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A randomized double blind placebo-controlled clinical trial of Cetirizine in horses affected by seasonal headshaking

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Summary: Headshaking is a threat to the welfare of affected horses. As seasonal headshaking may be triggered by allergic conditions, this clinical trial investigated whether the second-generation antihistamine cetirizine decreased headshaking. The objective was to assess the clinical effect of cetirizine versus placebo on seasonal headshaking. The hypothesis was that it would reduce headshaking by 50% in 50% of the horses. Thirty client-owned horses with seasonal headshaking were selected on the basis of information from the owner and a general clinical examination. In this crossover randomised double-blind placebo-controlled clinical trial, horses were given cetirizine (0.4 mg/kg twice daily PO for 7 days) or placebo (same number of tablets twice daily PO for 7 days) in a randomised order, with a washout period of 1 week in between. A 9-minute lunge protocol was recorded on video at the start and after both treatment weeks, and the number of headshakes in this 9-minute period was scored by two assessors in a blinded manner. Data of 29 horses were analysed. The number of headshakes decreased by more than 50% in 10 horses when they were given cetirizine and in 8 horses when they were given placebo. This difference was not significant ($p = 0.73$). In a mixed linear model incorporating weather conditions no significant treatment effect was found either. In conclusion: no significant effect of cetirizine on seasonal headshaking was found in the group of horses included in this study.

Keywords: equine, treatment, antihistamine, allergic rhinitis, crossover, trigeminal nerve

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Introduction

Headshaking is a condition where horses show sudden and often violent involuntary movements of their head. Other clinical signs can include rubbing of the nose on the limbs or objects and snorting (*Lane* and *Mair* 1987, *Mills* et al. 2002a). Over 60% of cases show a seasonal pattern, with symptoms typically being more severe in spring and summer in the northern hemisphere (*Lane* and *Mair* 1987, *Mills* et al. 2002a, *Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001, *Newton* et al. 2000). The aetiopathogenesis of headshaking has not been elucidated, and an apparent cause is rarely found (*Lane* and *Mair* 1987, *Mills* et al. 2002a, *Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001). In the remainder of cases, previously referred to as suffering from 'idiopathic headshaking', it is thought that an underlying neuropathological condition causes sensitisation of the trigeminal nerve (*Aleman* et al. 2013). For this reason, the syndrome is now referred to as trigeminal-mediated headshaking (*Pickles* et al.2014), in which trigeminal nerve activity is stimulated by trigger factors that differ from horse to horse. Suggested triggers include sunlight (*Madigan* et al. 1995) and allergic rhinitis (*Lane* and *Mair* 1987, *McGorum* and *Dixon* 1990), although some consider rhinitis a separate cause of headshaking (*Pickles* et al. 2014). Headshaking affects horses of all ages and breeds. Both males and females are affected, but geldings seem to be overrepresented (*Mills* et al. 2002a, *Lane* and *Mair* 1987, *Madigan* and *Bell* 2001).

Recognition that the syndrome shows clinical similarities with idiopathic trigeminal neuralgia in humans (*Aleman* et al. 2013) has increased awareness of the probably negative effect of the syndrome on the wellbeing of affected horses. This is not only because trigeminal sensitisation seems to be painful but also because headshaking prevents the horse from performing species-specific behaviour. In performance horses, the condition also may lead to economic losses.

