Pharmacokinetics of orally administered calcium dobesilate in Warmblood horses

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Pharmakokinetik von oral verabreichtem Calciumdobesilat bei Warmblutpferden

Calciumdobesilat wird seit kurzem zur Behandlung von Lahmheit bei Pferden eingesetzt, da es mikrovaskuläre Prozesse fördert und den intraossären Druck senkt. Lahmheiten, die durch Störungen des Knochenstoffwechsels und erhöhten intraossären Druck verursacht werden, wie z. B. Strahlbeinsyndrom, zystenartige Knochenläsionen und Hufbeinödeme, werden üblicherweise mit Stallruhe, Antiphlogistika und chirurgischen Eingriffen behandelt. Calciumdobesilat hat das Potenzial, die Pathophysiologie dieser Erkrankungen zu beeinflussen und so die Heilung zu verbessern. Ziel der Studie war es zu bestimmen, inwieweit oral verabreichtes Calciumdobesilat, respektive dessen Wirkstoff Calcium 2,5-dihydroxybenzene sulfonate (2,5HBSA), im Magen-Darm-Trakt des Pferdes resorbiert wird und nachweisbare Plasmakonzentrationen erzeugt.

Acht gesunde erwachsene Schweizer Warmblüter wurden für diese prospektive in-vivo-Studie untersucht. Calciumdobesilat (3 mg/kg, po, q12h) wurde in Mash über sieben Tage verabreicht. Nach der letzten Calciumdobesilat Verabreichung wurden Blutproben aus der Vena jugularis entnommen. Alle Pferde wurden täglich untersucht und vor und nach der Studie wurden hämatologische sowie plasmabiochemische Parameter bestimmt. Die Plasmakonzentrationen von 2,5HBSA wurden mittels Flüssigkeitschromatographie analysiert. Die pharmakokinetischen Parameter wurden mittels nichtkompartimenteller Analyse bestimmt.

2,5HBSA wurde nach oraler Verabreichung in Plasmaproben nachgewiesen und lag zwischen 2300 ng/ml und 3600 ng/ml mit einem Mittelwert von 2900 ng/ml. Die Ergebnisse der hämatologischen und plasmabiochemischen Untersuchungen lagen stets innerhalb der Referenzwerte, und es traten keine Nebenwirkungen auf.

2,5HBSA wurde in den Plasmaproben erst nach siebentägiger Verabreichung von Calciumdobesilat gemessen. Oral verabreichtes Calciumdobesilat wurde vom Magen-Darm-

Abstract

Calcium dobesilate has recently been used for treating lameness in horses because it enhances microvascular processes and reduces intraosseous pressure. Lameness caused by disorders in bone metabolism and increased intraosseous pressure, such as navicular disease, osseous cyst-like lesions and pedal bone oedema, are commonly treated with rest, anti-inflammatory agents and surgery. Calcium dobesilate has the potential to influence the pathophysiology of these diseases, thereby improving healing. To determine whether calcium dobesilate and its acting agent calcium 2,5-dihydroxybenzene sulfonate (2,5HBSA) is absorbed by the equine gastrointestinal system to generate detectable plasma concentrations.

The study was designed as a prospective in-vivo study. Eight healthy adult Swiss Warmblood horses were used in the study. Calcium dobesilate (3 mg/kg, PO, q12h) was administered orally in mash for seven days. Blood samples were collected from a jugular vein after the last dose of calcium dobesilate. All horses underwent daily physical examination and haematological and blood chemical analyses before and after the study. Liquid chromatography was used to determine plasma concentrations of 2,5HBSA. Noncompartmental analysis was used to estimate the pharmacokinetic parameters.

2,5HBSA was detected in plasma samples after oral administration and ranged from 2300 ng/ml to 3600 ng/ml with a mean of 2900 ng/ml. The results of haematological and plasma biochemical testing were within the reference limits at all times, and no adverse effects occurred.

Only plasma samples were analysed and calcium dobesilate was only measured after the treatment period of seven days. Calcium dobesilate was absorbed by the equine gastrointestinal system and reached detectable plasma concentrations.

Keywords: horse, calcium dobesilate, pharmacokinetics, bone marrow oedema, osseous cyst-like lesions

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Trakt des Pferdes resorbiert und erreichte nachweisbare 2,5HBSA Plasmakonzentrationen.

