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ORIGINAL ARTICLE

Preliminary observations on the use of ertugliflozin in the management of hyperinsulinaemia and laminitis in 51 horses: A case series

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Summary

Background: Hyperinsulinaemia-associated laminitis (HAL) is encountered commonly in equine practice. There are currently no registered medications which specifically target hyperinsulinaemia in horses and ponies. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been demonstrated to limit post-prandial insulin responses and prevent the development of diet-induced laminitis.

Objectives: The objective of the study was to evaluate the efficacy of an SGLT2i, ertugliflozin, in the management of hyperinsulinaemia and laminitis.

Study design: Retrospective case series.

Methods: Medical records of 51 horses and ponies that had presented with laminitis and hyperinsulinaemia and had been treated with oral ertugliflozin at 0.05 mg/kg once daily for a minimum of 30 days were reviewed.

Results: After 30 days of treatment with ertugliflozin, there was a reduction in insulin concentrations from a median of >300 μu/ml (IQR: 149, >300) to 43 μu/ml (IQR: 20, 66) ($p < 0.001$). Modified Obel laminitis scores improved, reducing from a median of 10/12 to 1/12 ($p < 0.001$). Median serum triglyceride concentrations increased from 0.6 (IQR: 0.4, 0.9) before treatment to 1.4 (IQR: 0.8, 3.7) mmol/L after 30 days of treatment ($p < 0.001$) before declining, however, none of the horses developed any clinical signs of hyperlipaemia. Ten horses (19%) were reported to have polyuria and polydipsia during treatment, otherwise no adverse clinical effects were identified.

Main limitations: The study was limited by the absence of a control group, the retrospective data collection and the short period of follow-up.

Conclusions: Ertugliflozin may be effective in reducing insulin concentrations in horses and ponies with equine metabolic syndrome and its use may hasten recovery from laminitis associated with hyperinsulinaemia.

KEYWORDS
horse, endocrine, equine metabolic syndrome, insulin, podiatry, SGLT2 inhibitor

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INTRODUCTION

Hyperinsulinaemia has been identified to be central to the development of laminitis in horses and ponies (hereafter referred to collectively as horses) with equine metabolic syndrome (EMS) (de Laat & Sillence, 2020; Frank & Tadros, 2014). Laminitis can be induced experimentally following exogenous administration of insulin (Asplin et al., 2007; de Laat et al., 2010), and high serum insulin concentrations are a reliable predictor of future episodes of laminitis (Knowles et al., 2021; Meier et al., 2018a, 2018b; Menzies-Gow et al., 2017). Whilst the exact mechanism by which hyperinsulinaemia causes laminitis is unclear, and other theories are postulated, it has been suggested that insulin may stimulate insulin-like growth factor-1 receptors within the lamellae resulting in cellular proliferation, weakening and subsequent lamellar failure (de Laat et al., 2011, 2013). Reducing serum insulin concentration is therefore considered to be an effective means of preventing hyperinsulinaemia-associated laminitis (HAL) and is advocated in the management of horses with laminitis and equine metabolic syndrome (de Laat & Sillence, 2020).

Currently, no registered medications are available for the treatment of hyperinsulinaemia in horses, although both metformin and levothyroxine have been used to manage horses with equine metabolic syndrome (Durham et al., 2019). Whilst metformin has been demonstrated to limit insulin responses to orally administered dextrose (Rendle et al., 2013) the oral bioavailability of metformin in horses is poor and studies showing its effectiveness at improving insulin sensitivity have yielded inconsistent results (Durham et al., 2008, 2019; Hustace et al., 2009, Tinworth et al., 2012). Levothyroxine administration is associated with a reduction in insulin concentrations and a doubling of insulin sensitivity (Frank et al., 2008; Sommardahl et al., 2005). Compounds such as glucagon like peptide-1 inhibitors, pioglitazone and sweet taste inhibitors have also been identified as having potential for reducing hyperinsulinaemia but are not used in clinical practice currently (de Laat & Sillence, 2020; Durham et al., 2019).

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have recently been developed for the treatment of diabetes in humans (Kalra et al., 2016; Nauck, 2014) and may have the potential to reduce insulin concentrations in horses through promotion of urinary glucose excretion (Kalra et al., 2016; Nauck 2014). The SGLT2i velagliflozin has been demonstrated to reduce hyperinsulinaemia and prevent the development of HAL in experimental models in which ponies were fed diets high in nonstructural carbohydrates (Meier et al., 2018a, 2018b, 2019). Canagliflozin, another SGLT2i, has also been reported to be effective in decreasing the insulin response to an oral sugar test in horses when used in combination with octreotide (Frank, 2018). To date, there are no SGLT2i registered for the treatment of hyperinsulinaemia in horses. Velagliflozin is unavailable currently, and canagliflozin is unavailable in a number of countries. Ertugliflozin (Steglatro: Merck Sharp & Dohme) is more widely available and is relatively inexpensive. This study reports the short-term clinical outcomes associated with the administration of ertugliflozin in the treatment HAL.

