

Use of the chasteberry preparation Corticosal[®] for the treatment of pituitary pars intermedia dysfunction in horses

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Summary

The objective of this study was to describe the efficacy of PPID treatment with the combined supplement corticosal[®] containing chasteberry. Thirty-eight horses and ponies with PPID were divided into three groups and received either the chasteberry preparation (group T1) or pergolide in addition to the chasteberry preparation (group T2) for six months or pergolide in addition to a placebo for the first three months and pergolide in addition to the chasteberry preparation for the following three months (group T3). Clinical and laboratory examinations were performed at three time points. Within group T1, a significant difference in clinical parameters between the first and second examination ($p=0.0042$) as well as between the second and third examinations ($p=0.0001$) was observed. The clinical signs improved significantly based on the clinical overall score. On the basis of the collected data, beneficial effects of the chasteberry preparation corticosal[®] on clinical parameters for PPID were determined.

Keywords: Cushing's syndrom / horses / pituitary / epidemiology / Vitex agnus-castus / PPID

Der Einsatz des Mönchspfeffer-Präparats Corticosal[®] zur Behandlung des Equinen Cushing Syndroms (PPID)

Ziel dieser Studie war die Überprüfung der Wirksamkeit des mönchspfefferhaltigen Kombinationspräparats Corticosal[®] zur Behandlung des Equinen Cushing Syndroms (PPID). 38 an PPID erkrankte Pferde und Ponys wurden in drei Versuchsgruppen eingeteilt und erhielten über einen Zeitraum von sechs Monaten entweder das Kombinationspräparat (Gruppe T1) oder Pergolid zusammen mit dem Kombinationspräparat (Gruppe T2) oder die ersten drei Monate Pergolid und ein Placebo und die weiteren drei Monate Pergolid und das Kombinationspräparat (Gruppe T3). An drei Untersuchungszeitpunkten wurden die klinische Symptomatik und verschiedene Blutparameter anhand eines festgelegten Score Systems ermittelt. In Gruppe T1 konnten sowohl zwischen den ersten und zweiten Untersuchungszeitpunkten ($p=0,0042$) als auch zwischen den zweiten und dritten Untersuchungszeitpunkten ($p=0,001$) signifikante Unterschiede der klinischen Parameter festgestellt werden. Die klinischen Symptome verbesserten sich signifikant gemessen am klinischen Gesamtscore. Anhand der erhobenen Daten konnte ein positiver Effekt des mönchspfefferhaltigen Präparates Corticosal[®] auf die klinische Symptomatik von den am Cushing Syndrom erkrankten Pferden festgestellt werden.

Schlüsselwörter: Cushing Syndrom / Pferde / Hypophyse / Epidemiologie / Vitex agnus-castus / PPID

Introduction

Pituitary Pars Intermedia Dysfunction (PPID) is a progressive neurodegenerative disease found in aged horses and ponies (McFarlane 2011). Even though the cause of PPID remains unclear, oxidative stress damaging neurons is suggested as initial event (Donaldson et al. 2005). Neuronal impairment leads to loss of dopaminergic inhibition of the pituitary pars intermedia, resulting in melanocytic proliferation and increased production of pro-opiomelanocortin (POMC) and POMC derivatives like adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone and beta-endorphin (Donaldson et al. 2005, Goudreau et al. 1992). The most commonly used treatment is pergolide-mesilate, an ergot-alkaloid derivative, which acts as D2-receptor agonist on the pituitary gland and decreases POMC production. The efficacy of pergolide has been proven in different studies that take the improvement of clinical symptoms and laboratory parameters into account (Coursen et al. 2001, Beech et al. 2002, Divers et al. 2002, Corazza et al. 2004).

It is hypothesized that Vitex agnus-castus (chasteberry) – a medicinal plant with dopaminergic action – shows effectiveness in the treatment of PPID by increasing dopaminergic activity in the equine pituitary. Chasteberry is a phytotherapeutic traditionally recommended for hyperprolactinemia and premenstrual syndrome in women (Schellenberg 2001). Meier et al. (Berger et al. 2000) identified diterpenes as the active substances in Vitex agnus-castus (VAC) extracts that bind to D2 and D3 pituitary receptors. The VAC extract therefore is a combined D2/D3 dopamine receptor agonist. In a study performed on rats, the binding of the VAC extracts to D2 receptors resulted in decreased prolactin secretion (Gorkow et al. 1994). As PPID in horses is also a D2 receptor-mediated disease, chasteberry has been evaluated as a single therapeutic. However, compared to pergolide treatment, no improvement of ACTH concentrations, the dexamethasone suppression test or clinical symptoms was shown (Beech et al. 2002).

