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Article type : Original Article

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Glucose and insulin response after intravenous and subcutaneous somatostatin administration in healthy horses

Short title: Insulin response after somatostatin administration

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Abstract

Background: Equine metabolic syndrome (EMS) is prevalent in the equine population, and somatostatin analogs might be useful for diagnosis and/or treatment of EMS in horses.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JVP.12793](https://doi.org/10.1111/JVP.12793)

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Objective: To evaluate the glucose and insulin responses to subcutaneous and intravenous administration of somatostatin

Animals: Six healthy research horses

Methods: Prospective study. An initial pilot study was performed to assess several different doses (10-22 µg/kg [4.5-10 µg/lb]) in 2 horses, then a final dosage of 22 µg/kg (10 µg/lb) was administered to 6 horses IV and SQ in a two-period randomized cross-over study performed over a 3-month study period. Blood samples were collected for measurement of plasma insulin and glucose concentrations during a 24-hour study period.

Results: Both IV and SQ somatostatin resulted in decreased insulin and increased glucose concentrations. SQ somatostatin resulted in a longer clinical effect, with return to baseline insulin occurring at 1.5 hours post-administration, vs. 45 minutes for IV.

Conclusions and Clinical Importance: Both IV and SQ administration of somatostatin to normal horses resulted in decreased insulin and increased glucose concentrations, likely due to suppression of insulin secretion by somatostatin. A more prolonged effect was seen following SQ administration as compared to IV administration, and no adverse effects were noted at varying doses. This study provides additional information regarding the effect of somatostatin administration on insulin and glucose concentrations in clinically healthy horses.

Introduction

Equine metabolic syndrome (EMS) is increasingly recognized in horses as an important disease, involving insulin dysregulation, increased adiposity, and a predisposition for laminitis (Durham et al., 2008; Geor et al., 2013; Toth et al., 2009; Toth et al., 2010; Frank et al., 2010). EMS is a major concern for horse owners and veterinarians, as hyperinsulinemia (HI) is a well-documented causal factor in endocrinopathic laminitis (Asplin et al., 2007; de Laat et al., 2010). The cornerstone of treatment and prevention for HI-induced laminitis in horses and ponies, particularly in those that are overweight or obese, is dietary control (especially restriction of nonstructural carbohydrate intake) and daily exercise (Geor et al., 2009; Tinworth et al., 2010). However, not all HI horses and ponies are overweight, and daily exercise presents several challenges, not least of which are owner compliance and the presence of lameness in laminitic horses and ponies (Tinworth et al., 2010).

Current medical interventions include L-thyroxine (Frank et al., 2005; Frank et al., 2008), metformin (Vick et al., 2006; Chameroy et al., 2010; Tinworth et al. 2012; Rendle et al., 2013),

and dietary management (Respondek et al., 2011). However, improvements in insulin sensitivity or reductions in basal serum insulin concentrations typically are only moderate. With L-thyroxine, the improvement may take weeks to implement safely. A more immediate and effective intervention is needed for horses and ponies at imminent risk of, or already experiencing, HI-induced laminitis.

Interest in somatostatin and its analogs has increased in recent years. Somatostatin, a 14-amino-acid peptide, is important in controlling insulin and glucagon production in normal animals and humans. It is secreted by the pancreatic delta cells and is known to inhibit gastric, enteric, and pancreatic secretion of hormones, including insulin, glucagon, pancreatic polypeptide, gastric inhibitory peptide, and gastrin (Strowski et al., 2003; Hansen et al., 2004). It also inhibits release of thyroid stimulating hormone and growth hormone. Its clinical use in human medicine has been limited by its very short half-life of 2-3 minutes, which necessitates continuous intravenous infusion and results in rebound hypersecretion of hormones after infusion termination (Harris, 1994). The bioactivity of somatostatin is short-lived, so synthetic analogs with longer plasma half-lives have been developed, including long-acting octreotide and lanreotide. Exogenous somatostatin and its synthetic analogs have been investigated in human medicine for the management of hyperinsulinemic forms of obesity and associated morbidities (Hansen et al., 2004; Bertoli et al., 1998; Boehm, 2003; Gambineri et al., 2005; Tzotzas et al., 2008). Based on these studies, exogenous somatostatin has potential for immediate inhibition of pancreatic insulin secretion in horses and ponies with basal HI at or above the theoretical threshold for inducing laminitis.