Various treatments have been proposed, such as blinders (*Madigan* et al. 1995), nose nets (*Mair* et al. 1992, *Mills* et al. 2002b, *Mills* and *Taylor* 2003), surgery (*Mair* 1999, *Roberts* et al. 2009, *Uhlendorf* et al. 2011), percutaneous electrical nerve stimulation (*Roberts* et al. 2016), and medical treatment with cyproheptadine (*Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001, *Newton* et al. 2000, *Madigan* et al. 1995, *Mair* 1999, *Feige* and *Wehrli-Eser* 1998, *Bell* 2004), carbamazepine (*Newton* et al. 2000), cromoglycate (*Mair* et al. 1992, *Stalin* et al. 2008) or corticosteroids (*Tomlinson* et al. 2013). Part of these treatments were, especially in seasonally affected horses, based on the suspicion of an allergic cause. Cyproheptadine, a first-generation H1 receptor antagonist, was shown to have a (partial) effect in over 60% of reported cases (*Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001, *Newton* et al. 2000, *Madigan* et al. 1995, *Mair* 1999, *Feige* and *Wehrli-Eser* 1998, *Bell* 2004). However, this was proposed not to be caused by the antihistaminic effects, but mainly attributed to the anticholinergic or antiserotonergic properties of the drug (*Madigan* et al. 1995, *Feige* and *Wehrli-Eser* 1998). Prospective studies of second-generation antihistamines are lacking. Varying results have been reported in small retrospective studies (*Madigan* et al. 1995), owner survey studies (*Madigan* and *Bell* 2001, *Mills* et al. 2002), and anecdotal non-published studies (*Pickles* et al. 2014). Cetizine, a second-generation antihistamine, has been studied for clinical conditions other than headshaking, for example eosinophilic keratitis (*Lassaline-Utter* et al. 2014) and insect bite hypersensitivity (*Olsén* et al. 2011). Additionally, its pharmacodynamics and pharmacokinetics in horses have been reported (*Olsén* et al. 2007, *Olsén* et al. 2008). In contrast to cyproheptadine where significant sedation and colic were reported side effects (*Madigan* et al 1995, *Feige* and *Wehrli-Eser* 1998), no adverse effects of cetirizine were seen in these studies (*Lassaline-Utter* et al. 2014, *Olsén* et al. 2011, *Olsén* et al. 2007, *Olsén* et al. 2008). The unknown mechanism of the efficacy of cyproheptadine, combined with the anecdotal reports of modern antihistamines being effective in treating headshaking, were the reason for performing this trial.

To quantify the headshaking behaviour, several grading systems have been used (*Newton* et al. 2000, *Tomlinson* et al. 2013, *Feige* and *Wehrli-Eser* 1998, *Talbot* et al. 2013). In the present study, a lunge protocol was recorded on video on several occasions to be able to objectively count headshaking movements.

To perform power calculations, some assumptions were needed; the authors considered a 50% reduction of headshaking to be clinically relevant and assumed that 50% of horses would respond. The latter was based on the reported effectiveness of cyproheptadine (>60% of horses) (*Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001, *Newton* et al. 2000, *Madigan* et al. 1995, *Mair* 1999, *Feige* and *Wehrli-Eser* 1998, *Bell* 2004) and anecdotal mention of the effect of other antihistamines (33% of horses, *Pickles* et al. 2014).

The aim of this double-blind crossover randomised placebo-controlled clinical trial was to investigate the effect of cetirizine on seasonal headshaking in horses with the hypothesis that cetirizine would cause a 50% reduction in headshaking in 50% of horses compared with placebo.

Materials and Methods

Animals

This clinical trial involved client-owned animals and was approved by the Advanced Veterinary Research Committee of the Department of Equine Science of the Faculty of Veterinary Medicine, Utrecht University, the Netherlands. Clients signed an informed consent form and all horses were excluded from human consumption according to European regulations concerning food safety and off-label use of (human) medication.

A two-sample comparison of proportions power calculation was conducted to determine the number of animals needed. The significance level was set at 0.05, the power at 0.8 and the proportion responding to treatment at 0.50 and on placebo at 0.10. 'Responding' was defined as a 50% decrease in headshaking on treatment (or placebo) relative to baseline. The number of horses per group was calculated at 15, and although the crossover design of the study was not taken into account in this calculation, 30 horses were included.

The owners of horses were invited to enrol in the trial by means of an announcement on social media, in a national equine magazine, and the magazine of the Royal Dutch Veterinary Association. More than 100 owners responded, of which 83 returned a questionnaire with information regarding their horse and its history of headshaking. On the basis of this information 32 horses were selected. Inclusion criteria were: showing signs of seasonal headshaking (in spring/summer) in at least the previous year, showing symptoms on the lunge, shaking at least once every minute. Horses with obvious lameness, ataxia, or known visual impairment were excluded.