In Germany, a combined feed additive containing chasteberry (Corticosal[®]) was specially developed for horses with PPID.

The aim of this study was to evaluate the efficacy of this special Vitex agnus-castus preparation in the treatment of PPID based on clinical signs and plasma ACTH, insulin and glucose concentrations before, during and after administration.

Materials and Methods

Horses

Thirty-eight horses and ponies with PPID were included in this study. The inclusion criteria were an ACTH plasma concentration >50 pg/ml and a clinical score above five. All horses were privately owned and lived under different housing conditions. In the course of the study, neither the stable environment nor the feeding regimen changed.

Group assignment

Groups were defined according to their pre-treatment. Untreated horses and ponies were assigned to group T1. This was the largest group (25 horses) and it was established to determine the efficacy of the chasteberry preparation in untreated animals. Thirteen horses which had received pre-treatment with pergolide were randomly divided into control groups T2 (6 horses) or T3 (7 horses). For pre-treated horses, the inclusion criteria were pergolide treatment for at least three months and no dosage changes throughout the six-month duration of the study. For animal welfare reasons, there was no group without any treatment.

Study period

The study period was six months, between January and August 2011. The parameters for each horse had to be docu-

mented for at least six months. A second examination was performed three months after the initial examination and a final examination took place after six months.

Treatment group definition

During the study period, the horses in group T1 received the chasteberry preparation¹ only, whereas the horses in group T2 received the chasteberry preparation and pergolide². Horses in group T3 received pergolide for six months with the addition of a placebo for the first three months and then switched to pergolide in addition to the chasteberry preparation for the following three months (Table 1). Neither the owners nor the investigator knew whether the animals received the placebo or the active treatment. The chasteberry formulation was administered according to the manufacturer's instructions (0.05 g/kg PO/q24h) mixed with feed. Besides chasteberry, it contains phytotherapeutics like ginseng and artichoke, special nutrients and antioxidants. The pergolide dosage was adjusted by the veterinarian in the field and ranged from 2 to 3 g/kg PO/q24h.

Clinical examination

The same investigator performed a standardized clinical examination for PPID at different times using a composite scoring system (Table 2) to assess clinical parameters. To avoid additional stress for the animals all examinations were performed at the stables the horses were housed. At each examination time, the following parameters were investigated: hypertrichosis, hyperhidrosis (excessive sweating), swayed back, pendulant abdomen, skeletal muscle atrophy, behavior and abnormal fat distribution. The symptoms were rated using a score from 0 (non-existent) to 3 (severe). Furthermore, polyuria and polydipsia, reported by the owners, were evaluated

Table 1 Group assignment (T1-T3) and different treatment regimen / *Gruppeneinteilung (T1-T3) und unterschiedliche Behandlungsmethoden*

Group	Horses	Treatment
T1	n=25	Chasteberry preparation (six months)
T2	n=6	Pergolide + Chasteberry preparation (six months)
T3	n=7	Pergolide + 1.) Placebo (1 st three months) 2.) Chasteberry preparation (2 nd three months)

Table 2 Scoring system of the typical clinical parameters of PPID (score grade 0-3) / *Score-System der typischen klinischen Symptome von PPID*

Score	0	1	2	3
hirsutism	none	hair coat long, at least visible in parts of the body, eg. legs and lower jaw	hair coat generalized long, partly curly	hair coat generalized long, curly
hyperhidrosis	none	occasional localized sweating or extensive sweating after exercise	occasional to frequent sweating on at least two parts of the body	generalized severe hyperhidrosis
sway back	none	minor	moderate	severe
pendulous abdomen	none	minor	moderate	severe
muscle atrophy	none	in one region of the body	in two regions of the body	generalized
behaviour	alert, unremarkable	mildly depressed	lethargic	apathic
abnormal fat distribution	none	one body part (eg. neck, supraorbitally or croup)	two body parts	at least three body parts
polydipsia	no	yes		
polyuria	no	yes		

and rated (a score of 0 if non-existent and of 1 if existent). The evaluation of polyuria and polydipsia was performed by the animal owner and therefore a subjective assessment based on the state of the litter and water intake in case of housings where watering was performed manually in drinking troughs. Standardization of measuring polyuria and polydipsia was not possible due to the different housing and management of the horses. At each examination time, an overall score for clinical presentation was established for each patient.