Schlüsselwörter: Pferd, Calciumdobesilat, Pharmakokinetik, Knochenmarködem, zystenartige Knochenläsionen

Introduction

Calcium dobesilat (CD) is a vasoactive and angio protective agent, well known in human medicine. It is a calcium salt, with dissociates into Calcium 2,5-dihydroxybenzene sulfonate (2,5HBSA, Figure 1) plus calcium ions. CD is blocking the release of histamine and bradykinin, both of which can have negative influences on capillary permeability. Following this, CD reduces capillary permeability.[19] In addition, it leads to increased retention of albumin in blood vessels, which as well reduces fluid leakage into the surrounding tissues.[19] Both of these effects have an angio protective effect on vessels as they prevent fluid leakage. Calcium dobesilate decreases intraocular pressure and lowers blood hyperviscosity, which makes it an effective treatment for the early stages of diabetic retinopathy and diabetic glaucoma in humans.[20] It also has beneficial effects on diseases affecting bony structures and joints by promoting microvascularisation. Oral administration of CD rapidly reduced pain and bone marrow oedema (BME) in the hip joints of human patients suspected of having early-stage femoral head osteonecrosis (ONFH).[3] Equine navicular disease (ND) is phenotypically similar to femoral head osteonecrosis and is thought to be associated with bone marrow oedema in the early stages.[6,4] In horses, ND, osseous cyst-like lesions (OCLL) and BME result in lameness because of increased intraosseous pressure (IOP).[11,13,7] Bone marrow oedema in general and to some extent ND are treated surgically via core decompression.[10,5] Although other surgical methods are described, the two most common treatments for OCLL are arthroscopic debridement and screw insertion.[5]

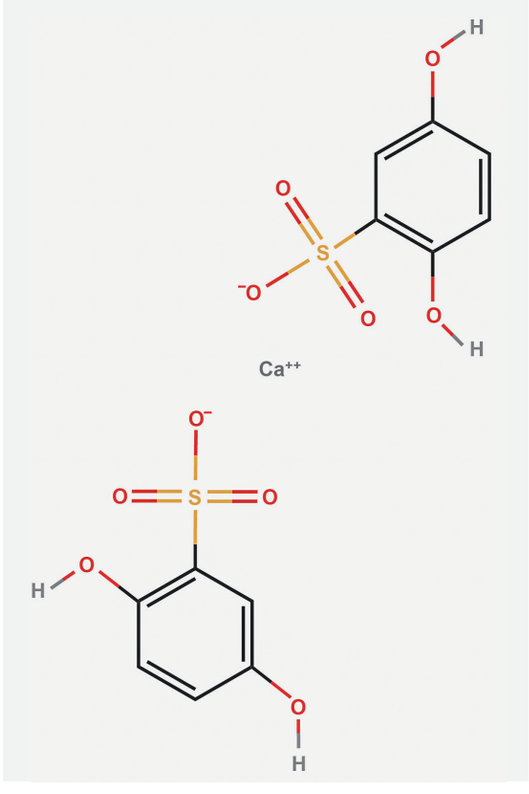

Figure 1: Chemical formula of calcium dobesilate (calcium 2,5-dihydroxybenzene sulfonate). On the calcium dobesilate structure the colours are used to emphasis the different heteroatoms. In this figure the red colour indicates the oxygens, the yellow indicates sulfur. Carbons and hydrogens are the default black.

The vasoactive properties of calcium dobesilate are likely to reduce intraosseous pressure making it a potential conservative treatment option for horses with lameness caused by microvascular lesions of the skeleton.[9,14,5] Calcium dobesilate appears to be a safe drug with minimal side effects based on its long-term use in human medicine and the results of several studies in rabbits and dogs.[9,14,15] The authors found that long-term treatment of horses with CD had no adverse effects (unpublished data). To the authors' knowledge, the pharmacokinetic profile of 2,5HBSA in horses has been described in only one study, which focussed on a pharmacokinetic model for 2,5-HBSA in thoroughbred horses.[12] Thus, the aim of the present study was to generate a pharmacokinetic profile of orally-administered CD in healthy Warmblood horses and to gather information about its practicality in daily use. We hypothesised that 3 mg/kg bodyweight of CD administered orally, b.i.d. is absorbed by the equine gastrointestinal tract and generates detectable and stable 2,5HBSA plasma concentrations. We also hypothesised that the administration of CD to Warmblood horses has no side effects.