Limited information exists about the effects of administration of somatostatin or its analogs to horses. Early literature focused on the gastrointestinal effects, where octreotide was shown to substantially increase gastric pH (Sojka et al., 1992). Octreotide was subsequently utilized in two studies to suppress growth hormone to study the regulation and effects of growth hormone in horses (Aurich et al., 2003; de-Graaf-Roelfsema et al., 2011). A recent study evaluating the effect of octreotide administration on blood glucose and insulin concentrations in both normal horses and horses with insulin dysregulation showed that octreotide suppressed insulin secretion and thereby induced hyperglycemia (Frank et al., 2017). That study evaluated a single low dose of octreotide (1 ug/kg) administered intravenously, but did not examine higher doses or subcutaneous administration.

The primary objective of this study was to evaluate the glucose and insulin responses to SQ and IV administration of somatostatin. We hypothesized that somatostatin would result in decreased insulin concentration and increased blood glucose concentrations, and that subcutaneous administration would have an equal but prolonged effect compared to intravenous administration.

Materials and Methods

Animals

All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. Six healthy adult research horses (median age 14.5 years; range, 2-26 years) were included: Thoroughbred (n=2), Warmblood (n=2), Standardbred (n=1) and Friesian (n=1). Median weight was 557 kg (range, 510-659 kg). Horses were screened for general systemic health with a complete physical examination and measurement of packed cell volume (PCV) and total solids (TS). All baseline physical examinations were considered normal, and minimum database results (PCV and TS) fell within normal reference ranges for each horse. Baseline insulin and glucose concentrations were measured before drug administration (time 0).

Experimental design

The study was designed to assess blood insulin and glucose responses to a dose of somatostatin that would suppress pancreatic secretion of insulin in healthy horses. An initial pilot study was performed to assess several different doses (10-22 $\mu\text{g/kg}$ [4.5-10 $\mu\text{g/lb}$]) in Horse 1 and Horse 2 initially. Based on the pilot study, a final dosage of 22 $\mu\text{g/kg}$ (10 $\mu\text{g/lb}$) was chosen to administer to six healthy horses (Horses 1-6) by intravenous or subcutaneous injection in a two-period randomized cross-over study performed over a three-month study period (June to August). Blood samples were collected for measurement of plasma insulin and glucose concentrations over 24 hours, and horses were monitored for adverse effects. There was a minimum one-week washout period for horses between each study period based on the results of the pilot studies and previous pharmacokinetic studies.

Experimental protocol

Horses were on pasture turnout before and in between study periods. Horses were acclimated in stalls for one day before the beginning of each trial and held in stalls for one day after each trial to monitor for adverse events. Water and grass hay were available ad libitum during the entire period the horses were stalled but no grain meals were fed. (D-Trp⁸)-somatostatin was prepared by reconstituting a commercial powder^a with sterile water to a final concentration of 500 µg/mL. Horses were continually visually monitored during the study period. Horses received twice daily physical examinations including heart rate and respiratory rate, but heart rate, respiratory rate, and blood pressure were not continuously measured during administration. On the morning of each trial, an intravenous catheter^b was inserted into the left jugular vein after aseptic skin preparation. A pre-injection (time 0) blood sample was collected, and then (D-Trp⁸)-somatostatin^a was administered IV or SQ. Post-injection blood samples were collected at 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, and 720 minutes after drug administration. All blood samples were immediately placed into vacutainer tubes containing EDTA. Plasma was removed and frozen at -80°C until analysis. Plasma glucose analysis was performed at the New Bolton Center clinical laboratory^c. Plasma insulin analysis was performed at the Animal Health Diagnostic Center at Cornell University.

For the initial pilot study, Horse 1 received dosages of 10 µg/kg IV, 11 µg/kg IV and SQ, 16.5 µg/kg IV and SQ, and 22 µg/kg IV and SQ, while Horse 2 received dosages of 16.5 µg/kg IV and SQ and 22 µg/kg IV and SQ. For the main study, Horses 1-6 received 22 µg/kg IV and SQ.

Statistical analysis

Statistical analysis was performed using standard statistical software^{d,e}. All analyses were conducted with two-sided tests of hypotheses and a p-value < 0.05 as the criterion for statistical significance. Descriptive analyses included computation of means (with 95% confidence intervals [95%CI]) and standard error of the mean (SEM). Tests of normal distribution were performed to determine extent of skewness, and transformation methods (e.g., logarithmic) were used to normalize the distribution of seriously skewed variables. Frequency counts and percentages were used for summarizing categorical variables (e.g., sex, signalment and others). Inference statistics were based on multilevel mixed-effect linear regression model with the random effects set on the level of individual animal. To correct for small departures from

normality, we used robust estimator of the variance. The fixed effect was set on the level of sample.

