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Final report

Optimize canagliflozin doses – decrease hyperinsulinemia and prevent laminitis

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Part 1: Detailed summary

Projektets syfte var att undersöka de farmakokinetiska (PK) och farmakodynamiska (PD) egenskaperna hos läkemedlet Canagliflozin (CFZ), en SGLT2-hämmare, hos häst. Hypotesen var att CFZ har en tydlig glukossänkande effekt genom ökad glukosutsöndring i urin, och att dess PK-egenskaper möjliggör effektiv och säker klinisk användning vid insulinrelaterad fång. Tre delstudier genomfördes: ***Studie I:*** *8 friska islandshästar gavs 1,8 mg/kg CFZ i en crossover-design. PK och respons på glukosinfusion (GGI) analyserades.* ***Studie II:*** *8 friska varmblodiga travhästar gavs placebo, 1,8 mg/kg eller 3,6 mg/kg CFZ. Glukos- och insulinrespons samt urin-glukos mättes.* ***Studie III:*** *En populationsbaserad PK-modell utvecklas med data från totalt 63 hästar (varav 30 med insulinrubbning) och >1100 prover. Uringlukosdata används för en enkel PK-PD-modell. De två första studierna slutfördes som planerat utan allvarliga biverkningar. Studie III förändrades till viss del gentemot ansökan med avseende på dosering och utvärdering beroende på resultatet i studie 1 och 2 samt studier publicerade av andra forskargrupper. Från studie III är samtliga prover är insamlade men analysen av cirka hälften av proverna är tillfälligt försenad p.g.a. ombyggnation av analyslaboratoriet. Sammanfattningsvis så uppvisade CFZ god absorption och lång halveringstid (21,8–28,5 h), vilket stödjer en gång per dag-dosering. Glukos- och insulinrespons på GGI minskade signifikant i båda dosnivåerna i studie I och II, utan dosberoende skillnad. Uringlukos ökade kraftigt och ihållande efter behandling.Lätta förändringar i leverenzym (GLDH) och triglycerider observerades, främst vid hög dos.Den pågående populationsmodellen kommer att klargöra interindividuell variation och dosoptimering. Projektet adresserar ett stort kliniskt behov: behandling av insulinrelaterad fång. Genom att etablera vetenskapligt baserad dosering lägger projektet grunden för bredare klinisk användning av CFZ. Resultaten har presenterats i vetenskapliga sammanhang (Michanek et al. 2024), och analysen av populationsdata är nästa steg. För framtida implementering krävs: Kliniska långtidsstudier hos fånghästar samt utbildningsinsatser till kliniskt verksamma veterinärer om evidensbaserad användning.*

The project has been financed by:

Part 2: Main report (max. 10 pages)

Introduction

Laminitis is a common, painful, and potentially life-threatening condition in horses that poses a significant threat to their welfare. Specifically, it causes damage to the laminae, the tissue that connect the hoof wall to the pedal bone. Hyperinsulinemia induce laminitis (Asplin et al., 2007; de Laat et al., 2010), but the exact mechanism is still not known (Menzies-Gow and Knowles, 2024). While laminitis can be triggered by several factors, hyperinsulinemia is recognized as the predominant underlying cause (Karikoski et al., 2011).

Traditionally, laminitis treatment involves restricted movement and non-steroidal anti-inflammatory drugs (Durham et al., 2019). To address the underlying hyperinsulinemia, increasing exercise and modifying the diet to reduce non-structural carbohydrates are beneficial. However, horses with acute laminitis should not be actively exercised, as this can exacerbate tissue damage in the hooves. In many cases, these management changes are insufficient or impractical for owners to implement, often hindering full recovery and making laminitis a common cause of euthanasia in affected horses (Luthersson et al., 2017; Sundra et al., 2024a). Pharmacological therapies for treating hyperinsulinemia-associated laminitis such as metformin (Colmer et al., 2023), levothyroxine (Chameroy et al., 2010), and pioglitazone (Legere et al., 2019; Suagee et al., 2011) have been used but not consistently demonstrated high efficacy in ID horses.

Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) represent a relatively novel class of pharmacological agents. These drugs first received regulatory approval for human use in 2012 (Haas et al., 2014), with the first reports of their use in horses emerging in 2018 (Frank, 2018; Meier et al., 2018). Since then, several SGLT2-i, namely canagliflozin, dapagliflozin, ertugliflozin, and velagliflozin, have been studied in horses and demonstrated high efficacy in decreasing hyperinsulinemia and preventing laminitis in insulin-dysregulated (ID) horses (Kellon and Gustafson, 2022, 2023; Lindase et al., 2023; Meier et al., 2019; Meier et al., 2018; Sundra et al., 2023; Sundra et al., 2024a; Sundra et al., 2024b, 2025).