MATERIALS AND METHODS

Horses

A convenience sample of clinical records of horses treated at Avon Ridge Equine Veterinary Services between January 2021 and February 2022 were reviewed to identify horses in which ertugliflozin had been administered for the treatment of HAL. According to the practice protocol, ertugliflozin had only been administered where lameness and insulin concentrations had failed to improve after diet and management changes had been implemented for a minimum of 6 weeks. All horses had been treated with ertugliflozin at 0.05 mg/kg once daily per os. Only horses where complete clinical and clinical chemical assessments had been performed at 0 and 30 days were included in the study (Figure 1). Horses were not included if follow-up was not available, other treatments that might affect insulin concentrations (for example metformin or levothyroxine) had been administered or if diet was altered during or within 6 weeks prior to the administration of ertugliflozin to avoid these potentially confounding effects on insulin concentrations. Clinical data retrieved included modified Obel lameness scores (Meier et al., 2021) and measures of adiposity including the estimated weight assessed with a validated weigh tape (Virbac) and measurements of neck circumference (Martinson et al., 2014), heart girth (Martinson et al., 2014) and abdominal girth (Jones et al., 1989). In accordance with practice protocols, blood samples had been collected consistently 90 min after the provision of forage for the assessment of insulin concentration. All horses treated with ertugliflozin had an insulin concentration above the reference limit for the laboratory (40 u/L) prior to commencing treatment. Clinical chemical assessments included measurement of serum concentrations of triglycerides, gamma-glutamyl transferase (GGT) and creatinine in addition to insulin. In a subset of horses, further clinical and clinical chemical assessments were performed at Days 60, 90, 120, 150, 180, 210 and 240, as part of routine monitoring.

Laboratory investigations

Clinical chemistry had been performed at a commercial laboratory (Vetpath Laboratory Services) with insulin concentration measured using an Immulite 2000 (Siemens) with an upper limit of the validation of 300 μu/ml. Creatinine, gamma glutamyl transferase (GGT) and triglyceride concentrations had been measured using a Cobas Pro (Roche Products Pty Limited).

Following commencement of ertugliflozin, owners had been asked to obtain a free-catch urine sample and measure urinary glucose concentration via a Covetrus Vet 10-Way Urine Test Strip. Timing for urine collections had not been standardised.

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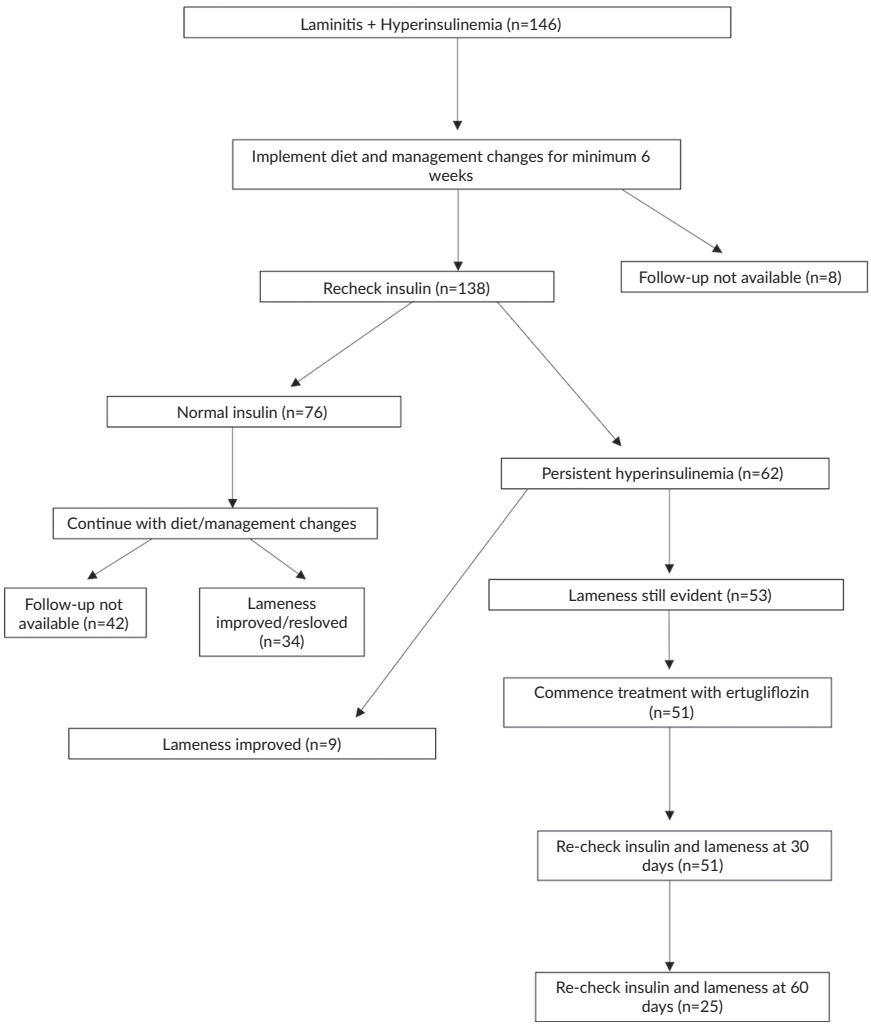

