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Treatment of growth hormone excess in dogs with the progesterone receptor antagonist aglépristone

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Abstract

Acromegaly or hypersomatotropism in dogs is almost always due to progestin-induced hypersecretion of GH originating from the mammary gland. The aim of this study was to investigate whether aglépristone, a progesterone receptor antagonist, can be used to treat this form of canine acromegaly. In five Beagle bitches hypersomatotropism was induced by administration of MPA for over 1 year. Subsequently, aglépristone was administered. Blood samples were collected before MPA administration, immediately before, during, and 3.5 and 5.5 weeks after the last administration of aglépristone for determination of the plasma concentrations of GH and IGF-I. In addition, blood samples for the determination of the 6-h plasma profile of GH were collected before MPA administration, before aglépristone administration, and 1 week after the last aglépristone treatment.

MPA administration resulted in a significant increase of the mean plasma IGF-I concentration, whereas analysis of the pulsatile plasma profile demonstrated a trend ($P = 0.06$) for a higher mean basal plasma GH concentration and a higher mean AUC_0 for GH. Treatment with aglépristone resulted in a significant decrease of the mean plasma GH and IGF-I concentrations. Analysis of the pulsatile plasma profile showed a trend ($P = 0.06$) for a lower mean basal plasma GH concentration and a lower mean AUC_0 for GH 1 week after the last aglépristone treatment compared with these values before aglépristone administration. Three and a half and 5.5 weeks after the last aglépristone administration the mean plasma IGF-I concentration increased again.

In conclusion, aglépristone can be used successfully to treat dogs with progestin-induced hypersomatotropism.

Keywords: Acromegaly; Hypersomatotropism; Insulin-like growth factor-I; Medroxyprogesterone acetate; Progesterone receptor blocker

1. Introduction

Acromegaly is characterized by bony and soft tissue overgrowth due to excessive growth hormone (GH) secretion. The syndrome is known to occur in humans, dogs, and cats. However, the pathogenesis differs among these species. Acromegaly in humans and cats is commonly caused by a somatotroph adenoma of the pituitary gland [1], whereas in dogs the GH excess usually originates from an extra-pituitary site [2]. In dogs, endogenous progesterone secreted during the luteal phase of the estrous cycle or exogenous progestins such as medroxyprogesterone acetate (MPA) used for estrus prevention may promote

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hypersecretion of GH from foci of hyperplastic ductular epithelium of the mammary gland [2–4]. In contrast to the pulsatile secretion pattern of GH in healthy dogs [5–7], the plasma GH profile in bitches with progestin-induced acromegaly is not pulsatile [8]. In addition, progestin-induced GH hypersecretion cannot be stimulated with GH-releasing hormone (GHRH) and α-adrenergic agonists, nor can it be inhibited by somatostatin [8,9]. The progestin-induced increase in plasma GH concentrations are associated with increased plasma concentrations of insulin-like growth factor-I (IGF-I) [2].

The physical changes of progestin-related hypersomatotropism in dogs tend to develop gradually and consist of prominent skin folds, abdominal distension, and widening of the interdental spaces [10]. Due to the insulin-antagonistic action of GH, hyperglycemia and eventually diabetes mellitus may occur [11]. Ovariectomy is the treatment of choice in female dogs with spontaneous progesterone-induced acromegaly. Plasma GH concentrations rapidly return to normal after ovariohysterectomy [12]. However, in dogs with acromegaly due to progestin administration the detrimental effects of the depot progestins may continue for a long time after cessation of administration [10,13].

Progesterone receptor blockers such as aglépristone (RU 46534) and mifepristone (RU 38486) are competitive antagonists of the progesterone receptor [14,15]. Aglépristone is the first progesterone receptor blocker licensed for veterinary use and has been used efficiently to terminate pregnancy [16,17] and to induce parturition [18]. Furthermore, it is successfully used for the treatment of fibroadenomatous mammary hyperplasia in cats [19–21] and may be a useful adjunct in the medical treatment of endometritis and pyometra in the dog [22].

The presence of progesterone receptors in mammary gland tissue of dogs [23] allows for a targeted endocrine therapy with progesterone receptor blockers in dogs with progestin-induced hypersomatotropism. The aim of this study was therefore to investigate whether the progesterone receptor antagonist aglépristone can be used to treat canine acromegaly.