Results

All trials were completed without any adverse events recorded during or after the trials. Baseline insulin levels were within normal range (10-40 μ IU/mL) for all horses except for Horse 1 during the pilot study, before administration of 16.5 μ g/kg IV (58.93 μ IU/mL). Horse 1 was tested on 5 other occasions throughout the study period and had normal baseline insulin levels on all other occasions (range 8.84-18.58 μ IU/mL). Corresponding baseline hyperglycemia (134.7 mg/dL; reference range 72-114 mg/dL) was noted on the day Horse 1 had baseline hyperinsulinemia. Horse 2 had baseline hyperglycemia on a single occasion, before administration of 22 μ g/kg IV (118.9 mg/dL); this horse had a normal corresponding baseline insulin (21.16 μ IU/mL) and was normoglycemic (99.3 mg/dL) at baseline on the other occasion when it was tested.

Based on the two horses (Horse 1 and 2) trialed at increasing doses of somatostatin, 22 μ g/kg was chosen as the dose for comparison between IV and SQ routes of administration. Table 1 shows the mean insulin and glucose across horses by route of administration and time. Greater than 50% reduction in baseline insulin was apparent after both routes of administration, but suppression lasted longer after SQ administration (Table 1). After IV administration, insulin level dropped by more than 50% within 15 minutes ($p=0.008$) but returned to baseline by 45 minutes. After SQ administration, insulin level dropped by more than 50% within 15 minutes ($p=0.004$) but returned to baseline 1.5 hours post-administration. Blood glucose levels increased in response to the suppression of insulin, with the highest mean levels occurring at 4 hours post IV and SQ administration. Figure 1 shows the mean insulin levels over time for both IV (Figure 1a) and SQ (Figure 1b) somatostatin administration. Figure 2 shows the mean glucose levels over time for both IV (Figure 2a) and SQ (Figure 2b) somatostatin administration.

Discussion

As expected, transient decreases in insulin and increases in glucose were seen in response to somatostatin administration. The magnitude of the change in insulin and glucose was similar between intravenous and subcutaneous administration, while the duration of effect was

prolonged after subcutaneous administration. This study broadens the body of knowledge available regarding the effects of somatostatin on insulin and glucose concentrations.

Secretion of somatostatin from pancreatic delta cells is stimulated by glucose, amino acids, and glucagon-like peptide-1 to result in inhibition of insulin, glucagon, pancreatic polypeptide, gastric inhibitory peptide, and gastrin secretion (Patel, 1999; Brereton et al., 2015). The bioactivity of somatostatin is short-lived, so synthetic analogs with longer plasma half-lives have been developed, including long-acting octreotide and lanreotide. Somatostatin analogs have been used in humans for the treatment of Cushing disease and acromegaly (Hofland, 2008; McKeage, 2015), as well as for the management of hyperinsulinemic forms of obesity (Hansen et al., 2004; Bertoli et al., 1998; Boehm, 2003; Gambineri et al., 2005; Tzotzas et al., 2008). Studies in horses have reported effects on gastric pH and testicular function in ponies (Sokja et al., 1992; Aurich et al., 2003), with the most recent study evaluating the effects on insulin responses (Frank et al., 2017).

Clinically oriented studies of somatostatin in horses are limited, but three reports show that exogenous (intravenously or subcutaneously administered) somatostatin is well tolerated and profoundly inhibits the secretion of insulin or its proxy, connecting-peptide (C-peptide) (Toth et al., 2010; Geor et al., 2010; Frank et al., 2017). The first study investigated pancreatic insulin secretion and hepatic insulin clearance in normal horses and insulin-resistant horses, using serum C-peptide as a proxy measure of pancreatic insulin secretion (Toth et al., 2010). Administration of somatostatin decreased the mean serum endogenous C-peptide concentration by >50% over baseline values. Serum insulin was not measured following somatostatin administration, but as insulin and C-peptide are co-secreted, it is reasonable to assume that exogenous somatostatin would similarly regulate serum insulin concentrations. Indeed, in the second study, on the effect of exercise on whole-body glucose uptake, somatostatin-14 lowered baseline serum C-peptide concentrations by >75% and maintained serum insulin concentrations at or below baseline levels throughout a 2-hr period of induced hyperglycemia in 8 healthy horses (Geor et al., 2010). Although that study was undertaken to investigate insulin-mediated and noninsulin-mediated glucose uptake post-exercise in horses, it confirmed the ability of exogenous somatostatin to profoundly inhibit pancreatic insulin secretion, even in the face of persistent hyperglycemia. The third study evaluated octreotide, a somatostatin analog, and found that octreotide resulted in

suppression of insulin secretion and therefore hyperglycemia in both normal horses and horses with insulin dysregulation (Frank et al., 2017).