FIGURE 1 Flow chart detailing the treatment of horses with laminitis and hyperinsulinaemia

Medication

All horses were administered ertugliflozin at 0.05 mg/kg bwt by mouth once daily in the horse's first morning feed. Fifteen horses received Steglatro (Merck Sharpe & Dohme [Australia] Pty Limited) as 5 mg or 15 mg tablets and 36 horses received a compounded ertugliflozin paste at 5 mg/ml (BOVA Aus). The decision on which formulation was administered was made in consultation with the owners following discussions of the advantages and disadvantages of registered versus unregistered medicines and tablets versus paste. All owners provided informed written consent for the use of medications not registered for use in horses. Owners were advised of potential side effects including inappetence, colic, polyuria/polydipsia, hyperlipidaemia, lethargy or altered demeanour and were instructed to report any abnormal signs or events immediately.

Data analysis

The study made use of a convenience sample (retrospective cohort); thus, no formal sample size calculation was performed. Signalment and clinical data were transposed from case records to Microsoft Excel for subsequent analysis. Comparisons between continuous measures taken at baseline and 30 days were made using Wilcoxon matched pairs signed rank tests. A nonparametric test was selected to account for the lack of normally distributed data and for the upper limit of detection for insulin (>300 μu/ml). Analysis was carried in out in StataMP version 17 (StataCorp).

RESULTS

Horses

A total of 146 horses were presented for the treatment of HAL during the study period. Clinical records from 51 horses that fulfilled the inclusion criteria were identified (Figure 1). A range of breeds were represented. Pony breeds were dominant, including 17 Welsh/Welsh cross ponies (33%), nine Shetland/Shetland cross ponies (18%) and eight miniature ponies (16%). Other breeds included Quarter horses (8%), Arabian/Arabian crosses (6%) and Warmbloods (4%). Of the 51 horses, 23 were mares (45%) and 28 were geldings

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(55%). The median age was 17 years (range 4–28 years). All horses had lameness as a result of laminitis which had been present for a median of 41 weeks (range 6–304).

All horses were already being managed for equine metabolic syndrome and laminitis and had previously been changed to a low sugar hay fed at 1%–1.5% bodyweight, for a minimum of 6 weeks prior to treatment with ertugliflozin (Figure 1). A range of forage types were fed including meadow hay (47%), lucerne hay (16%), rhodes grass hay (12%), rhodes/lucerne hay mix (14%) and meadow/lucerne mix (12%). Water-soluble carbohydrate values of forage (obtained from a local hay supplier, Western Hay) ranged from 6.5% to 10%. All horses were regularly attended by a farrier and were unshod. For each horse, the diet had remained consistent throughout the period of treatment and was thus the same at pre- and post-treatment testing. Similarly, the timing of testing in relation to feeding had been consistent in each horse. Two horses had received access to grazing in addition to being fed hay at 1% bodyweight, and in these horses, measurements had been taken at the same time of day, following the same period of turn-out. No changes in diet or management had been made at the onset of treatment with ertugliflozin or whilst horses were receiving it. Twelve horses had concurrent pituitary pars intermedia dysfunction (PPID). Previously measured ACTH concentrations demonstrated the PPID was well-managed, and the horses had received pergolide (Prascend, Boehringer Ingelheim) at 2mcg/kg whilst they were on treatment with ertugliflozin. Thirty-three out of fifty-one horses were receiving phenylbutazone paste (Ranvet) at 1–2.2 mg/kg for lameness associated with laminitis when they commenced treatment with ertugliflozin.

Following the commencement of ertugliflozin, the owners of 10 of the horses (19%) had reported polyuria and polydipsia, no other changes or adverse effects had been reported by owners or identified on clinical examination. All owners reported that they had complied with treatment recommendations except for one owner who missed a single dose of ertugliflozin on Day 13 of treatment.