Despite promising clinical observations, a significant gap exists in the pharmacokinetic (PK) understanding of SGLT2-i in horses, with a complete absence of published, peer-reviewed PK data. While very limited PK data for velagliflozin have been reported in a patent application (Reiche et al., 2015) comprehensive PK characterization remains absent from scientific publications. This lack of studies does not only limit the ability to define optimal dosages but also hinders a thorough understanding of potential adverse effects and the variability in plasma concentrations among individual equine patients. There are also, naturally, no pharmacokinetic-pharmacodynamic studies investigating what plasma concentrations are effective in horses.

Building upon this identified knowledge gap, the primary objective of the present project is to gain a more thorough understanding of the PK and pharmacodynamic (PD) properties of the SGLT2-i canagliflozin in horses. This research aims to provide data necessary for optimizing dosing regimens and expanding the knowledge base regarding potential adverse effects. This understanding is fundamental to establishing effective and safe clinical application of canagliflozin in equine patients.

Material and methods

Study I - Pharmacokinetics and Alterations in Glucose and Insulin Levels After a Single Dose of Canagliflozin in Healthy Icelandic Horses

Pharmacokinetic (PK) and pharmacodynamic (PD) effects of canagliflozin (CFZ) was investigated in eight healthy Icelandic horses. Each horse received a single oral dose of 1.8 mg/kg CFZ and placebo treatment on separate occasions, allowing for a crossover comparison.

Figure 1 presents a schematic overview of the treatment protocol and the associated sampling time points. To assess the PD effects, after receiving treatment with placebo or CFZ, the horses underwent a graded glucose infusion (GGI). The GGI consisted of glucose infused at incremental rates of 0.4, 0.8, 1.2, 1.6, 2.4, and 3.2 mg/kg/min, with each infusion rate maintained for a 40-min duration. Throughout the study, serum and plasma samples were collected at predetermined time points. These samples were used to evaluate the PK, PD response to the drug during the GGI, and the overall effect on key biochemical parameters.

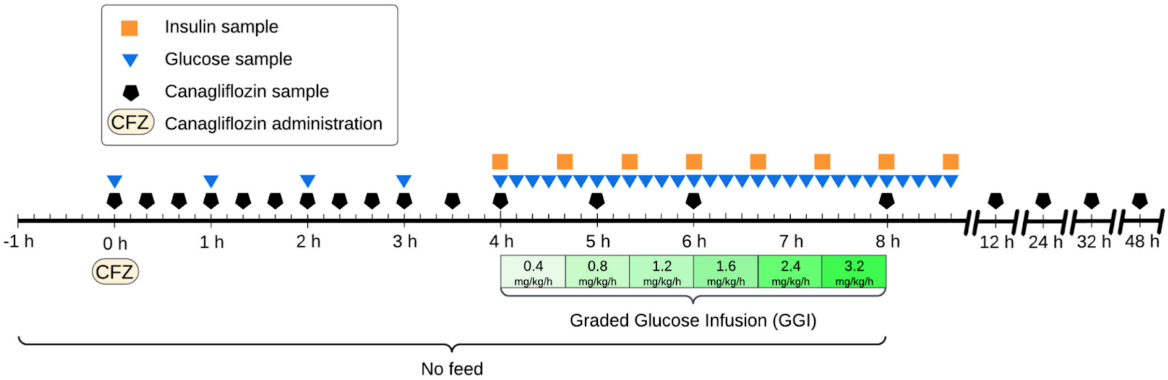

Figure 1. Schematic representation of the study design and timeline for sample collection in study I. Placebo treatment mirrored the study timeline, excluding drug administration and the last four sample collections.

CFZ was quantified using UHPLC coupled to tandem quadrupole mass spectrometry (UHPLC-MS/MS) and pharmacokinetics were evaluated using a non-compartmental model. Plasma glucose was analyzed using YSI 2500 Glucose/Lactate Analyzer, insulin was analyzed using Mercodia Equine Insulin Elisa and biochemical parameters was analyzed using a biochemistry analyzer, DxC 700AU.

PK data was analyzed using non-compartmental analysis (NCA). To determine statistically significant differences between the placebo and active treatment groups, a paired t-test was conducted. However, if the assumptions for the paired t-test were not met, a non-parametric alternative, the Wilcoxon signed-rank test, was used.

Study II - Canagliflozin: Pharmacokinetics, Tolerability and Glucose/Insulin Effects of Supratherapeutic Doses in Healthy Horses.