Blood examinations

At each examination time, blood samples were collected from the horses to evaluate the efficacy of treatment. Among other parameters, plasma ACTH as well as insulin and glucose levels were determined after a fasting period of 12 hours. For evaluating plasma ACTH, 4 ml venous blood was sampled into EDTA vacutainers (Vacuette® K3, Greiner, Germany). Samples were centrifuged immediately at 3000rpm for 15 minutes to obtain EDTA plasma, which was filled into a labelled Eppendorf vacutainer and immediately refrigerated at +4° to +8°C until shipment on the same day. All samples were sent to the laboratory in a cooled container and analyzed the following day. ACTH levels were measured using chemiluminescence immunoassay (CLIA; Immulite 2000XPi³, Laboklin, Germany). A validated chemiluminescence immunoassay was used for determining insulin levels (CentaurXP, Testkit IRI⁴, Laboklin, Germany). For evaluation of insulin, 4 ml venous blood was sampled into a serum separator tube (Vacuette®Z, Greiner, Germany) and for the evaluation of glucose, 2 ml venous blood was sampled into a tube containing potassium oxalate and sodium fluoride (Vacuette®FX, Greiner, Germany). All samples were sent to the laboratory (Laboklin, Germany) and analysed by validated assays.

Statistical analysis

Analyses were carried out using the statistical software Easy-Stat 4.4. Parameters were indicated as arithmetic mean, standard deviation and median. Correlations were made using the same program. Statistical analysis of ACTH values between the groups was performed by the non-parametric Kruskal-Wallis test and by the Wilcoxon test and by means of the statistical software SAS® 9.25. Comparison of values within the groups was performed using univariate analysis and Student's t-test. Clinical scores were also analyzed with the Kruskal-Wallis and Wilcoxon tests. Differences were considered statistically significant at $p < 0.05$. Inclusion criteria for statistical analysis were at least values of two different examinations per patient.

Results

Study population

The study group comprised 17 ponies, 16 warmbloods, four thoroughbreds and one draft horse. The median age was 24 years (range, 16–38 years), 61% of the animals were 16 to 25 years old, 66% of the horses were kept in stables and

34% on pasture. There were 22 mares (57.9%) and 16 geldings (42.1%).

Twelve horses did not finish the full study period, eight of them dropping out before the second examination and four before the third. Nine of the drop-outs belonged to group T1, two to group T2 and one to group T3. The reasons for the loss of these twelve animals were euthanasia in eight cases (colic (2), heart failure (2), tendon rupture, fracture, laminitis and sepsis) and at the request of owners (start of pergolide treatment (2), stop of pergolide treatment and no reason given).

Clinical symptoms

Within group T1, a significant difference concerning the clinical score between the first and second examinations ($p = 0.0042$) as well as between the second and third examinations ($p = 0.0001$) was observed. At the third examination time, there was no difference in clinical score between the groups (Fig 1).

Improvement of clinical symptoms was evident to the examiner at the different examination times. Especially remarkable changes were the normalization of hair coat (Figs. 2a, b) and behavioral changes. Owners described their horses and ponies as more lively and alert; these behavioral changes were also observed by the veterinarian during the examinations. Hypertrichosis improved in all groups. At the beginning of the study, all horses showed a minimum score of one or two. The mean score for T1 and T2 was 2.4 and for T3 1.8. There was no statistical significant difference between groups at any time. When the third examination was performed, a significant statistical difference was observed from that of the first examination within each group (Fig. 3). The mean score for T1 was 0.7, for T2 0.3 and for T3 0.8. Hyperhidrosis was determined in 47.4% of horses at the first examination but was not correlated with hypertrichosis. Polydipsia and polyuria were present in 33% of the horses at the first examination