Follow-up information was obtained for a median of 60 days (range 30–240 days). When records were reviewed, 33 horses remained on treatment either because insulin concentration remained increased, or it had increased when treatment was withdrawn. All horses that remained on treatment were all sound and had returned to their previous (prior to laminitis) level of exercise without the need for nonsteroidal anti-inflammatories or other analgesic medications. Of the 18 horses that were no longer recorded as being on treatment, 10 had had treatment discontinued as laminitis and insulin concentrations had improved and were being controlled with diet and management alone. Further records were not found for the remaining 8 horses, 5 had changed ownership, and 3 owners declined further follow-up due to financial constraints.

Insulin and triglyceride concentrations

Prior to treatment, 27 horses (53%) had post-prandial insulin concentrations exceeding 300μu/ml (Table 1) with the lowest concentration being 46 μu/ml. Following 30 days of treatment with ertugliflozin the highest insulin concentration was 233 μu/ml. Median insulin concentration reduced from >300 μu/ml (IQR: 149, >300) at Day 0 to 43 μu/ml (IQR: 20, 66) at Day 30 ($p < 0.001$). There was no significant difference in serum insulin concentration between horses treated with the ertugliflozin tablets versus paste. For the subset of horses with follow-up data beyond 30 days, insulin concentrations remained below baseline values (Figure 2), with a median concentration of 32 μu/ml (IQR: 17, 77) for the samples taken between Days 60 and 240.

Before treatment, 30 horses (59%) had triglyceride concentrations above the laboratory reference interval of 0–0.6 mmol/L, with results ranging from 0.1 to 2.6 mmol/L (median 0.62 mmol/L). Treatment was associated with an increase in triglycerides ($p < 0.001$), with 45 horses (88%) having triglyceride concentrations above the reference interval at Day 30, with results ranging from 0.2 to 16.1 mmol/L (median 1.4 mmol/L). In a subset of 21 horses

TABLE 1 Clinical and clinical chemical data for 51 horses with hyperinsulinaemia and laminitis treated with ertugliflozin for 30 days

	Laboratory ref intervals	Day 0	Day 0 ranges	Day 30	Day 30 ranges	*p*-Value
Insulin[a] (μu/ml), median (IQR)	10–30	>300 (149, >300)	46 - >300	43 (20, 66)	1–233	**<0.001**
Insulin >300 μu/ml, *n* (%)	-	27 (53%)	-	0 (0.0%)	-	-
Triglycerides (mmol/L), median (IQR)	0.0–0.6	0.6 (0.4, 0.9)	0.1–2.6	1.4 (0.8, 3.7)	0.2–16.1	**<0.001**
Modified Obel laminitis score, median (IQR)	-	10 (4, 12)	2–12	1 (0, 2)	0–8	**<0.001**
Bodyweight (kg), median (IQR)	-	272 (182, 492)	-	251 (173, 470)	-	**<0.001**
Heart girth (cm), median (IQR)	-	151 (130, 183)	-	145 (130, 179)	-	**<0.001**
Neck girth (cm), median (IQR)	-	81 (73, 97)	-	76 (70, 93)	-	**<0.001**
Belly girth (cm), median (IQR)	-	167 (148, 202)	-	160 (145, 196)	-	**<0.001**
GGT (u/L), median (IQR)	10–50	29 (23, 37)	9–150	31 (21, 48)	8–161	>0.9
Creatinine (u/L), median (IQR)	60–168	79 (65, 87)	41–134	76 (62, 90)	47–162	>0.5

[a]300 μu/ml was the upper limit of quantification for measures of insulin.

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with triglyceride concentrations measured at Day 60, 13 (62%) were above the normal range, with a range of values from 0.2 to 5.3 mmol/L (median 1.0 mmol/L). Beyond Day 60 concentrations ranged from 0.2 to 3.9 mmol/L (Figure 3).

Laminitis

Prior to treatment, the modified Obel laminitis score ranged from 2 to the maximum score of 12 with a median of 10 (IQR: 4, 12). Following 30 days of treatment, there was a reduction in laminitis score ($p < 0.001$) (Video S1–S3), with a maximum score of 8 and a median of 1 (IQR: 0, 2) (Table 1). Scores were also available for a subset of horses up to 240 days following the commencement of treatment. Median laminitis scores remained below two from Day 30 onwards (Figure 4). Between Days 7 and 14 of ertugliflozin treatment, 28 horses that were receiving phenylbutazone had sufficient improvement in lameness such that phenylbutazone was discontinued without any regression in laminitis score.