In a crossover design, eight standardbred horses received three different treatments: a placebo, 1.8 mg/kg CFZ, or 3.6 mg/kg CFZ, administered in randomized order. As in Study I, the horses underwent a GGI and were sampled to determine PK and PD responses, along with biochemical and hematological changes. Urinary glucose concentrations were also measured at predetermined time points. NCA was used for PK data analysis, and group differences were analyzed with a paired t-test (comparing PK between 1.8 mg/kg and 3.6 mg/kg doses). Mixed mixed effects modeling/Friedman test for non-parametric data was used to compare the three treatments regarding PD responses as well as biochemical changes to treatment.

Study III – Canagliflozin Pharmacokinetics and Urinary Glucose Dynamics in Equine Populations: A Population Modeling Approach

This study aims to develop a population PK model for Canagliflozin in horses, utilizing a non-linear mixed-effects modeling (NLME) approach. This approach allows for the analysis of sparse data from various individuals and dosages, capturing inter-individual variability in drug disposition.

Our population pharmacokinetic (pop PK) model will be developed using over 1100 samples from the following studies:

- Healthy Horses (Single Dose):
  - 8 healthy Icelandic horses received a single dose of 1.8 mg/kg CFZ (Study I)
  - 8 healthy Standardbred horses received single doses of 1.8 mg/kg and 3.6 mg/kg CFZ (Study II).
  - 9 healthy Standardbred horses received a single dose of 400-600 mg CFZ (0.6-1.1 mg/kg).
- Healthy Gotland Russ Horses (Multiple Dose):
  - 8 healthy Gotland Russ horses received 100 mg CFZ every 24 hours for a total of four doses (0.3-0.42 mg/kg per dose).
- Diagnosed ID horses (Multiple Dose)
  - 30 horses diagnosed with insulin dysregulation (ID) received CFZ treatment, with most receiving daily doses between 0.4-0.6 mg/kg.

In addition to the PK model, a simple PKPD model will be developed. This will make use of the developed PK model and urinary glucose concentration PD data from the 17 healthy Standardbred horses.

While all 1100 samples are collected, CFZ quantification for about half of the samples is on hold due to the analytical lab's temporary closure for renovation/relocation.

Results and discussion

Study I - Pharmacokinetics and Alterations in Glucose and Insulin Levels After a Single Dose of Canagliflozin in Healthy Icelandic Horses

Seven of the eight healthy Icelandic horses successfully completed all study interventions, with one horse completing the pharmacokinetic portion but excluded from glucose dynamics due to a perivascular hematoma, which resulted in the removal of one catheter. No overt adverse effects associated with CFZ treatment were observed.

A non-compartmental analysis characterized the pharmacokinetics of CFZ after a single oral dose of 1.8 mg/kg. Key findings included a median time of maximum concentration (Tmax) of 7 hours , a maximum plasma concentration (C_{max}) of 2350 ng/mL , and a terminal half-life ($t_{1/2Z}$) of 28.5 hours. While significant inter-individual variation was noted during the absorption phase, the terminal elimination phase showed less variability. The concentration-time course of plasma CFZ is displayed in Figure 2.

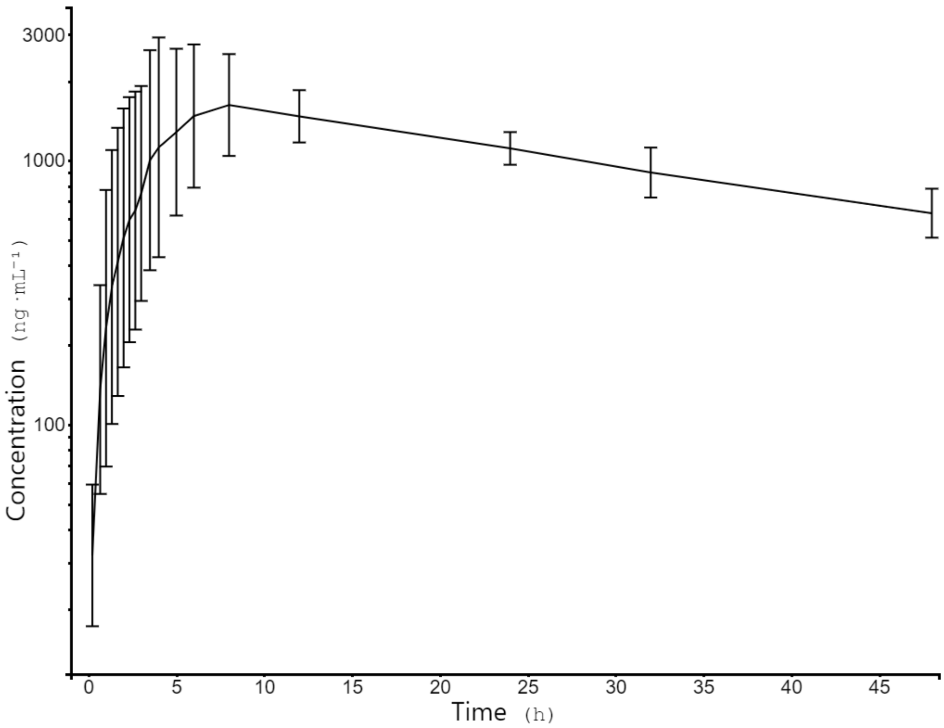

Figure 2. Semi-logarithmic plot displaying the canagliflozin concentration time-courses following oral administration of 1.8 mg/kg canagliflozin to eight Icelandic horses. The plot shows the geometric mean ± standard deviation. Figure reproduced from Michanek et al (2024).