Materials and Methods

Animals

Eight, randomly-selected, adult, Swiss Warmblood horses belonging to the Swiss Federal Department of Defence, Civil Protection and Sport, were used in this study. A con-

venience sample of eight horses is similar to the number of animals used in comparable pharmacokinetic studies.[1,8,16] The study design and number of horses were proved and accepted by the Federal Food Safety and Veterinary Office (*BE70/2021)*. The study population consisted of two mares and six geldings, which weighed 510 to 590 kg and were 3 years of age (Table 1). The horses were healthy and free of lameness based on the results of physical examination and haematological and serum blood chemical analyses, which were performed immediately before the start of the study. None of the horses received non-steroidal antiinflammatory drugs or other medications in the 2 weeks before the start of the study or during the study. Horses were housed individually and had daily access to paddocks except when blood samples were collected via a jugular vein catheter. They were fed hay and water ad libitum and a concentrated feed twice daily.

Table 1: Overview of all eight horses used in the study. Presented are gender, age and weight of the horses.

Number	Sex	Age in Years	Weigh in KG
1	male	3	590
2	female	3	570
3	male	3	510
4	male	3	540
5	male	3	570
6	female	3	510
7	male	3	590
8	male	3	510

Administration of CD and health monitoring

A dose of 3 mg/kg bodyweight CD (Compounded formulation of 18 % Calcium dobesilat monohydrate, produced by Pharmacy Roter Ochse, Switzerland) was added to a small portion of a mash and fed under observation q12h (8am and 8pm) for 7 days. During this time, the horses underwent a daily physical examination. Haematological and blood chemical analyses were carried out before and after CD administration. The haematocrit (%), total leucocyte count (*10E3/ul) and concentrations of creatinine (umol/l) and urea (mmol/l) were determined.

Blood sampling and processing

An intravenous catheter was placed in one of the jugular veins after aseptic preparation of the skin. Blood samples of 30 ml at each point were taken 0,5, 1, 2, 4, 8, 12, 24, 36, 48, 72 and 96 hours after the last oral administration of CD. The catheter was flushed with 20 ml heparinised saline after each blood sample collection and removed 36 h after placement. The remaining blood samples were collected from the contralateral jugular vein using a vacutainer system. The blood samples were placed or collected into K3-EDTA tubes and immediately centrifuged at 1500G for 10 min. In addition, blood was collected into one K3-EDTA tube and one serum clot activator tube per horse and sent directly to the veterinary laboratory of the Vetsuisse Faculty, University of Zurich, Zurich, Switzerland for blood analysis (Meaning the multivalent Laboratory, performing hematology, cytology, clinical chemistry, endocrinological and urine analyses, serological and molecular biological analyses). Approximately 15 ml of plasma was removed and immediately frozen at -20°C until being transported directly after the last sample taking. All samples were kept on dry ice and transferred to the laboratory via courier for further analytics.

Determination of plasma concentration of calcium dobesilate

Instruments and equipment

High-purity water needed for the study was produced by a laboratory water purification system (Suez Select Analyst). Analyses were carried out using a Shimadzu LC30 UHPLC system equipped with a Shimadzu SPD-M20A diode array detector (Shimadzu Schweiz GmbH, Muttenz, Switzerland) and a Phenomenex® Kinetex® C_{18} EVO chromatographic column (50 x 4,6 mm; 2,6 µm) (Phenomenex Helvetia GmbH, Basel Switzerland). Eluent 'A' was 50 mM ammonium-acetate solution in water (pH adjusted to 5 with acetic acid). Eluent 'B' was 100 % acetonitrile.

Sample preparation

Sample preparation was carried out using a slightly modified method described by Róna & Ary.[27] A total of 200 µL of the internal standard (100 µg/ml 2,4-dihydroxybenzoic acid [24DHBA] from Sigma-Aldrich (part of Merck, Budapest, Hungary) was added to 2 mL of plasma followed by 2 mL of a mixture of 80 % 0,2 M KH_2PO_4 (pH=2,5) and 20 % tetrabutylammonium hydroxide (TBAH; both from Avantor/VWR International, Hungary). The content of the tube was mixed with a vortex mixer for 15 sec, and then 8 mL of dichloromethane was added. It was shaken at 250 rpm for 10 minutes. The two-phase mixture was placed in a refrigerator at -20 °C for 30 minutes to facilitate separation of the phases. It was then centrifuged at 1500 rpm and 4 °C for 10 minutes. Six mL of the supernatant was pipetted into a glass tube and evaporated to dryness under N_2 flow at 40 °C. The sample was reconstituted in 500 µL of 90 % NH_3/H_2O (4,7 %) and 10 % CAN (both from Avantor/VWR International, Hungary). Samples were mixed with a vortex mixer, filtered through a 0,22 µm pore-size syringe filter and injected into the UHPLC system.

Matrix-matched calibration and quality control (QC) samples were prepared using the blood plasma of untreated horses (the same horses used in the study) and adding the calculated amount of CD) and 2,4-dihydroxybenzoic acid (24DHBA) solutions. Calibration and QC samples then

underwent the same sample preparation procedure as described above.