These 32 horses were examined, at their homes, by at least one of the authors (CW and/or AS). A clinical exam was performed, including evaluation of eyes, ears, and cranial nerve function. Moreover the horses were evaluated for obvious lameness (≥grade 1/5) and ataxia. As this was in early spring, not all horses had complete recurrence yet and some did not show headshaking during this examination. One horse was excluded because of lameness and 1 was withdrawn by the owner. The remaining 30 horses (10 mares and 20 geldings) were included. The gelding-to-mare ratio was similar to that of the horses of the 83 respondents (58 geldings and 25 mares).

The collected data of 1 horse (mare) were excluded afterwards because the owner administered fewer tablets to the horse than prescribed, therefore the data of 29 horses were used for final analysis. The group consisted of several breeds: 10 Dutch Warmbloods, 6 other European Warmblood breeds, 4 Quarters/Paints, 1 Haflinger, 1 Standardbred, 1 Welsh Cob, 1 Merens, 1 Appaloosa, and 4 crossbreds. The median age was 11 years (range 4–19 years; mean ± SD 12 ± 4 years); the median weight (assessed using a weigh tape, rounded up to nearest 25 kg) was 550 kg (range 350–675 kg; mean 528 ± 71 kg). Headshaking had been present for 1–15 years (median 3 years; mean ± SD 4.7 ± 3.6 years); '1 year' (3 horses) meant that the horse first showed headshaking in the spring or summer of the previous calendar year, and had recurrence of signs at the time of the selection procedure.

Study protocol

A randomised, crossover, double-blinded, placebo-controlled clinical trial was conducted. Treatment consisted of 0.4 mg/kg cetirizine dihydrochloride (unmarked 10 mg tabletsa) or the same number of tablets of commercially available placebo[b] (visibly similar tablets[a]) given twice daily per os for 7 days. There was a 1-week washout period between both treatments, based on the half-time of cetirizine in horses (5.8 h) (*Olsén* et al. 2008) and including a safety margin. Fifteen horses started with cetirizine and 14 with placebo, determined by drawing lots. Geldings and mares were equally divided over the two treatment orders. The homes of participating horses were spread all over the Netherlands. To be able to visit several horses at one day, groups were made on the basis of geographical location and owner report of when headshaking occurred in previous years. Treatment was started at the end of April (11 horses), the beginning of May (10 horses), and the beginning of June (8 horses). The owners kept a diary on treatment compliance, headshaking behaviour (not analysed in this report), and possible side effects during the study period.

A lunge protocol, consisting of 1 minute standing at rest, 4 minutes walking (2 minutes left-hand, 2 minutes right-hand), and 4 minutes trotting (2 minutes right-hand, 2 minutes left-hand) was recorded on video at the start of the study (day 1, to have a baseline value) and after a week of treatment with either cetirizine or placebo (day 8 and day 22). This took place at the properties where the horses lived. The owners lunging the horses and the students who made the video recordings were blinded to the treatment order. Green and red marks were used by the video crew to mark when the counting periods started and ended, so that on every recording exactly 9 minutes could be counted. The students who made the video recordings also recorded the weather as being sunny, lightly cloudy, or totally overcast and whether it was dry or whether there was light or heavy rain. They also noted the (approximate) temperature and the amount of wind, according to a weather application for smartphones[c]. Recordings for the 29 horses at three time points (before, after treatment, after placebo), resulting in 87 recordings, were collected and scored for the number of headshakes by two of the authors (CW and AvdB) in a blinded manner.

Statistics

The data of 29 horses were analysed. Data were collected using MS Excel software and statistical analysis was performed using SPSS[d]. Interobserver agreement on headshake scores was determined using a Bland Altman plot with 95% limits of agreement and an intraclass correlation coefficient (two-way mixed model, absolute agreement, average measures) was calculated. The number of headshakes was evaluated for normality by using a Shapiro Wilk test combined with Q-Q plots. When the natural logarithm (ln) of the number of headshakes was used, a normal distribution and homogeneity of variances was obtained.