CFZ treatment significantly lowered both total glucose and insulin exposure during a GGI. This was measured by the area under the curve for glucose (AUC_{GLU}, p=0.001) and the area under the curve for insulin (AUC_{INS}, p=0.04). Reductions were also observed in the incremental area under the curve for glucose ($iAUC_{GLU}$, p=0.006) and insulin ($iAUC_{INS}$, p=0.02), as well as peak glucose concentrations (Max_{GLU}, p=0.004) with CFZ treatment. However, no statistically significant impact was observed on peak insulin concentrations (MAX_{ins}) or parameters measuring beta cell responsiveness. The concentration-time course of insulin and glucose during the GGI and 40 minutes post infusion is displayed in figure 3.

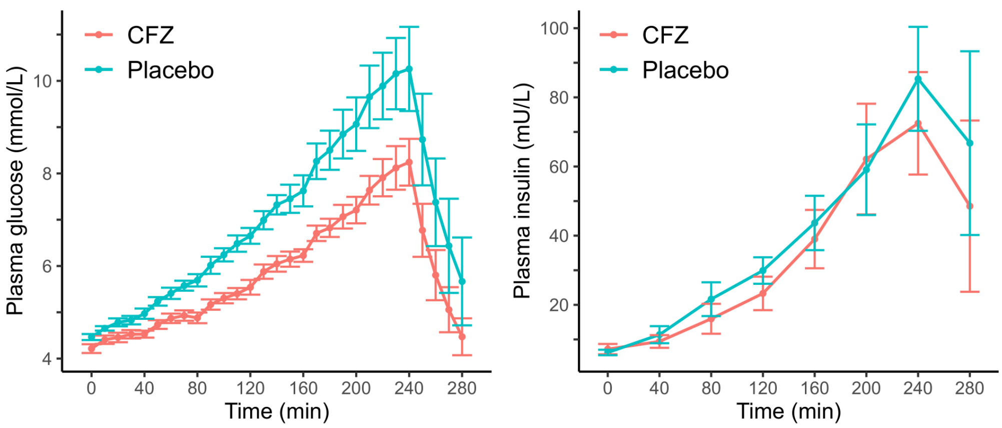

Figure 3. Time-course profiles of mean plasma glucose (left panel, in mmol/L) and plasma insulin concentrations (right panel, in mU/L) for both placebo and canagliflozin (CFZ) treatments during, and 40 min post a graded glucose infusion in seven Icelandic horses. Figure reproduced from Michanek et al (2024).

While some biochemical parameters showed statistically significant differences, the changes were generally minor and remained within established laboratory reference ranges. A notable, but not statistically significant, increase in glutamate dehydrogenase (GLDH) (median 402%) was observed following CFZ administration. A mild elevation in triglycerides was also noted.

Study II - Canagliflozin: Pharmacokinetics, Tolerability and Glucose/Insulin Effects of Supratherapeutic Doses in Healthy Horses.

All eight healthy Standardbred mares completed the study without observed clinical signs of adverse effects.

A non-compartmental analysis revealed that for 1.8 mg/kg CFZ, median C_{max} was 2623 ng/mL, T_{max} was 2.2 hours, and $t_{1/2Z}$ was 21.8 hours. For 3.6 mg/kg CFZ, median C_{max} was 4975 ng/mL, T_{max} was 2.8 hours, and $t_{1/2Z}$ was 23.0 hours. No significant differences were observed in pharmacokinetic parameters between the two dose levels, with exposure parameters (AUC_{0-72h}, AUC_{0-inf} and C_{max}) being dose-adjusted (all comparisons: $p>0.17$). The concentration-time course of plasma CFZ is displayed in Figure 4.

Insulin and glucose responses, as measured by AUC_{INS} and AUC_{GLU}, to a GGI were significantly reduced compared to placebo ($p<0.001$) for both CFZ doses, but similar between the two CFZ doses. Max_{GLU} were significantly lowered by both CFZ doses compared to placebo ($p<0.05$) but there was no significant difference in Max_{INS} between treatments ($p>0.63$). The concentration time course for plasma glucose and insulin in all treatments in response to a GGI is depicted in figure 5.