Instrumental analysis

Isocratic elution was used for the chromatographic separation at 20 % 'B' concentration. The flow rate was 0,5 mL/min, the column temperature was 30 °C and the temperature of the autosampler was 12 °C. A total of 15 µL of the sample was injected into the chromatograph. All the samples (including the calibrators) were injected 3 times. Detection of 2,5HBSA and 24DHBA occurred at 301 nm and 254 nm, respectively. An internal biochemical standard method was used for the quantitation of 2,5HBSA. The calibration curve consisted of 11 points in the concentration range of 0,05–5 µg/mL. Linear regression was carried out by the Shimadzu LabSolutions® software with $1/C^2$ weighting. Post-processing of the raw data was carried out using Microsoft Excel software.

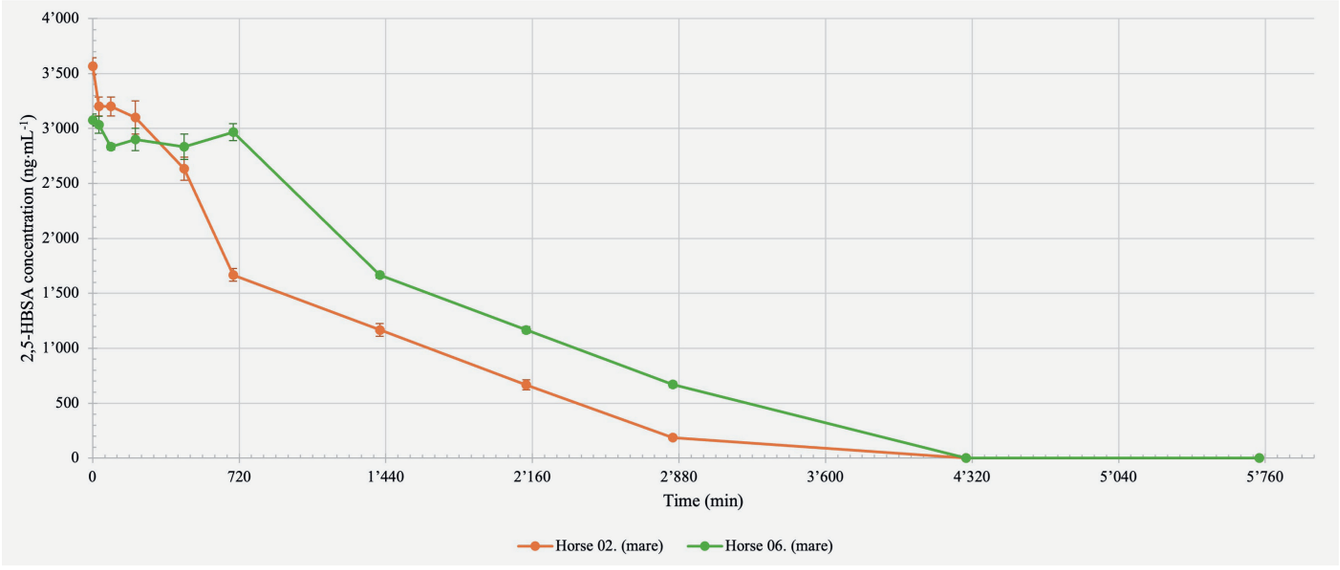

Figure 2: Plasma concentration of calcium 2,5-dihydroxybenzene sulfonate (2,5HBSA, ng/mL) female horses over time in hours. Time 0 marks the first measurement after the last dose of calcium dobesilat (CD). Horse 2 is marked in orange horse 6 in green.