To determine whether data for all horses could be analysed together, groups were compared with regard to the number of headshakes at baseline. Baseline ($t = 0$) data for geldings and mares, the different times when treatment was started (referred to as 'time group'), and the two treatment order groups were compared using a one-way ANOVA on Ln transformed data.

To test the hypothesis that 50% of horses would show a 50% decrease in headshaking (=improvement) with cetirizine compared with placebo, a McNemar test was performed on the proportion of horses responding to cetirizine and placebo, respectively.

To take improvement less than 50% into account and to investigate the effect of weather conditions (temperature, wind, sunshine), gender, starting moment and treatment order, a mixed linear model was built using these data as fixed factors and the (Ln transformed) number of headshakes as dependent variable. Different versions of the model were compared, and the model with the lowest small-sample-size corrected version of the Akaike information criterion (AICC) was accepted. Residuals were checked for normality and linearity. Significance level was set at $p < 0.05$.

Results

The intraclass correlation coefficient (two-way mixed model, absolute agreement, average measures) was 0.992 (95% confidence interval: 0.982–0.996). Based on this and the Bland Altman plot (Figure 1) interobserver agreement was considered acceptable and therefore the mean number of headshakes per video recording was used in analyses. As there were no significant group differences at baseline (t=0), the data of all horses were analysed without subdivision regarding gender, 'time group', and treatment order (table 1). Ten

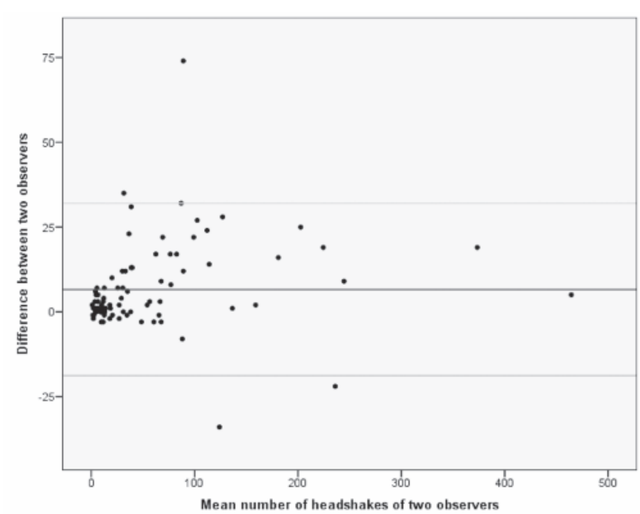

Fig. 1 Bland Altman plot showing interobserver agreement for the number of headshakes recorded in 87 videos of 29 horses. The lines represent the mean difference (middle line) and the 95% limits of agreement (upper and lower line).

Table 1 Comparison of the number of headshakes at t=0 in different groups. § A one way ANOVA test on Ln transformed data show no significant differences between groups at t = 0

Baseline at t=0		Number of shakes (mean ± SD) (median)	Significance
Gender	male	63 ± 68 (23)	p=0.25§
	female	90 ± 144 (38)	
Time group	April/May	55 ± 64 (33)	p = 0.16§
	May/June	68 ± 69 (16)	
	June	97 ± 154 (35)	
Treatmemt order	Placebo - Cetirizine	70 ± 118 (23)	P = 0.71§
	Cetirizine - Placebo	73 ± 75 (33)	

out of 29 horses showed a 50% or greater decrease in the number of headshakes when on cetirizine, as did 8 horses when on placebo. This difference was not significant ($p = 0.73$).

In the linear model, gender, treatment, treatment order, time group, sunshine and temperature did not have a significant effect on headshaking. The best fitting model contained treatment and wind as factors (the data used for this model are presented in figure 2 and 3). Residuals of this model were checked for normality and linearity and found acceptable. Wind had a significant effect on the number of headshakes ($p = 0.037$) in this model. For every m/s increase in wind, the number of headshakes decreased with 10% (95% confidence interval 6–18%).