Estimated bodyweight and morphometric measurements

A significant reduction in estimated bodyweight and morphometric measurements were observed after 30 days of ertugliflozin treatment ($p < 0.001$) (Table 1). Reductions in estimated bodyweight were observed in 48 horses (94%) with reductions ranging from 2 to 71 kg (median 16 kg) or 0.6% to 19% bodyweight (median 6%).

Hepatic and renal markers

Serum GGT activity was outside the laboratory reference interval in eight horses (16%) at Day 0, and in 11 horses (22%) at Day 30. Overall, there was no difference in GGT concentrations between Day 0 and Day 30 ($p > 0.9$) (Table 1). All the horses with increased GGT activity at 30 days subsequently had normal activity at later follow-up periods despite remaining on treatment with ertugliflozin. No horses had creatinine values that exceeded normal reference intervals and there was no difference in median creatinine concentration from Day 0 to Day 30 ($p > 0.7$).

Urinary glucose

Urinary glucose measurement was available in nine horses with a median concentration of 27.8 mmol/L (range 2.8–55.5).

DISCUSSION

The use of ertugliflozin was associated with a marked reduction in insulin concentrations and lameness associated with laminitis at 30 days. Whilst these results need to be interpreted with caution given the limited case numbers and the absence of a control group, ertugliflozin clearly merits further investigation for the treatment and prevention of HAL. Many of the horses in the study had shown limited or no response to previous treatments and management interventions. The 0.05 mg/kg dose of ertugliflozin reflects the dose that is being used in equine practice based on publications from other species and

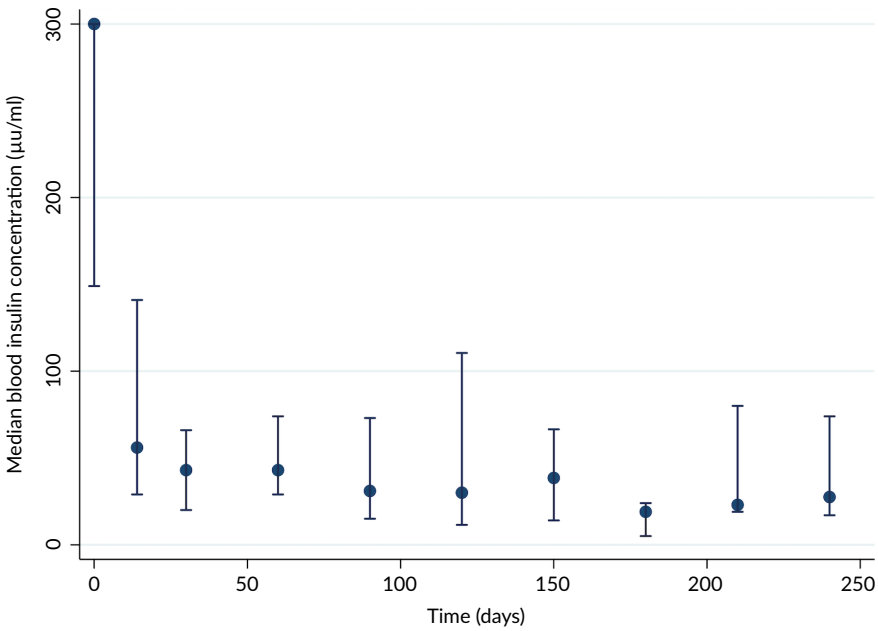

FIGURE 2 Median blood insulin concentration (µu/ml) and interquartile range following the commencement of treatment with ertugliflozin. Day 0: $n = 51$, Day 14: $n = 27$, Day 30: $n = 51$, Day 60: $n = 25$, Day 90: $n = 19$, Day 120: $n = 8$, Day 150: $n = 8$, Day 180: $n = 5$, Day 210: $n = 6$, Day 240: $n = 6$

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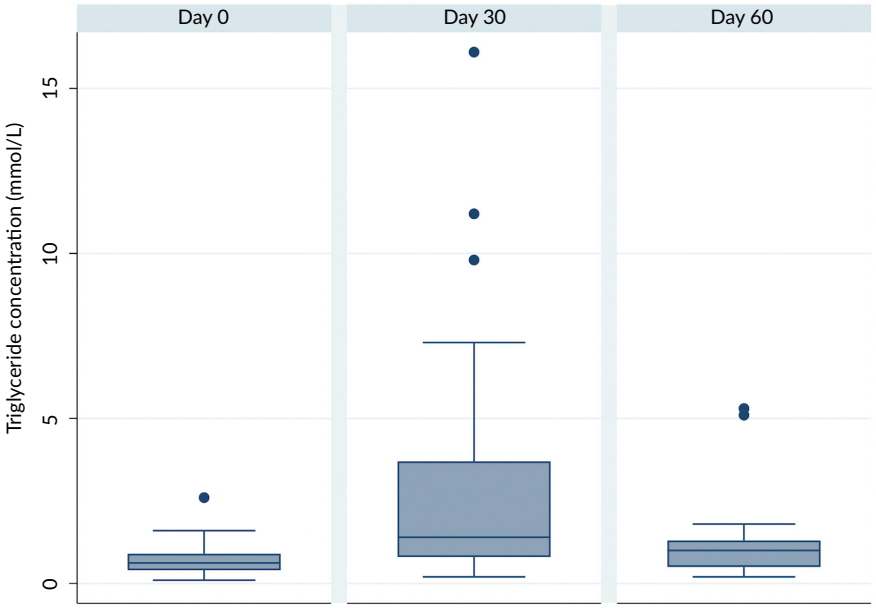