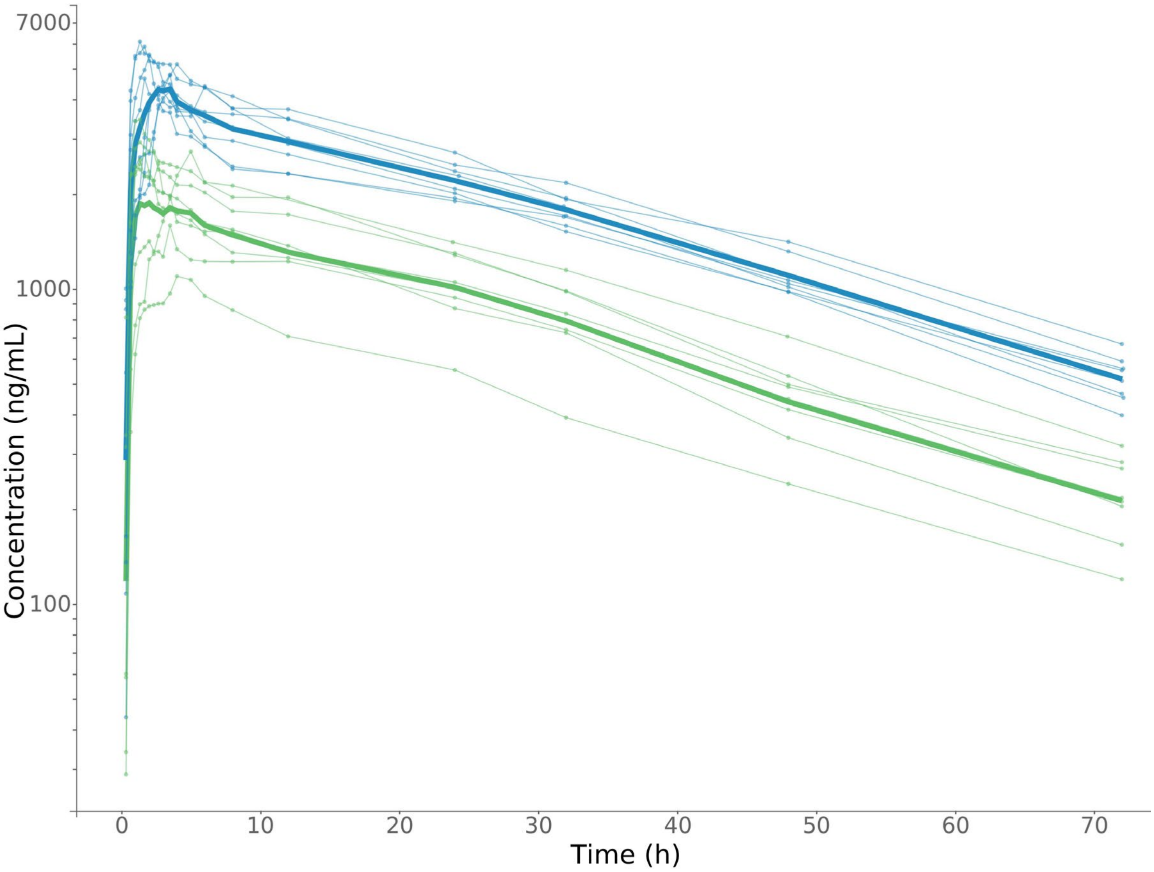

Figure 4. Concentration-time profile of canagliflozin in eight Standardbred horses. Green lines represent the 1.8 mg/kg dose, while blue lines represent the 3.6 mg/kg dose. Thin lines depict individual horse data, and thick lines indicate the geometric mean concentrations for each CFZ treatment. Points represent observed data points.