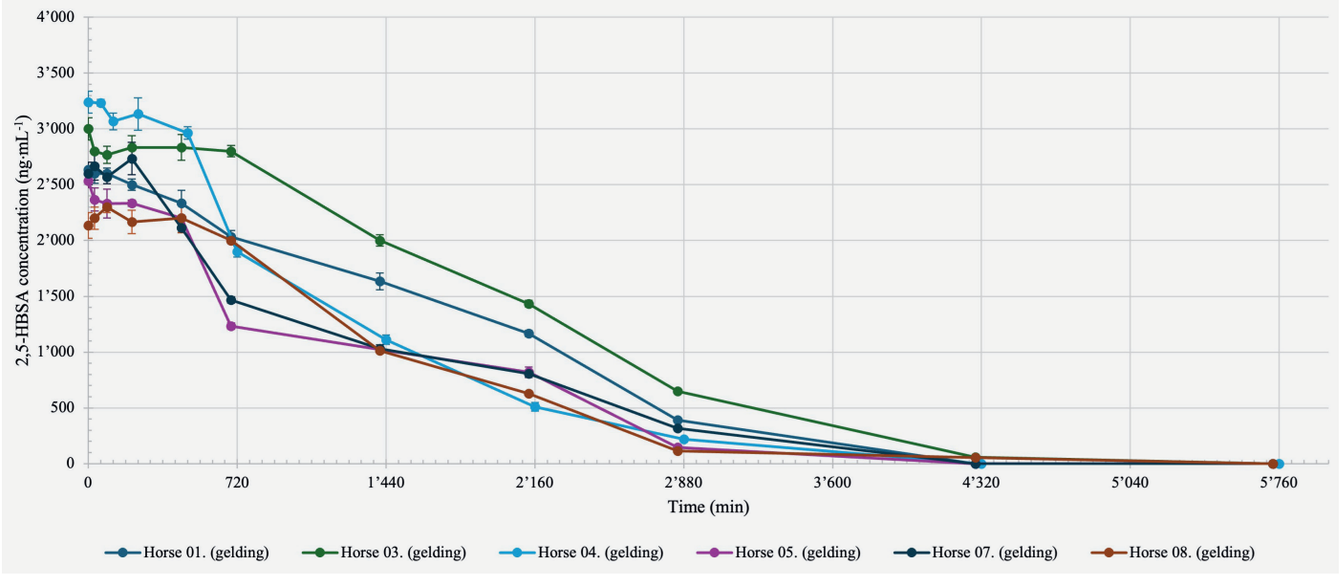

Figure 3: Plasma concentration of calcium 2,5-dihydroxybenzene sulfonate (2,5HBSA, ng/mL) for male horses over time in hours.
Horse 1 is marked in dark blue, horse 3 is marked in green, horse 4 is marked in light blue, horse 5 is marked in violet, horse 7 is marked in dark green and horse 8 in brown.

Data analysis

Noncompartmental analysis was used to estimate the pharmacokinetic parameters. Measurement of the 2,5HBSA concentration started 30 min after the administration of the last dose in the dosing regimen and was performed with all blood samples. The maximum concentration (C_{max}), last nonzero concentration (C_{LST}), time of last nonzero concentration (T_{LST}), half-life ($T_{1/2}$), area under the curve (AUC), volume of distribution (Vd/F) and clearance (Cl/F) were estimated using the NonCompart package of the R statistical environment (R Foundation for Statistical Computing).[1] The time of the last administration of the drug was taken as time 0. The parameters related to drug absorption were not considered in the multiple dosing regimen.

First-order compartmental analysis was performed to calculate the elimination rate and clearance based on fitting individual nonlinear elimination curves. Common curves involving measurements from all animals were also fitted. Package 'nlme' of the R statistical environment was used for curve fitting and parameter estimation. The lower and upper confidence limits (95 %) were calculated using Microsoft Excel version 16.72.

Results

Calcium dobesilate pharmacokinetics

Calcium dobesilate was absorbed and 2,5HBSA detected in all eight horses. The C_{max} ranged from 2300 ng /ml (minimum) to 3600 ng/ml (maximum) with a mean of 2900 ng/ml. The plasma concentration of 2,5HBSA over time is shown in Figures 2 and 3. Female and male horses had similar patterns of 2,5HBSA absorbance (Figure 2 and 3). The individual values and summary measures for $C_{max,}$ T_{max}, $T_{1/2,}$ and AUC for each horse are displayed in Table 2. The apparent clearance ranged between 0,23 – 0,49 L/min.

The time of C_{max} was reached after an average of 1,2 hours (minimum 0,5 hours, maximum 4,0 hours). The $T_{1/2}$ varied from 7,7 to 20 hours with a mean of 14 hours. The AUC (as AUCALL) ranged from 55000 h*ng/ml (minimum) to 103000 h*ng/ml (maximum), with a mean of 72125 h*ng/ml (95 % CI: 60526.9;83723.1h*ng/ml). The values of $C_{max,}$ T_{max}, $T_{1/2,}$ Cl and AUC for each horse are listed in Table 2. The time of C_{max} was seen 30 minutes after ingestion of the drug in six horses, 240 minutes in one and 120 minutes in one other horse. After 72 hours, the plasma concentration of 2,5HBSA reached non-quantifiable values in three horses and was no longer detectable in another three horses. The other two horses showed detectable plasma concentrations 72 hours after the last CD administration. 94 hours after administration of CD, the plasma concentrations were within the non-quantifiable range in four horses and not detectable in four others.