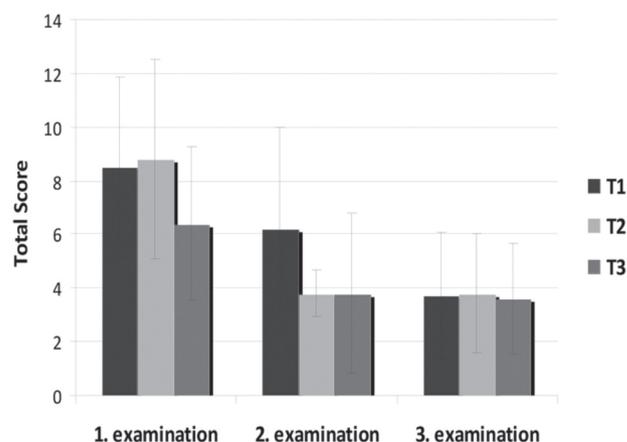
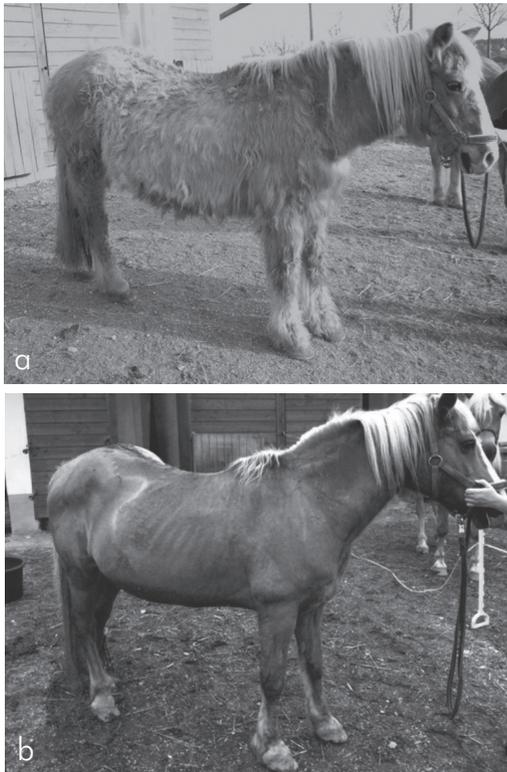


Fig. 1 Clinical overall score at first (day 1), second (after three months) and third (after six months) examination in the different treatment groups T1-T3. The difference between the first and third examination in group T1 and T2 tends to be significant ($p = 0.0719$). *Klinischer Gesamt-Score im Rahmen der ersten (Startzeitpunkt), zweiten (nach drei Monaten) und dritten (nach sechs Monaten) Untersuchung in den verschiedenen Behandlungsgruppen T1-T3. Der Unterschied zwischen der ersten und dritten Untersuchung in den Gruppen T1 und T2 ist tendenziell signifikant ($p = 0.0719$).*

and improved to 13%. In group T1, they decreased to 7%, in group T2 to 25% and in group T3 to 20%.

Plasma ACTH

In treatment groups T1 and T2, ACTH levels decreased slightly between the first and second examinations, but increased to above initial levels at the third examination (Fig. 4). In



Figs. 2a and b 23-year-old Haflinger mare of group 1, at initial examination in January 2011 (a) and at 3rd examination in July 2011 (b), showing a distinct improvement in clinical signs. Eine 23-jährige Haflingerstute aus der Gruppe T1 zeigt eine deutliche Verbesserung der klinischen Symptome bei der ersten Untersuchung im Januar 2011 (a) und bei der dritten Untersuchung im Juli 2011 (b).

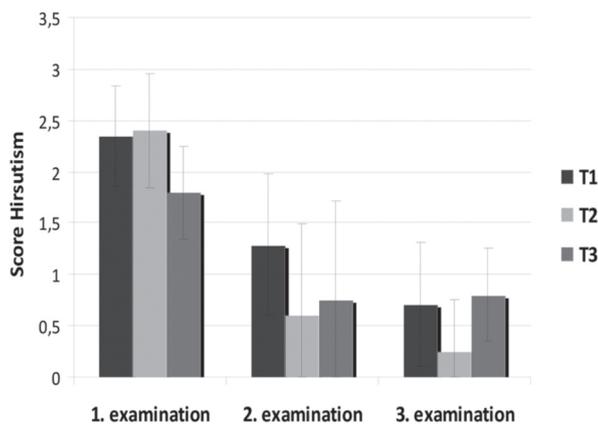


Fig. 3 Scores (0–3) for hypertrichosis in the different groups (T1–T3), at first, second and third examination ($p < 0.05$ = statistically significant), T1 $p = 0.04$, T2 $p = 0.001$, T3 $p = 0.007$. Auswertungen (0–3) zur Hypertrichose in den einzelnen Behandlungsgruppen (T1–T3) bei der ersten, zweiten und dritten Untersuchung ($p < 0.05$ = statistisch verbessert), T1 $p = 0.04$, T2 $p = 0.001$, T3 $p = 0.007$.