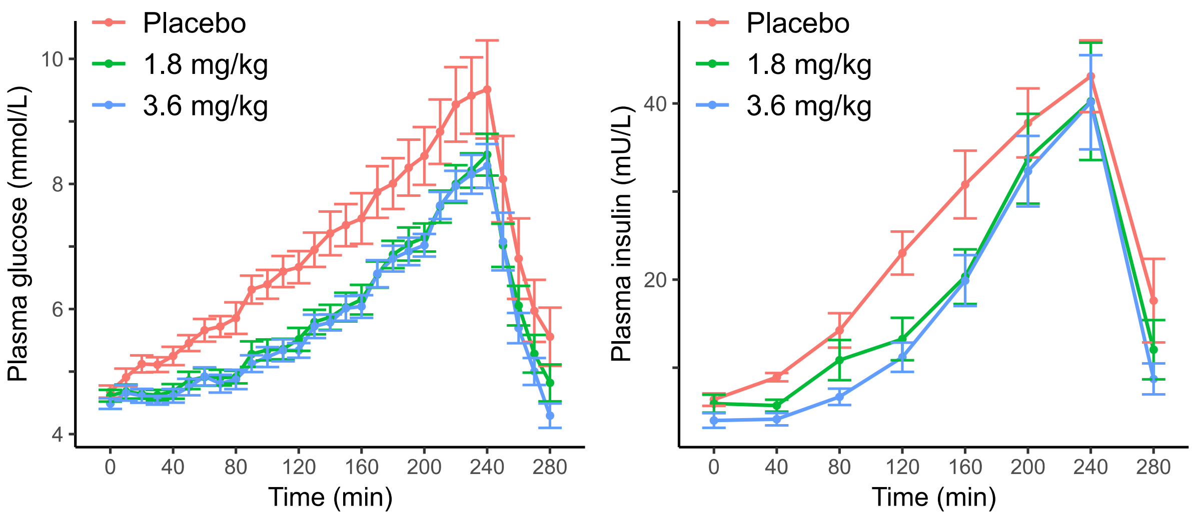

Figure 5. Mean concentration-time profiles for plasma glucose (left) and plasma insulin (right) during and after a graded glucose infusion in eight Standardbred horses, starting at time 0 and completed at 240 minutes. Data for an additional 40 minutes post-infusion are also shown. The red line represents the placebo treatment, the green line represents the 1.8 mg/kg canagliflozin dose, and the blue line represents the 3.6 mg/kg dose. Error bars represent ± SEM.

Urinary glucose concentrations markedly increased after CFZ administration and remained highly elevated over 72 hours, irrespective of dose. No significant differences in urinary glucose concentrations were observed between the 1.8 mg/kg and 3.6 mg/kg doses at 24, 48, and 72 hours . For CFZ-treated horses, mean urinary glucose concentrations ranged from 277 to 347 mmol/L at 24, 48, and 72 hours post-administration. The concentration-time course for urinary glucose concentration is shown in figure 6.

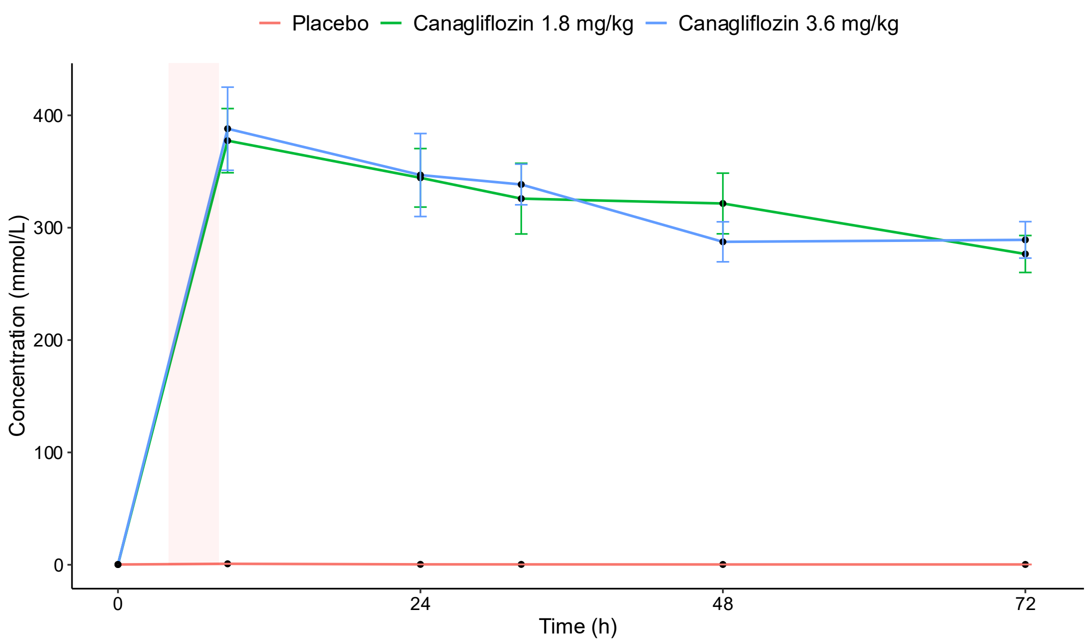

Figure 6. Mean urinary glucose concentrations over time in eight Standardbred horses. Treatment was administered at time 0. The red line represents the placebo treatment, the green line represents the 1.8 mg/kg canagliflozin dose, and the blue line represents the 3.6 mg/kg dose. Error bars represent ± SEM. The red shaded area represents the time of the graded glucose infusion.

Hematological variables (analyzed only pre- and post CFZ 3.6 mg/kg) remained unchanged. Serum glutamate dehydrogenase (GLDH) levels significantly increased with the 3.6 mg/kg CFZ dose compared to placebo ($p<0.05$). A slight, statistically significant increase in triglycerides was observed with the 3.6 mg/kg CFZ treatment ($p<0.01$ vs. placebo, $p<0.05$ vs. 1.8 mg/kg CFZ).