Potential indications for somatostatin use in horses may include immediate control of hyperinsulinemia for laminitis prophylaxis or treatment, or to aid in determining metabolic responses and identifying abnormal horses. A recent study evaluating octreotide, a somatostatin analog, found similar decreases in insulin following intravenous octreotide administration, but did not find a statistically significant difference between normal horses and horses with insulin dysregulation (Frank et al., 2017). That study evaluated intravenous octreotide only. Subcutaneous administration of somatostatin in our study resulted in longer effects compared to intravenous administration. Further studies are required to evaluate the appropriate dosing regimen for use in horses as a potential treatment for HI. Additional studies are also required to assess the utility of somatostatin in assessing the metabolic status of horses by comparing horses with insulin dysregulation and normal horses and whether prolonged reduction in insulin concentration is achievable using a combination of the IV and SQ routes in those horses considered at the greatest risk for laminitis based on laboratory testing and clinical examination.

No adverse effects were noted in any of the horses in this study during or after the study period, consistent with previous studies evaluating somatostatin and its analogs (Sokja et al., 1992; Aurich et al., 2003; Frank et al., 2017). Even with escalating doses of somatostatin, no adverse events were recorded in any of the horses in our study. However, future studies should further evaluate the safety index of somatostatin administration in normal horses as well as horses with insulin dysregulation and HI-induced laminitis.

Limitations of this study include the use of healthy research horses rather than horses with confirmed insulin dysregulation or lack thereof, the lack of screening for insulin dysregulation using dynamic testing, such as the oral sugar test, before the study period, and the lack of a negative control group housed under the same conditions. The variety of breeds used in this study is also sub-optimal, as horses of different breeds are known to be affected by EMS at different rates. However, this study is the first study to the authors' knowledge to evaluate differences between intravenous and subcutaneous administration of somatostatin, and to evaluate higher doses of somatostatin in normal horses.

In conclusion, both intravenous and subcutaneous administration of somatostatin to healthy horses resulted in decreased insulin and increased glucose concentrations, likely related

to somatostatin's suppression of insulin secretion. A more prolonged effect was seen following subcutaneous administration as compared to intravenous administration, and no adverse events were recorded at a variety of doses. This study provides additional information regarding the effects of somatostatin administration on insulin and glucose concentrations in healthy horses.

Footnotes

- a. Bachem Americas, Torrance, California, USA
- b. Angiocath, 14 G, 11.5 cm, Angiocath, Becton Dickinson, Sandy, UT
- c. Vitros GLU colorimetric assay, Ortho-Clinical Diagnostics Inc., Rochester, NY
- d. Stata 15.1MP, StataCorp, State College TX
- e. WinSAAM, University of Pennsylvania, Kennett Square PA

All work was done at the University of Pennsylvania

Acknowledgements: The authors would like to acknowledge the technical help provided by Jennifer Wrigley, Margret Lenfest, and Sraboni Chatterjee; as well as funding from the Roemer Foundation and Spot Castle Memorial Fund.

The authors have no conflicts of interest to disclose.

There was no off-label antimicrobial use to disclose.

Author contribution statement:

JO, DS, and AJ contributed to study design. JO performed the experiments. DL, DS, and RB performed data analysis. DL composed the manuscript with help from AJ, JO, DS, and RB. All authors have read and approved the final document.