group T3, ACTH values increased slightly at the second examination and showed a slight decrease towards the third examination. The difference between treatment groups T1 and T3 at the third examination was statistically significant ($p = 0.0407$). The increase within treatment group T1 was statistically significant ($p = 0.0054$), while the increase within group T2 was shown not to be statistically significant ($p = 0.0625$).

Glucose and insulin metabolism

At each of the three examination time points, fasting levels of insulin and glucose were measured. Based upon the reference range of the laboratory, seven horses (18.4%) showed hyperglycemia and three horses (7.9%) hyperinsulinemia, while five animals (13.2%) had hyperglycemia combined with hyperinsulinemia.

To sum up, 15 of 38 horses (39.5%) suffering from PPID had an altered glucose and insulin metabolism. Forty percent of

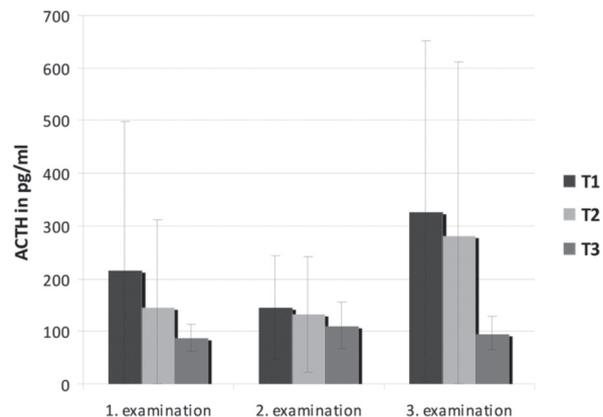


Fig. 4 Endogenous ACTH levels in the course of the study, measured at the first, second and third examination in the different groups T1–T3. The difference between T1 and T3 at the 3rd examination was determined to be statistically significant ($p = 0.0407$). ACTH-Werte im Verlauf der Studie, gemessen zum ersten, zweiten und dritten Untersuchungszeitpunkt in den Behandlungsgruppen T1–T3. Der zwischen T1 und T3 im Rahmen der dritten Untersuchung ermittelte Unterschied war statistisch signifikant ($p = 0.0407$).

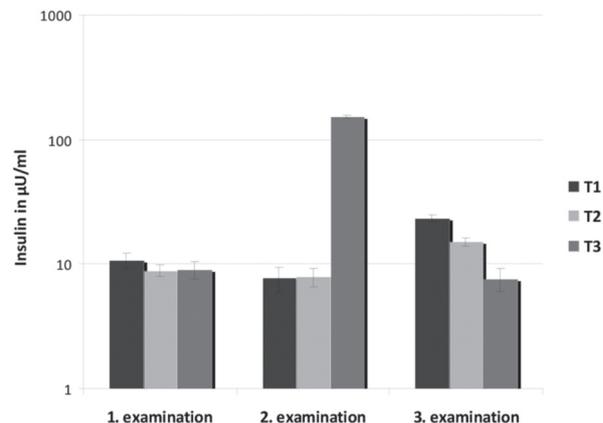


Fig. 5 Logarithmic delineation of insulin values at first, second and third examination in the different groups T1–T3. * $p < 0.05$. Logarithmische Beschreibung der Insulinwerte der ersten, zweiten und dritten Untersuchung in den unterschiedlichen Untersuchungsgruppen T1–T3. * $p < 0.05$



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these horses were treated with pergolide. In the course of the study, no improvement in glucose and insulin metabolism was observed. Regarding insulin values, a significant difference between T1 and T3 as well as between T2 and T3 was evident at the second examination time. Insulin values in treatment group T3 were considerably higher compared to the other treatment groups (Fig. 5). Glucose levels showed no difference between the different treatment groups at any time during the study period. ACTH levels did not correlate with insulin and glucose values. Insulin and glucose levels showed a wide variance in horses with similar ACTH values.