Study III – Canagliflozin Pharmacokinetics and Urinary Glucose Dynamics in Equine Populations: A Population

Our current progress, as depicted in Figures 2 and 4, focuses on the PK analysis. Figures 6 and 7, on the other hand, showcase the PD aspects of the PK-PD model. Upon completion of all sample analyses, we plan to develop a robust population PK model. This model will subsequently be combined with our PD data to construct a simplified PK-PD model, a crucial step in determining the therapeutic drug concentration.

Conclusions

This project aimed to investigate the PK and PD properties of CFZ in horses, a SGLT2-i with growing clinical use for equine ID. Our studies provide the first comprehensive, peer-reviewed PK data for canagliflozin in horses, addressing a significant knowledge gap.

The PK analysis conducted to date has yielded favorable results, demonstrating the achievement of high plasma concentrations. We have observed no indications of non-linearity in the PK parameters, which enhances the predictability of plasma concentrations and mitigates the risk of toxicity events stemming from saturable kinetics. A notably long half-life, with a median range of 21.8 to 28.5 hours was observed in the aforementioned studies. This long half-life strongly supports the suitability of once-daily dosing.

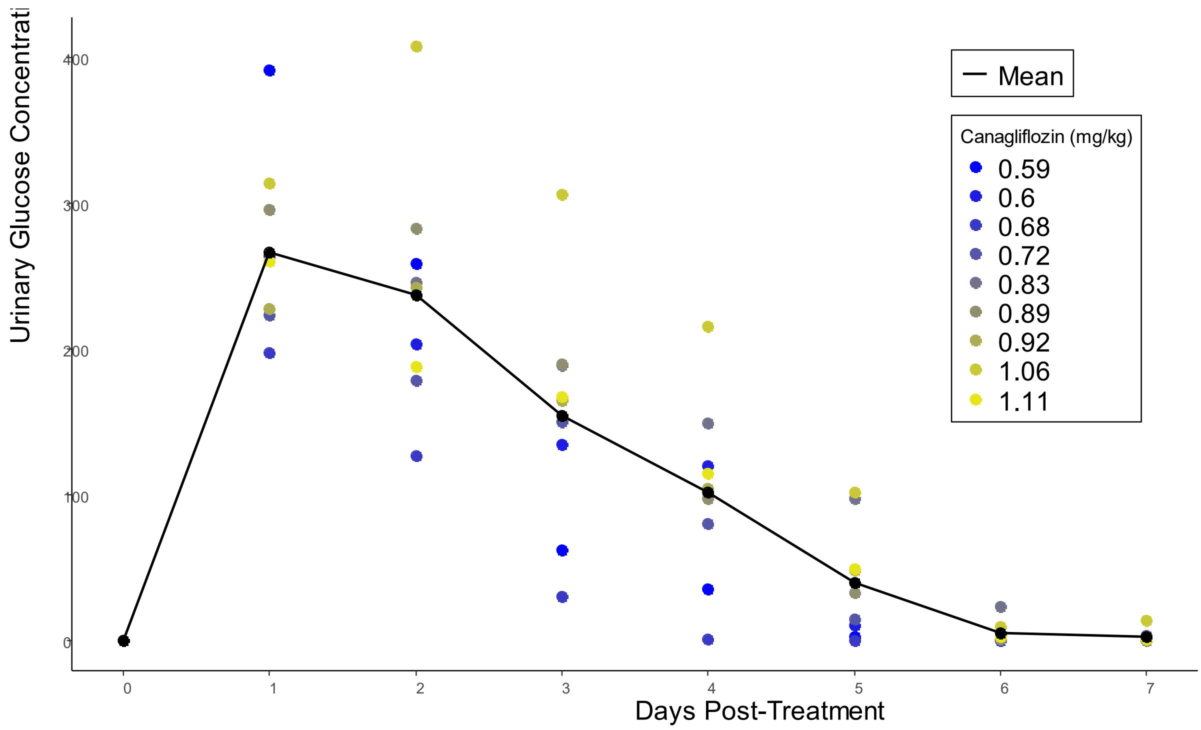

Figure 7. Time course of urinary glucose concentration in horses administered a single canagliflozin dose. individual data points represent urinary glucose concentrations (mmol/L) from 9 horses given a single oral dose of CFZ at varying concentrations (0.59 to 1.11 mg/kg). The solid black line indicates the mean urinary glucose concentration across the study population over seven days post-treatment.

Our findings indicate that CFZ is generally well-tolerated, even at supratherapeutic doses. Furthermore, it has demonstrated high efficacy in reducing both glucose and insulin responses during a GGI. CFZ consistently and markedly increased urinary glucose excretion, irrespective of the administered dose within the tested range, suggesting a robust glucose-lowering action via glucosuria.

