7 hours after PO administration [30,34]. In dogs, 30%–40% of PO administered gabapentin is metabolized to N-methyl-gabapentin by the liver with an elimination half-life of 3–4 hours [34,35]. In horses, gabapentin appears to be exclusively excreted unchanged by the kidney [10]. Most common side effects associated with gabapentin in people include somnolence, dizziness, ataxia, fatigue, and asthenia; however, convulsions have occurred in less than 1% of treated cases [36,37]. In dogs, mild sedation and ataxia have been the primary complaints by the owners [14,15]. No sedation or ataxia was observed in any of the horses at any time during the course of this study.

In horses, choices of PO analgesics that can be safely administered long term are limited. Gabapentin is recognized to be effective in treating maladaptive pain such as partially to nonmanaged pain resulting from ostearthritis, neurologic, or postorthopedic procedure origins in humans [20]. Davis et al. [9] found that gabapentin administered at a dose of 2.5 mg/kg bwt PO every 8 hours to a pregnant draft horse was effective in the treatment of femoral neuropathy after colic surgery. Contrary to that suggested by Matthews and Dyson [26] of a slow onset of effective pain relief, the mare appeared to be more comfortable and less agitated within 2 hours after administration of the first dose [9]. However, instead of a fast onset of analgesia, gabapentin induced a central nervous system-calming effect and sedation may explain the reason that the mare appeared to be more comfortable 2 hours after administration. One pharmacokinetic study of gabapentin in horses indicated that the drug was absorbed rapidly after a single PO dose of 5 mg/kg bwt and peak plasma concentration occurred within 1.4 hours with an elimination half-life of 3.4 hours [11]. However, a more recent pharmacokinetic study found that the bioavailability of the drug when administered PO at a dose of 20 mg/kg bwt was only 16%, suggesting a poor gastrointestinal absorption profile in horses [10]. In another recent case report, gabapentin therapy markedly reduced violent head-shaking behavior in a horse being treated for temporohyoid osteoarthropathy with 48 hours of its introduction [38]. Conversely, the use of gabapentin as an add-on analgesic along with phenylbutazone in the treatment of a mare with severe laminitis did not result in improved clinical analgesia; however, treatment was only continued for 2 days, and the plasma concentration of gabapentin in the mare was well below that reported to provide analgesia in humans [39].

An overall lack of significant reduction in chronic lameness level in horses administered gabapentin PO could be due to inadequate dosages used in this trial. In clinical management of small animal cases, frequent adjustment of gabapentin dosages to achieve maximum pain relief is often required. Perhaps a higher dosage range is required to provide effective pain relief in horses suffering pain from chronic lameness. In addition, because it has been suggested that in small animals, a longer duration of treatment is required for effective pain relief [26], the 2-week treatment duration in the present study may not be sufficient to build up the steady state level of drug concentration to have adequate pain relief for horses suffering chronic lameness. In addition, previous reports indicated a low intestinal bioavailability of this drug in horses; therefore, a higher dose may be necessary for beneficial effects to be observed clinically. Furthermore, gabapentin may be effective as an add-on therapeutic in conjunction with other NSAIDs as some studies report a synergistic response [32,38,39]. This combination may allow for a lower dose of NSAIDs that could potentially minimize adverse side effects as seen with traditionally higher dosages of these compounds.

The utilization of subjective lameness scoring by blinded observers has limitations. An objective method of gait analysis for lameness assessment in horses is becoming more widely used (Equinosis, LLC, Columbia, MO). This type of lameness analysis is more sensitive to gait asymmetries in the horse, which may have identified significant differences in lameness level in this trial. In addition, kinetic measurement systems (stationary force plate, pressure measuring pads or shoes, or force measuring treadmills) may have detected differences in peak vertical ground reaction forces between treatment groups that were not evident with subjective visual lameness assessment. The small sample population of horses used in this trial may have also contributed to difficulties in detecting a significant difference between treatments.

5. Conclusions

Statistically significant differences in the level of chronic lameness in horses receiving either 5 or 10 mg/kg bwt of
gabapentin were not observed during this study; however, clinical and anecdotal reports suggest that gabapentin is beneficial in reducing pain in horses [9]. Because of the previously reported poor oral bioavailability of gabapentin in horses, a trial with higher dosages and/or longer treatment periods may be beneficial in reducing chronic pain in horses. Further clinical trials with gabapentin are needed to determine whether this drug will be useful alone or as an adjunctive therapy with other analgesics in horses with chronic pain and/or lameness.

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References

[25] Fink K, Meder W, Dooley DJ, Gothert M. Inhibition of neuronal Ca(2+)

\[\text{influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices. Br J Pharmacol 2000;130:900–6,}\]