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	Intravenous		Subcutaneous	
Time (hour)	Insulin (μIU/mL)	Glucose (mg/dL)	Insulin (μIU/mL)	Glucose (mg/dL)
0	22.64 ± 7.43	97.35 ± 9.62	13.26 ± 2.36	93.77 ± 4.02
0.25	8.73 ± 2.29*	104.07 ± 11.03	5.37 ± 1.30*	103.05 ± 7.10
0.5	14.08 ± 3.42*	106.47 ± 16.49	4.79 ± 1.51*	94.3 ± 9.09
0.75	18.48 ± 3.11	105.73 ± 8.65	4.94 ± 1.29*	95.94 ± 10.09
1	20.71 ± 4.25	109.15 ± 9.44	7.27 ± 1.34*	96.43 ± 8.02
1.5	22.35 ± 4.16	108.85 ± 8.07	7.42 ± 1.49	112.48 ± 8.29*
2	21.32 ± 2.84	107.1 ± 10.51	10.23 ± 1.34	123.68 ± 12.9*
3	22.78 ± 3.88	107.23 ± 7.88	15.39 ± 3.29	123.8 ± 12.22*
4	19.04 ± 3.22	115.12 ± 4.73	20.08 ± 4.30*	129.78 ± 14.52*
6	17.36 ± 2.33	92.88 ± 8.16	27.63 ± 8.51	111.55 ± 7.61
8	18.45 ± 2.30	96.58 ± 12.18	19.12 ± 3.32	98.78 ± 9.71
12	19.73 ± 2.86	95.15 ± 8.56	16.06 ± 2.06	103.52 ± 2.80

Table 1. Effect of administration of 22 µg/kg somatostatin on plasma insulin and glucose levels in 6 healthy research horses. Model adjusted means ($\pm$ standard error) results are shown for IV and SQ routes of administration. * - indicates significantly different ($p < 0.05$) from baseline (timepoint 0)

Figure 1. Mean $\pm$ SEM plasma insulin concentrations (µIU/mL) over time in 6 healthy research horses following: a) IV administration of 22 µg/kg somatostatin; b) SQ administration of 22 µg/kg somatostatin. Bars represent SEM. * - indicates significantly different ($p < 0.05$) from baseline (timepoint 0)

Figure 2. Mean $\pm$ SEM plasma glucose concentrations (mg/dL) over time in 6 healthy research horses following: a) IV administration of 22 µg/kg somatostatin; b) SQ administration of 22 µg/kg somatostatin. Bars represent SEM. * - indicates significantly different ($p < 0.05$) from baseline (timepoint 0)

	Intravenous		Subcutaneous	
Time (hour)	Insulin (μ IU/mL)	Glucose (mg/dL)	Insulin (μ IU/mL)	Glucose (mg/dL)
0	22.64 $\pm$ 7.43	97.35 $\pm$ 9.62	13.26 $\pm$ 2.36	93.77 $\pm$ 4.02
0.25	8.73 $\pm$ 2.29*	104.07 $\pm$ 11.03	5.37 $\pm$ 1.30*	103.05 $\pm$ 7.10
0.5	14.08 $\pm$ 3.42*	106.47 $\pm$ 16.49	4.79 $\pm$ 1.51*	94.3 $\pm$ 9.09
0.75	18.48 $\pm$ 3.11	105.73 $\pm$ 8.65	4.94 $\pm$ 1.29*	95.94 $\pm$ 10.09
1	20.71 $\pm$ 4.25	109.15 $\pm$ 9.44	7.27 $\pm$ 1.34*	96.43 $\pm$ 8.02
1.5	22.35 $\pm$ 4.16	108.85 $\pm$ 8.07	7.42 $\pm$ 1.49	112.48 $\pm$ 8.29*
2	21.32 $\pm$ 2.84	107.1 $\pm$ 10.51	10.23 $\pm$ 1.34	123.68 $\pm$ 12.9*
3	22.78 $\pm$ 3.88	107.23 $\pm$ 7.88	15.39 $\pm$ 3.29	123.8 $\pm$ 12.22*
4	19.04 $\pm$ 3.22	115.12 $\pm$ 4.73	20.08 $\pm$ 4.30*	129.78 $\pm$ 14.52*
6	17.36 $\pm$ 2.33	92.88 $\pm$ 8.16	27.63 $\pm$ 8.51	111.55 $\pm$ 7.61
8	18.45 $\pm$ 2.30	96.58 $\pm$ 12.18	19.12 $\pm$ 3.32	98.78 $\pm$ 9.71
12	19.73 $\pm$ 2.86	95.15 $\pm$ 8.56	16.06 $\pm$ 2.06	103.52 $\pm$ 2.80

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Luethy, D;Johnson, AL;Stefanovski, D;Boston, RC;Orsini, JA

Title:

Glucose and insulin response after intravenous and subcutaneous somatostatin administration in healthy horses.

Date:

2019-09

Citation:

Luethy, D., Johnson, A. L., Stefanovski, D., Boston, R. C. & Orsini, J. A. (2019). Glucose and insulin response after intravenous and subcutaneous somatostatin administration in healthy horses.. J Vet Pharmacol Ther, 42 (5), pp.541-547. <https://doi.org/10.1111/jvp.12793>.

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