Laminitis

Twenty-four horses (63.2%) of the study group had had laminitis before. At the beginning of the study no horse or pony showed laminitis. In the course of the study, two ponies developed acute laminitis following the second examination. One horse belonged to group T1 and one horse to group T2. Both ponies had been out on pasture before development of acute laminitis and showed increased insulin and glucose levels at the second examination.

Discussion

Regarding the study population, the ratio of warmbloods to ponies was quite balanced. According to other studies, there was no breed predilection for PPID (McFarlane 2011, McGowan 2008, McGowan 2008). The average age was 24 years. An average age of 20 years was described in a study by Breukink et al. (1995). PPID can also be recognized in younger horses, as previous studies have shown (Baumgartner et al. 1990, Brüns 2001, Sommer 2003). There was no relationship between age or breed and the treatment received. The proportion of mares (58%) was higher than that of male horses (42%) but no statistically significant sex difference was determined. Other studies did not show any sex predilection for developing PPID either (Breukink et al. 1993, Couëttil et al. 1996, Schott 2002).

This study had no control group without any treatment for animal welfare reasons, as PPID is a severe disease leading to an impaired quality of life for the affected horses. The disease takes a progressive course and improvement of symptoms cannot be expected without therapy (McFarlane 2011, Breukink et al. 1995, Schott 2002).

Concerning clinical signs, a significant improvement was observed within treatment group T1. These horses, which had not received any treatment before, responded well to the chasteberry preparation. At the third examination after six months, almost no difference was observed between group T1 and the control groups T2 and T3 which had been treated with pergolide. Based on the overall clinical score it can be concluded that clinical symptoms improved significantly based on the overall clinical scores. Treatment with the chasteberry preparation resulted in a significant clinical improvement in the previously untreated animals. Compared to group T1, the influence of the chasteberry preparation on horses receiving constant pergolide medication was much lower. This can be explained by the proven efficacy of pergolide

lide treatment in PPID horses (Beech et al. 2002, Divers 2008), indicating that the dosage was appropriate for them.

Between the first and second examinations, all three groups showed a distinct reduction in the overall clinical score, a fact partly based upon the seasonal shedding of the hair coat. However, owners reported delayed or no shedding of hair coat in the years before. Even horses which had received pergolide before showed a great improvement in hypertrichosis when they were fed the chasteberry preparation compared to previous years. To conclude, the chasteberry preparation seemed to have a great influence on the parameter hypertrichosis and shedding of the hair coat. Furthermore, behavioral changes were observed. The patients became more alert throughout the study and owners reported positive mental development. This was not only based on subjective statements by the owners but was also noticed by the investigator.

Acute laminitis occurred once in group T1 and once in group T2. Both horses had already experienced laminitic episodes before and acute laminitis occurred shortly after the second examination, after they had been taken out to pasture. This shows the inability of the chasteberry preparation to prevent laminitis either alone or in combination with pergolide treatment in patients with a preexistent condition when they have access to pasture.

To date, only one study has evaluated the potency of a chasteberry preparation in horses with PPID. Beech et al. (Beech et al. 2002) observed no positive effect of *Vitex agnus-castus* on clinical symptoms, some horses even showed deterioration of PPID symptoms. The study used *Vitex agnus-castus* extract without further information regarding its concentration or other ingredients. On the other hand, the chasteberry preparation used in this study is specially developed for horses with PPID and contains not only chasteberry but other useful phytotherapeutics and nutrients. The chasteberry showed dopamine-agonistic properties and in combination with the other ingredients it could be responsible for improving the other parameters like shedding of hair coat or improvement of behavior.

ACTH plasma levels decreased between the first and second examination in treatment groups T1 and T2, but they increased in group T3. These variations might be explained by the influence of the chasteberry preparation, although the differences were not statistically significant.

Between the second and third examinations, plasma ACTH levels increased markedly in treatment groups T1 and T2. This increase was statistically significant within group T1 between the first and third examination. Furthermore, the difference between treatment group T1 and T3 at the third examination was statistically significant. Although clinical symptoms improved, the ACTH levels increased in group T1 and in group T2. This is contrary to a study of Donaldson et al. (2002), in which ACTH values normalized in 60% of the horses under pergolide.