Figure 4 displays the elimination curves based on the nonlinear mixed model including data of all horses. The model estimated an elimination constant of 0,0005 (95 % CI:0.0004;0.0007) and a clearance of 0,316 L/min (95 %CI: 0,24; 0,41 L/min).

Uptake of calcium dobesilate and side effects

All horses ingested the drug in the small portion of mash without hesitation. No undesirable side effects occurred in the 7 days of oral administration of CD or in the following 7 days of blood sampling and observation. The results of haematological (haematocrit and total leucocyte count) and plasma blood chemical (kidney values) analyses were with the reference ranges throughout the study period and are shown in Table 3.

Table 2: Noncompartmental pharmacokinetic parameters of 3 mg/kg bodyweight of calcium dobesilate given orally. Listed are Cmax in ng/mL, Tmax in h, T1/2 in h, and AUC to last nonzero concentration in h*ng/mL. The last line shows further the mean value of the listed parameters.

Horse	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	AUC to last nonzero concentration (h*ng/mL)
1	2600	0,5	20	77000
2	3600	0,5	12	65000
3	3000	0,5	8	103000
4	3200	1	10	67000
5	2500	0,5	14	55000
6	3060	0,5	17	90000
7	2700	4	16	60000
8	2300	2	12	60000
Mean (95 % CI)	2870	1,2	13,6 (10,9;16,3)	72125

Discussion

2,5HBSA was present in the plasma of all Warmblood horses, and therefore, our first hypothesis that 3 mg/kg CD, administered orally, b.i.d., is absorbed from the gastrointestinal tract and generates detectable plasma concentrations was accepted. Our results were in agreement with those of another study, in which the same dosage was used.[12] To the authors' knowledge, the study by Paine et al. (2023) is the only other report concerning the pharmacokinetics of 2,5BSA in horses. While Paine et al. (2023) were focusing on mainly pharmacokinetics of CD in thoroughbred racehorses, the focus of this study was on the one hand the availability of this active ingredient in Warmblood horses in daily training and on the other hand the assessment of possible side effects. The C_{max} varied from 2300 ng/mL to 3600ng/mL and was seen 30 minutes to 4 h after the last dose of the drug. The plasma concentration of 2,5HBSA over time was similar in all horses and non-quantifiable levels occurred 72 or 96 h after the last dose. The mean $T_{1/2}$ minutes occurred approximately 14 h after the last administration and serves to emphasise the need for twice daily dosing to maintain constant plasma concentrations.

Horses 7 and 8 (both geldings) had a markedly higher T_{max} compared with the other horses. Possible reasons for this include individual variations in absorption rate or inconsistencies in measurement procedures.

In Paine's study, 2 horses were used to show an unstability of the results when the samples are stored at -20°C. The concentrations decreased significantly; in the first four weeks in one horse by approx. 10 % and in the other horse by approx. 20 %. After 16 weeks, only approx. 15 % of the original concentration was still detectable. However, if the samples were stored at -80°C, there was only a very slight decrease. Due to infrastructural limitations, it was not possible to store our samples at -80°C. The samples in this study were stored at -20°C, so it must be assumed that the measured concentrations were lower than the initial concentrations. Since the blood samples were analysed within 2 weeks, it can be assumed on the basis of the studies by Paine et al that the reduction is below to 15 – 20 %. Until the work of Paine et al, pharamcokinetic analyses were always carried out in blood samples stored at -20°.[14]

In powder form, CD was easy to add to the feed and was readily ingested by all the horses, which was in agreement with the findings of a study by Paine et al.[13] This practical factor is important considering that CD is usually administered as a long-term treatment by horse owners and caretakers.