While most observed changes in biochemical parameters were minor and remained within established laboratory reference ranges, there are indications of increased liver enzyme GLDH levels, particularly at supratherapeutic doses. An elevation in triglycerides was also noted after a few days of treatment, suggesting these parameters should be monitored during CFZ administration.

A robust population PK model is under development using over 1100 samples, which will allow for a deeper understanding of inter-individual variability and optimization of dosing regimens. A simple PK-PD model integrating PK with urinary glucose data will establish therapeutic concentration thresholds.

Relevance for the practical horse sector incl. recommendations

This project directly addresses a critical need in equine veterinary medicine: the effective and safe management of ID and hyperinsulinemia-associated laminitis, a leading cause of pain, morbidity, and euthanasia in horses. Our findings validate the strong glucose-lowering effects of canagliflozin, confirming its therapeutic potential. By providing foundational pharmacokinetic data, this research moves beyond anecdotal observations and enables evidence-based dosing strategies. The development of a population PK-PD model will be important in defining optimal therapeutic concentrations, allowing veterinarians to more precisely manage CFZ dosages to maximize efficacy while minimizing potential side effects. This contributes significantly to improving the welfare and longevity of horses affected by these challenging metabolic conditions.

Future research should focus on several key areas to further enhance our understanding and application of CFZ in horses. Controlled clinical trials are needed to specifically assess CFZ's long-term impact on laminitis recurrence and quality of life within a larger cohort of ID horses. Additionally, comparative studies with other SGLT2-i drugs, such as dapagliflozin and ertugliflozin, are warranted to evaluate their respective PK, PD, and long-term efficacy, which could refine treatment choices.

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Sundra, T., Knowles, E., Rendle, D., Kelty, E., Lester, G., Rossi, G., 2025. Short-term clinical and biochemical responses following treatment with dapagliflozin or ertugliflozin in horses with hyperinsulinemia: A retrospective case series. Domest Anim Endocrinol 90, 106894.

Part 3: Result dissemination

State all result dissemination from the financed project into the appropriate section, including information as indicated in each section. Additional rows can be added to the table.

Scientific publications, *published*	*Michanek, P., Bröjer, J., Lilliehöök, I., Fjordbakk, C. T., Löwgren, M., Hedeland, M., Bergquist, J., & Ekstrand, C. (2025). Pharmacokinetics and Alterations in Glucose and Insulin Levels After a Single Dose of Canagliflozin in Healthy Icelandic Horses. Journal of veterinary pharmacology and therapeutics, 48 Suppl 1(Suppl 1), 41–49. https://doi.org/10.1111/jvp.13476*
	Michanek P, Bröjer J, Lilliehöök I, Fjordbakk C, Erkas M, Löwgren M, Hedeland M, Bergquist J, Ekstrand C. 2025. Pharmacokinetics, tolerability, and glucose/insulin effects of supratherapeutic doses in healthy horses. The Veterinary Journal. 313 (2025) 106412 doi: 10.1016/j.tvjl.2025.106412.
Scientific publications, *submitted*	
Scientific publications, *manuscript*	*Author(s), title*
Conference publications/ presentations	*Michanek, P, Löwgren, M., Ekstrand C. (2023), O103 | The effect of canagliflozin on blood glucose and insulin in healthy standardbred horses, 15th International Congress of the European Association for Veterinary Pharmacology and Toxicology held Bruges, Belgium, July 2–5, 2023*
	Abstract has been submitted to the annual congress of European college of equine internal medicine and is pending confirmation. *Michanek, P., Bröjer J. and Ekstrand C. (2025) | Canagliflozin: Dose-response of urinary glucose excretion in healthy horses*
Other publications, *media etc.*	*Our research has also been featured in public-facing platforms, including an article on the SLU homepage (https://www.slu.se/canagliflozin) and a popular science article in Veterinärmagazinet (https://www.veterinarmagazinet.se/2024/09/hopp-om-effektiv-behandling-av-ems-hos-hast/).*
	We're currently preparing an article for the Swedish Veterinary Journal (Svensk Veterinärtidning) on SGLT2 inhibitors in horses.

Oral communication, *to horse sector, students etc.*	*The effect of canagliflozin on blood glucose and insulin in healthy Standardbred horses, Oral presentation at internal SLU seminar series in equine research, Sweden, Uppsala, 10th October 2023*
	Pharmacokinetics and Alterations in Glucose and Insulin Levels After a Single Dose of Canagliflozin in Healthy Icelandic Horses, oral presentation 15 minutes for Department of Animal Biosciences, Swedish University of Agricultural Sciences.
Student theses	*Author/Student, co-authors/supervisors, year, title, type of thesis (doi/link if applicable)*
Other	