FIGURE 3 Box plot showing triglyceride concentrations (mmol/L) in horses treated with ertugliflozin for the management of hyperinsulinaemia and laminitis, at baseline ($n = 51$), Day 30 ($n = 51$) and Day 60 ($n = 21$)

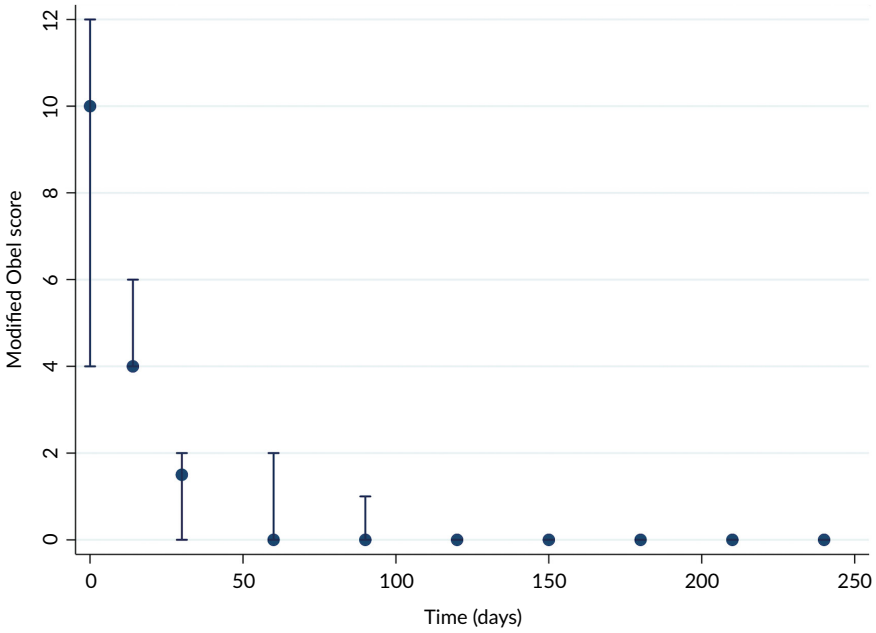

FIGURE 4 Median and interquartile range of modified Obel score assessing lameness, following the commencement of treatment with ertugliflozin. Day 0: $n = 50$, Day 14: $n = 5$, Day 30: $n = 50$, Day 60: $n = 16$, Day 90: $n = 16$, Day 120: $n = 8$, Day 150: $n = 5$, Day 180: $n = 3$, Day 210: $n = 7$, Day 240: $n = 6$

anecdotal experience, it does not have an evidential basis in the horse. Pharmacokinetic and pharmacodynamic studies are warranted to establish the most appropriate dosing regimen for this drug in horses.

Sodium-glucose cotransporter 2 inhibitors reduce insulin concentrations through promotion of urinary glucose excretion (Kalra et al., 2016; Nauck, 2014). Under normal circumstances, almost all glucose is reabsorbed from the proximal convoluted tubule of the human kidney leaving minimal amounts excreted in urine (Gerich, 2010). The regulation of glucose reabsorption from glomerular filtrate in humans is mediated by both SGLT1 and SGLT2 receptors (Gerich, 2010) with SGLT2 being responsible for reabsorption of more than 90% of filtered glucose in the human kidney and SGLT1 the remaining 10%. SGLT2i therefore decrease renal glucose resorption resulting in a lowering of blood glucose concentrations (Bays, 2013; Kalra, 2014; Sha et al., 2011) and subsequent reduction in secretion of insulin from the pancreas. SGLT2i have been demonstrated to

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reduce insulin concentrations in humans, rodents, dogs and horses (Frank, 2018; List & Whaley, 2011; Meier et al., 2018a, 2018b, 2019; Neumiller, 2014, Paskiewicz et al., 2018). Whilst there is no pharmacokinetic data for ertugliflozin in horses, studies performed in other species demonstrate that ertugliflozin is rapidly absorbed, reaching peak plasma concentrations 1 h following a single oral dose with a bioavailability of 69% in rats and 94% in dogs (Fediuk et al., 2020). Given the clinical responses observed, the dosage used in this study appears to be effective and well tolerated but investigation of the pharmacokinetics and pharmacodynamics of ertugliflozin in horses are warranted to optimise dosing regimens.