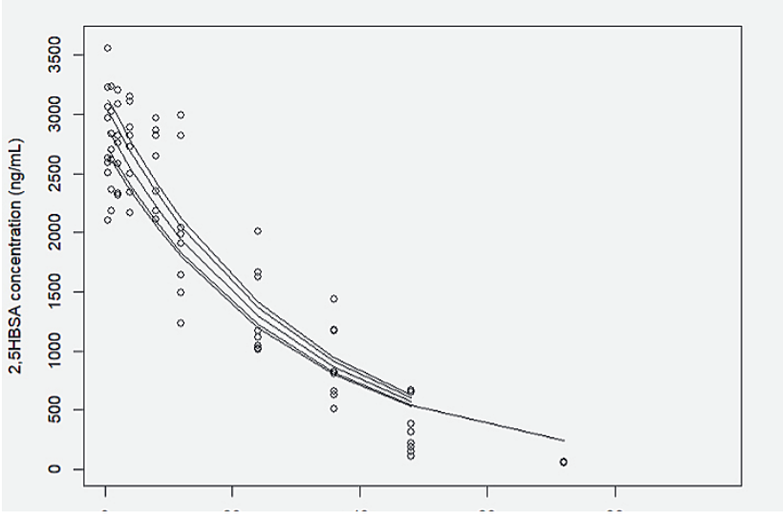

Figure 4: Model estimates of first-order compartmental analysis (nonlinear mixed model). Calcium dobesilat was dosed at 3 mg/kg bodyweight. The five starting points of the curves represent the five different absolute starting doses applied to the horses, according to their individual bodyweight. Calcium 2,5-dihydroxybenzene sulfonate concentration over time in hours is provided in this graph.

Table 3: The results of haematological and biochemical analyses carried out before and after administration of calcium dobesilate.
Listed are haematocrit in %, leukocytes in *10E3/ul, creatinine in umol/l, urea in mmol/L, GGT in U/L, GOT in U/L. Parameters are listed as pre/post calcium dobesilate administration. *For horse No. 2, the total leucocyte count was not available due to a technical problem.

Horse	Haematocrit in %	Leukocytes *10E3/ul	Creatinine in umol/l	Urea in mmol/l	GGT in U/l	GOT in U/l
1	34/31	7/7,7	100/106	3,4/2,3	11/	447/456
2	36/36	*	116/109	3,6/3,8	17/15	369/325
3	29/30	8,1/8,9	106/103	3,5/3,1	22/18	297/285
4	36/34	7,5/8,1	110/110	4,3/3,5	/13	/329
5	35/33	5,9/6,1	110/108	3,2/2,1	18/17	487/486
6	30/31	6,9/7,6	121/109	3,9/4,6	19/16	462/373
7	33/33	9,0/7,7	114/113	4,9/3,8	24/18	427/394
8	38/37	8,5/8,7	138/116	4,4/4,0	26/17	487/467

Our study showed that CD is a highly tolerable and safe agent for horses, similar to the findings of Janssen et al.[7] Therefore, our second hypothesis was accepted. An unpublished (personal data) case series of horses treated with CD for lameness also showed no side effects over a treatment period of 3 to 4 months.

Based on the results of other studies, the most commonly used dosage of CD in horses is 3 mg/kg bw, administered orally, twice daily.[13,6] Calcium dobesilate has been shown to be safe in much higher doses when administered parenterally or orally in various species. Doses of up to 25 mg/kg bw administered orally b.i.d. in rabbits and a one-time dose of 100 mg/kg administered intravenously in beagle dogs were well tolerated.[10,15] The lethal dose of orally administered CD was estimated to be 7,7 g/kg bwt in mice and higher in rats.[20] Oral dosages used in human medicine vary to some extent; patients with ONFH were treated with 500 mg b.i.d. while patients with chronic venous insufficiency of the lower legs or acute retinopathy and open-angle glaucoma received 500 mg t.i.d.[3,2] Using an average bw of 75 kg, this is equal to a dose of 6,7 mg/kg, which is about the double of the dose used in horses. As orally and intravenously administered CD has been shown to be safe in all the animal species tested, which enables further studies on the use of higher doses.[10,15] To the authors' knowledge, there are no studies in either human or veterinary medicine that evaluate the effectiveness of CD in relation to the dosage used.

This study was designed to verify the uptake of orally administered CD in warmblood horses. The drug reached detectable plasma concentrations in all warmblood horses after one week of administration. Limitations of this study included the small study population and therefore the inability to compare different doses of CD. Future studies should include the pharmacokinetics of 2,5HBSA at higher doses and determining the effectiveness of the active ingredient, particularly its effect on IOP in horses.

Acknowledgements

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Conflict of interest

The authors declare no potential conflict of interest.

Data availability Statement

The data supporting the results of this study are available from the corresponding author upon reasonable request.

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Ethics Statement

The study design was approved and accepted by the Federal Food Safety and Veterinary Office, Switzerland. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The authors confirm that they have adhered to European/Swiss standards for the protection of animals used for scientific purposes.

Pharmacokinetics of orally administered calcium dobesilate in Warmblood horses

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Pharmacocinétique du dobésilate de calcium administré par voie orale chez les chevaux de sang

Le dobésilate de calcium a récemment été utilisé pour traiter les boiteries chez les chevaux, car il améliore les processus microvasculaires et réduit la pression intra-osseuse. Les boiteries causées par des troubles du métabolisme osseux et une augmentation de la pression intra-osseuse, tels que la maladie naviculaire, les lésions osseuses kystiques et l'œdème de l'os du pied, sont généralement traitées par le repos, des agents anti-inflammatoires ou la chirurgie.