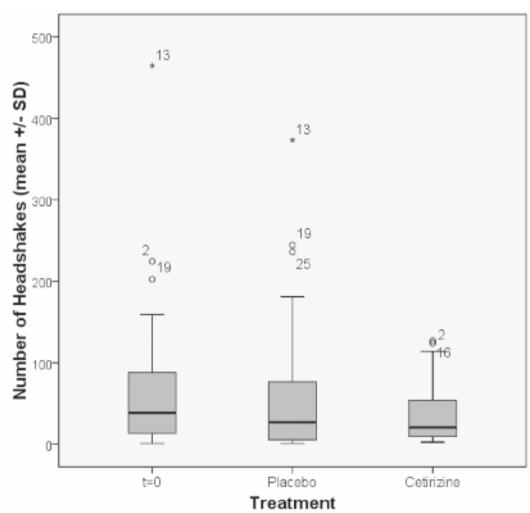

Fig. 2 The mean (+ SD) counts of headshakes at the start, after a week of placebo and after a week of cetirizine treatment (crossover, n=29, 9 minute recordings). The outliers are numbered; each number represents an individual horse. These data were (after Ln transformation) used in the mixed linear model and treatment was not found to be significantly influencing the number of headshakes ($p=0.22$)

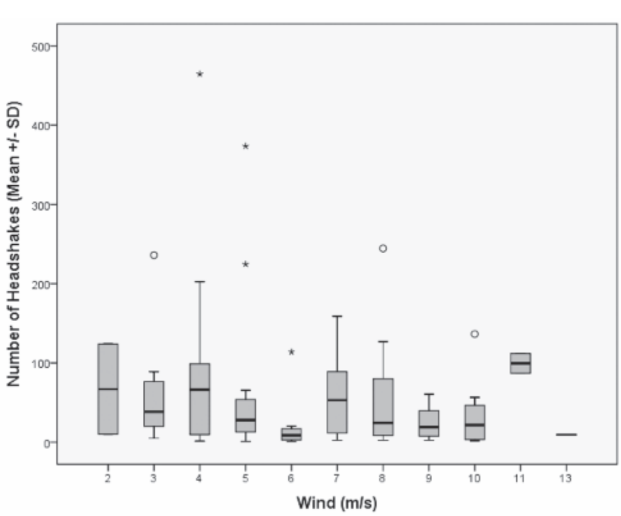

Fig. 3 The mean number of headshakes plotted against the wind flow velocity. The mixed linear model showed that there was a significant negative effect on the headshake count with increasing wind velocity ($p=0.037$)

Discussion

This placebo-controlled double-blind crossover study is the first clinical trial of the effect of the second-generation antihistamine cetirizine on seasonal headshaking in horses. A placebo was chosen because of the lack of a generally effective drug in this population to use for comparison. Although the study design was theoretically suited to this purpose, in practice there were a number of limitations.

First of all, the timing is essential when investigating seasonal conditions. While an attempt was made to establish when horses should be investigated on the basis of information from owners about the previous year(s), in some cases the horses showed less severe headshaking than usual in this period. The reason for this is unclear, but it may be due to weather conditions, because sunlight, wind, and pollen are recognised triggers of seasonal headshaking (*Mills* et al. 2002a, *Madigan* and *Bell* 2001).

Another limitation was the limited diagnostic work up in most participating horses. It is suspected that (seasonally) headshaking horses may be a diverse patient group with only part of them actually being considered as being affected by trigeminal mediated headshaking after a full diagnostic work up (endoscopy, CT, Maxillary nerve block, among others). Cetirizine would potentially be of value only in cases where a (histamine related) allergic reaction is involved. In this study, due to financial and practical limitations, no additional diagnostics were performed and the patient population as encountered in first opinion practice was used.

The 9-minute lunging protocol was designed to accurately determine the number of headshakes in a blinded manner and to avoid influence of the rider and harness. Horses could be lunged using a bridle or a halter (as long as the same was used in all three recordings) and it was tried to ensure that the same person lunged the horses as much as possible. However, the recorded lunging period (9 minutes at the end of the treatment weeks) was short relative to the 1-week treatment period.