Insulin concentrations reduced in all horses in association with 30 days of ertugliflozin treatment and in most horses remained low through subsequent follow-up tests (Figure 1). However, in eight horses an increase in insulin was identified beyond 30 days of treatment, and we speculate that this may have been due to upregulation of SGLT1 receptors. Studies in humans and rodents have demonstrated that despite SGLT2 accounting for 90% of glucose reabsorption, during SGLT2 inhibition, glucose reabsorption is only reduced to 40–50% which is hypothesised to be the result of a compensatory role of SGLT1 (Rieg et al., 2014). Whilst this potential mechanism has not been proven in human medicine, inter-patient variability and up-regulation of SGLT1 in response to SGLT2 inhibition may account for the increase in insulin concentration in a subset of horses in this study. SGLT2i vary in their selectivity for SGLT2 over SGLT1, and ertugliflozin is highly selective for SGLT2 (Fediuk et al., 2020). Alternatively, some owners may have failed to adhere to long-term diet and management recommendations resulting in increased dietary sugar intake and subsequent increase in serum insulin concentration.

The improvement in laminitis in association with a reduction in insulin concentration following ertugliflozin treatment is consistent with recent research that has demonstrated a link between hyperinsulinaemia and laminitis (de Laat & Sillence, 2020). Insulin concentrations have been shown to be associated with future risk of laminitis (Knowles et al., 2021; Menzies-Gow et al., 2017), and reduction in insulin concentration is therefore assumed to reduce the risk of clinical laminitis developing (de Laat & Sillence, 2020). The speed and magnitude of improvement in lameness was unexpected, given that these were chronic cases; to the authors' knowledge, this is the first study to report a rapid improvement in clinical laminitis following the use of drugs that reduce insulin concentrations. All owners reported rapid improvement in lameness and general demeanour within 7–21 days and where veterinary examination was performed at 14 days, a marked clinical improvement was observed. The use of phenylbutazone may have contributed to an improvement in lameness, however, the addition of ertugliflozin resulted in a further improvement in lameness grade. Without a control group the possibility of a temporal association, rather than a treatment effect, cannot be ruled out. Further investigations are warranted but if the findings of the current study translate to larger populations, then ertugliflozin and other similar drugs might have the potential to improve the speed of recovery from laminitis and alleviate considerable suffering. New episodes of laminitis did not develop during treatment with ertugliflozin. As these were clinical cases with financial constraints, radiography was not performed consistently. However, some cases were radiographed and marked reduction in lameness was evident even when there was radiographic evidence of rotation and displacement of 3rd phalanx. If the administration of ertugliflozin was relevant to the improvement in lameness, the mechanism is unknown. Reduction in insulin concentrations might have prevented further laminar damage but would not be expected to ameliorate the pain associated with chronic pathology. Acute laminar pathology associated with hyperinsulinaemia may be a significant source of pain and may be a greater factor relative to chronic mechanical changes than assumed previously. In humans, insulin resistance reproduces several aspects of neuropathic pain through cerebral hypoperfusion and modulation of ion channels in afferent neurons with administration of insulin-sensitising drugs being associated with a reduction in pain (Pappolla et al., 2021).

Although most horses lost weight (based on estimates obtained via a validated weigh tape) whilst they were on treatment with ertugliflozin, rates of weight reduction were variable. In humans, weight loss is reported with the use of SGLT2i and appears to be biphasic; there is initial weight reduction thought to be a result of caloric loss due to glucose excretion, loss of body water due to osmotic diuresis and reduction in fat mass (Janež & Fioretto, 2021; Kalra, 2014; Rosenstock et al., 2013), which is then followed by a slower rate of weight loss. Fat loss associated with SGLT2i is likely the result of a shift to fatty acid utilisation and lipolysis (Ferrannini et al., 2014, 2016) due to increased glucagon secretion from pancreatic alpha islet cells in response to reduced blood glucose and insulin concentrations (Janež & Fioretto, 2021; Sargent, 2015). The horses which lost the most weight were subjectively the horses that were the most obese which is consistent with findings in humans where the greatest reduction in bodyweight is seen in patients with a higher pretreatment weight (Kalra, 2014). Ertugliflozin merits further investigation to determine whether it offers a means of promoting reduction in adiposity beyond what can be achieved with dietary restriction alone.