Le dobésilate de calcium pourrait influencer la physiopathologie de ces maladies et ainsi améliorer leur guérison. L'objectif de cette étude était de déterminer si le dobésilate de calcium et son agent actif, le 2,5-dihydroxybenzènesulfonate de calcium (2,5HBSA), sont absorbés par le système gastro-intestinal équin afin d'atteindre des concentrations plasmatiques détectables.

L'étude a été conçue comme une étude prospective in vivo. Huit chevaux demi-sang suisses adultes en bonne santé ont été utilisés dans l'étude. Le dobésilate de calcium (3 mg/kg, PO, q12h) a été administré par voie orale dans un mash pendant sept jours. Des échantillons de sang ont été prélevés dans la veine jugulaire après la dernière dose de dobésilate de calcium. Tous les chevaux ont subi un examen physique quotidien et des analyses hématologiques et biochimiques avant et après l'étude. La chromatographie en phase liquide a été utilisée pour déterminer les concentrations plasmatiques de 2,5HBSA. Une analyse non compartimentale a été utilisée pour estimer les paramètres pharmacocinétiques.

Le 2,5HBSA a été détecté dans les échantillons de plasma après administration orale, avec des concentrations comprises entre 2300 ng/ml et 3600 ng/ml, pour une moyenne de 2900 ng/ml. Les résultats des tests hématologiques et biochimiques plasmatiques se sont toujours situés dans les limites de référence et aucun effet indésirable n'est survenu.

Seuls des échantillons de plasma ont été analysés et le dobésilate de calcium n'a été mesuré qu'après la période de traitement de sept jours. Le dobésilate de calcium a été absorbé par le système gastro-intestinal équin et a atteint des concentrations plasmatiques détectables.

Mots clés: cheval, dobésilate de calcium, pharmacocinétique, œdème de la moelle osseuse, lésions osseuses kystiques

Farmacocinetica del calcio dobesilato somministrato per via orale nei cavalli Warmblood

Il calcio dobesilato è stato recentemente utilizzato per il trattamento della zoppia nei cavalli, in quanto migliora i processi microvascolari e riduce la pressione intraossea. La zoppia causata da disturbi del metabolismo osseo e dall'aumento della pressione intraossea, come la sindrome navicolare, le lesioni ossee simil-cistiche e l'edema dell'osso distale, viene comunemente trattata con riposo, farmaci antinfiammatori e chirurgia.

Il calcio dobesilato ha il potenziale di influenzare la fisiopatologia di queste patologie, favorendo così la guarigione. L'obiettivo di questo studio era di determinare se il calcio dobesilato e il suo principio attivo, il calcio 2,5-diidrossibenzene sulfonato (2,5HBSA), vengano assorbiti dal tratto gastrointestinale equino fino a raggiungere concentrazioni plasmatiche rilevabili.

Lo studio è stato ideato come uno studio prospettico in vivo e ha utilizzato otto cavalli adulti sani della razza Warmblood svizzera. Il calcio dobesilato (3 mg/kg, per os, ogni 12 ore) è stato somministrato per via orale, mescolato a pastone, per sette giorni. I campioni di sangue sono stati prelevati da una vena giugulare dopo l'ultima dose di calcio dobesilato. Tutti i cavalli sono stati sottoposti a esame clinico quotidiano e ad analisi ematologiche e biochimiche prima e dopo lo studio. Le concentrazioni plasmatiche di 2,5HBSA sono state determinate mediante cromatografia liquida. I parametri farmacocinetici sono stati stimati con analisi non compartimentale.

Il 2,5HBSA è stato rilevato nei campioni plasmatici dopo la somministrazione orale, con valori compresi tra 2300 ng/ml e 3600 ng/ml, e una media di 2900 ng/ml. I risultati delle analisi ematologiche e biochimiche plasmatiche sono rimasti entro i limiti di riferimento in ogni momento e non si sono verificati effetti avversi.

Sono stati analizzati solo I campioni plasmatici e il calcio dobesilato è stato misurato solo dopo il periodo di trattamento di sette giorni. Il calcio dobesilato è stato assorbito dal tratto gastrointestinale equino e ha raggiunto concentrazioni plasmatiche rilevabili.

Parole chiave: cavallo, calcio dobesilato, farmacocinetica, edema del midollo osseo, lesioni ossee simil-cistiche

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