As the increase occurred in the pergolide-treated group as well, other factors must also be present to influence ACTH values. If the ACTH increase was only due to the inefficacy of the chasteberry preparation, no increase would be measurable in the pergolide-treated group. Different studies showed a

seasonal influence on ACTH levels. Plasma ACTH levels are higher in early fall (August to October) due to a reduction of daylight and decline in winter, reaching their lowest levels in January (Beech et al. 2009, Copas et al. 2012, Elliott 2010). In a recent study performed by Funk et al. (2011), a stronger reaction of ACTH levels after TRH stimulation in July than in February was seen.

In the present study, the characteristic clinical symptoms and ACTH values did not correlate. While clinical symptoms improved with therapy, ACTH values increased. Until now, determination of ACTH values has been regarded as the parameter of choice to evaluate efficacy of treatment and to change the dosage if needed.

As clinical symptoms improved considerably during the course of the study, adjustment of dosage was not necessary. However, the question arises whether monitoring of ACTH values is essential for adjustment of dosage or whether changes in dosage should be rather be based upon development of clinical symptoms.

On initial examination 39.5% of horses and ponies showed alterations in their insulin and glucose metabolism. In the literature up to 60% of the patients suffering from PPID show elevated serum insulin concentrations (McFarlane 2011). 40% of the horses in the current study with alterations in insulin and glucose metabolism were treated with pergolide. The results suggest that pergolide treatment does not necessarily lead to the regulation of insulin and glucose metabolism.

In the course of the study, the ratio of horses with altered glucose and insulin metabolism did not improve. A possible cause could be variations in access to pasture. In January and February, at the initial examination horses were not taken out on pasture and, apart from concentrated feed, no other source of starch was available. During the pasture season, the ratio of horses showing insulin resistance increased.

Other authors have also described a relation between grass intake and altered equine metabolism (McGowan 2008, Kronfeld 2006, Adair et al. 2008). The placebo group showed significantly higher insulin levels at the second examination time than the groups receiving the chasteberry preparation. It can be concluded that the chasteberry preparation seemed to have an influence on insulin levels.

Limitations of data collection

The limitation in performing this study was the failure rate within the study population mostly due to reasons other than PPID. Because of the failure rate, the groups were reduced and only 26 horses could be analyzed at the final examination. Groups T2 and T3 became quite small for statistical analysis and the results must be observed critically. A study analyzing long-term effects of pergolide therapy showed a low survival time of 7.9 months in horses with PPID (Graubner et al. 2010). Patients included in these kinds of studies are generally old and in advanced stages of PPID.

For a better understanding of the increase of plasma ACTH under the chasteberry preparation and pergolide in August,

horses should have been examined at the beginning of the year again when lower ACTH levels are generally expected due to seasonal variations in pituitary activity.

Conclusion

Based on the results of this study, the chasteberry preparation represents a treatment option for horses with PPID. Especially in cases in which horses do not tolerate pergolide treatment or owners decide against pergolide medication, the chasteberry preparation may serve as an alternative. To determine the long-term effect on clinical signs and laboratory parameters, further studies need to be performed. Continuing studies on the chasteberry preparation in combination with individually optimized stabling conditions and feeding regimens should be carried out in order to determine the effect on the disease state. These potential studies would be useful in determining disease progression under the influence of the chasteberry preparation. Furthermore, results could be compared with those of horses treated with pergolide. To sum up, the collected data provides evidence of the positive effects that this special chasteberry preparation has on the clinical symptoms of horses and ponies suffering from PPID. Quality of life was improved in the study population.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Manufacturer's addresses

1. Corticosal®, Navalis Nutraceuticals GmbH, Filderstadt, Germany
2. Prascend®, Boehringer Ingelheim, Ingelheim, Germany
3. Immulite 2000XPi, Siemens, Eschborn, Germany
4. CentaurXP, Testkit IRI, Siemens, Eschborn, Germany
5. SAS®9.2, SAS Institute Inc., Cary, USA

Abbreviations

ACTH	Adrenocorticotrophic hormone
PPID	Pituitary Pars Intermedia Dysfunction
ml	Milliliters
pg/ml	Picogram per milliliter
POMC	Proopiomelanocortin
VAC	Vitex agnus-castus

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