Two experienced clinicians counted the number of headshakes and there was sufficient agreement between them. There is no generally accepted system for the grading of the severity of headshaking. Some reported grading systems are based on 'rideability' (*Newton* et al. 2000), which might be influenced by the rider and excludes the use of a lunging protocol. Other grading systems are based on more subjective interpretation of severity ('mild', 'obvious') in combination with behavioural changes (*Talbot* et al. 2013) or based on counts (*Feige* and *Wehrli-Eser* 1998, *Tomlinson* et al. 2013). In the latter, no distinction is made between severe and very severe headshaking horses, since the cut off lies at approximately 1 headshake per minute. In the present study with average counts (at $t = 0$) of 2, 11, 25 and 51 headshakes per minute, for example, these horses would all have been graded the same in the grades based on counts but likely in different grades in the other grading systems. Therefore, in the present study, a lunging protocol with plain counting of headshakes was chosen. For future research, counting with electronic sensor-based devices might be helpful to objectify the movement recordings, after validation of this technique for this purpose.

Also, the value of incorporating additional clinical signs like nose-rubbing and striking with the limbs into a study protocol remains to be elucidated.

It is important to take the weather into consideration when interpreting our findings, because it affects seasonal headshaking in horses (*Mills* et al. 2002a, *Madigan* and *Bell* 2001). Sunshine and rain were scored by the students who made the video recordings at the exact time and location during the recording. In contrast, information about the wind and temperature was obtained by a smartphone application[c]. This information on the conditions of the geographical area where the horse was housed does not necessarily correspond to the circumstances of the exact location where the horse was lunged. Wind appeared to cause a significant decrease in headshaking severity with increasing wind velocity. This has been reported before (*Mills* et al. 2002a, *Newton* et al. 2000), although in the study of *Mills* et al (2002a) the same number of horses improved on windy days as showed more severe symptoms. Considering the limitations mentioned above, the reliability of the significance of wind in this study is questionable.

Concerning the study population, it was remarkable that 70% of the 83 horses that were subscribed, and correspondingly 69% of participating horses, were geldings. A similar ratio was previously reported by other authors; on average 68% in over 500 horses (*Lane* and *Mair* 1987, *Mills* et al. 2002a, *Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001, *Newton* et al. 2000, *Mair* 1999). The reason for this overrepresentation of geldings remains unclear.

Investigating treatment options for seasonal headshaking is complicated by its complex and only partly elucidated aetiology. The fact that no significant effect of cetirizine was found in this study may be because cetirizine does not always (totally) suppress allergic rhinitis, or because allergic rhinitis was not a major trigger (or cause) of headshaking. Previous studies have shown cyproheptadine to be effective in over 60% of horses (*Madigan* and *Bell* 1998, *Madigan* and *Bell* 2001, *Newton* et al. 2000, *Madigan* et al. 1995, *Mair* 1999, *Feige* and *Wehrli-Eser* 1998, *Bell* 2004). However, unlike cetirizine, cyproheptadine possesses, in addition to its H1-receptor antagonist activity, anticholinergic and antiserotonergic properties that may underlie its effect. Future studies are required to determine the role of these receptors in headshaking horses.

No significant effect of cetirizine was found in the group of horses participating in this study. However, as anecdotally reported (*Madigan* and *Bell* 2001, *Pickles* et al. 2014) some horses responded to cetirizine treatment, based on a large decline in headshake count and owner opinion. In a few cases this effect was observed even for an extended period after the study. A future study could be aimed at gathering evidence of true efficacy by initiation and cessation of therapy for several times while monitoring the effect. An extended diagnostic work-up of these horses then might shed light on the reason for efficacy in this small proportion of headshaking horses.

Conclusion

No significant effect of cetirizine on seasonal headshaking was found in the group of horses included in this study.

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[c] Accuweather®
[d] IBM SPSS Statistics 22 & 24

Statement of informed consent

The study was performed at the home addresses of participating owners, at 30 locations in the Netherlands.

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Conflict of interest statement

There are no conflicts of interest to declare

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