Ertugliflozin was well tolerated by all horses. All but four of the horses exhibited hypertriglyceridemia following 30 days of treatment yet clinical signs of hyperlipaemia were not observed. In the absence of other clinical or clinicopathological abnormalities that might have indicated hyperlipaemia or hepatic lipidoses, it was considered appropriate to continue ertugliflozin with further careful monitoring. Hypertriglyceridemia secondary to endocrine dysfunction, without any evidence of clinical abnormalities, has been reported previously (Dunkel et al., 2014). Given the potential for life-threatening complications and the predisposition of horses with EMS to hypertriglyceridemia (Durham et al., 2019; Morgan et al., 2014), it is important that horses on treatment with ertugliflozin are monitored closely for signs of hyperlipaemia and hepatic lipidosis and owners are counselled on the potential risk associated with the use of SGLT2i. Interestingly, a reduction in triglyceride concentrations are reported in humans treated with SGLT2i (Heymsfield

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et al., 2020; Pradhan et al., 2019); however, circulating ketone concentrations are increased, presumably due to a decrease in blood glucose concentrations (Ferrannini et al., 2017; Qiu et al., 2017). Given that ketogenic pathways are relatively unimportant in horses (Rose & Sampson, 1982), the authors' hypothesise that triglycerides are increased in response to lowered blood glucose and insulin concentrations, increased glucagon secretion and subsequent lipolysis (Janež & Fioretto, 2021; Sargent, 2015; Zhu et al., 2021).

Ten horses exhibited polyuria and polydipsia. Studies in humans have demonstrated that urinary excretion of glucose with SGLT2i leads to a chronic osmotic diuresis (List & Whaley, 2011) with volume depletion being a potential consequence (Neal et al., 2017). Whilst there were no clinical signs of dehydration or hypovolaemia in horses in this study, clinicians should be aware of the potential for volume depletion and should ensure free access to ample quantities of water in horses treated with ertugliflozin. SGLT2i have the potential to cause urinary tract infections (UTI) due to glucosuria (Washburn & Poucher, 2013). No signs of UTI were observed in horses in this study and in humans treated with dapagliflozin, the incidence of UTI did not increase despite increasing urinary glucose concentrations (Johnsson et al., 2013). A recent meta-analysis of human studies demonstrated that the use of SGLT2i was not associated with an increased risk of UTI (Wilding, 2019). Urinalysis performed in the current study confirms that glucosuria develops in association with the use of SGLT2i in horses.

The study was limited by small sample size, heterogeneity in treated horses, absence of blinding and the retrospective nature of data collection. In accordance with practice protocols, measures were taken to ensure consistency of the conditions around pre- and post-treatment sampling; however, this was not an experimental study in which all factors were under the investigators control. The administration of pergolide and phenylbutazone to some horses had the potential to confound assessments of insulin concentration and lameness. All horses were exhibiting clinical signs of laminitis prior to treatment and the presence of pain and stress may have the potential to falsely elevate insulin concentrations (Durham et al., 2019; Frank & Tadros, 2014). Given the absence of a prospective study design with a control group, it could be argued that some horses may have improved by 30 days irrespective of treatment; however, most of the horses presented in this study exhibited chronic laminitis which had not improved for several months. Whilst some follow-up data were available, data were less frequent at subsequent time points. Thus, more extensive studies would be needed to assess the long-term efficacy and potential side effects in animals treated with ertugliflozin. Significant findings in small populations do not always translate when larger, more robust clinical trials are performed (Button et al., 2013). This is a common challenge in veterinary research, and the findings of this study should prompt further work as the potential impact on animal welfare of an effective treatment for HAL is huge.

In conclusion, this study suggests that ertugliflozin may have potential as an effective pharmacological aid for the treatment of hyperinsulinaemia and the management of HAL in horses and ponies who have not responded to dietary management. Larger, blinded, randomised clinical trials, long-term safety data and investigations of the pharmacokinetics and pharmacodynamics of ertugliflozin and potentially other SGLT2i are warranted.

AUTHOR CONTRIBUTIONS

The study was conceived by D. Rendle and T. Sundra. Data were collated by D. Rendle and T. Sundra and analysed by E. Kelty. All authors contributed to the preparation and final approval of the manuscript.

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BOVA subsidised some laboratory testing for the study.

CONFLICT OF INTERESTS

D. Rendle provides consultancy services to BOVA who produce an extemporaneous ertugliflozin paste specifically for horses. T. Sundra has received subsidised travel expenses to CPD events organised by BOVA. Written client consent was obtained prior to the use of medications and consent provided for the use of patient clinical data.

ETHICS STATEMENT

The study was reviewed and approved by the Animal Ethics Office of The University of Western Australia under reference F78787.

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