2. Materials and methods

2.1. Dogs

Five intact Beagle bitches were housed with outdoor access, fed on a commercial dog food once a day, and given water ad libitum. The ages and body weights of the dogs ranged from 3 to 9 years (mean 5 years) and 9.0 to 10.3 kg (mean 9.5 kg), respectively. The dogs were accustomed to the laboratory environment and procedures such as collection of blood samples.

2.2. Treatments

The five Beagle bitches were treated with the synthetic progestin depot preparation Depo-Promone® (medroxyprogesterone acetate (MPA), Pharmacia Animal Health, Puurs, Belgium). MPA treatment was started during anestrus and consisted of subcutaneous injections in a dosage of 10 mg/kg body weight at 4-week intervals for a total of 14 (three dogs) or 15 (two dogs) administrations.

Five (=day 0) and six days (=day 1) after the last MPA administration (=day −5), aglépristone (Alizin®, Virbac Animal Health, Barneveld, The Netherlands) was administered subcutaneously in a dosage of 10 mg/kg body weight. One (=day 8), two (=day 15), and three (=day 22) weeks later a single aglépristone treatment was given in the same dose. Three randomly chosen dogs received the first aglépristone treatment after the 14th MPA administration, and the other two dogs after the 15th MPA administration so that these two dogs could serve as control dogs for the three dogs that received the aglépristone treatment first.

2.3. Blood sample collection

Blood samples for determination of the plasma progesterone concentrations were collected 5 and 12 months after the start of the MPA treatment.

Blood samples for determination of the plasma concentrations of GH and IGF-I were collected before MPA treatment, at days −9, −8, −7, −5, −3, −2, −1, and 0 (=immediately before aglépristone treatment and after MPA treatment for over 1 year), at days 1, 3, 5, 7, 8, 11, 13, 15, 18, 20, 22, and 25 (=during aglépristone treatment), and at days 46 and 60 (=3.5 and 5.5 weeks after the last aglépristone treatment). On days of treatment (MPA or aglépristone), blood samples were collected prior to the drug administration.

Blood samples for determination of the pulsatile plasma profiles of GH were collected at 15-min intervals between 08:00 and 14:00 h before MPA administration, before aglépristone administration, and 1 week after the last administration of aglépristone (at day 28).

All blood samples were collected by jugular venipuncture after an overnight fast, immediately transferred to ice-chilled EDTA-coated tubes and centrifuged at 4 °C for 10 min. Plasma was stored at −25 °C until assayed.

2.4. Assays

Plasma progesterone concentrations were determined with a previously validated radioimmunoassay (RIA) [24]. The intra-assay and inter-assay coefficients of variation were 8.8 and 7.1%, respectively. The sensitivity of the assay was 0.005 ng/L.

Plasma GH concentrations were measured using a commercially available RIA for porcine and canine GH (PGH-46HK; Linco Research, St. Charles, MS). The intra-assay coefficient of variation was 7.6% at a plasma concentration of 4.4 μg/L. The sensitivity of the assay was 1 μg/L.

Total plasma IGF-I was measured after acid–ethanol extraction to remove interfering IGF binding proteins. Plasma IGF was extracted using a mixture of 87.5% (v/v) ethanol and 12.5% 2 M formic acid. Tubes containing 100 μL plasma and 400 μL of the ethanol–formic acid mixture were mixed thoroughly and incubated for 30 min at room temperature. After centrifugation for 30 min at 5500 × *g* at 4 °C, a 50 μL aliquot of the supernatant was diluted 1:50 with assay buffer containing 63 mM Na_2HPO_4 (pH 7.4), 13 mM Na_2EDTA, and 0.25% (w/v) BSA. The extraction efficiency amounted to 92.5 ± 5.7%. IGF-I concentrations were measured in a heterologous RIA validated for the dog [25]. The intra-assay coefficient of variation was 8.6% at a plasma concentration of 100 μg/L. The sensitivity of the assay was 10 μg/L. IGF-I antiserum AFP4892898 and human IGF-I for iodination were obtained from the National Hormone and Peptide Program (Harbor-UCLA Medical Center, Torrance, CA).

2.5. Data processing and statistical analysis

To study the effect of MPA administration, the plasma GH and IGF-I concentrations before and after MPA treatment were compared using a mixed model with dog as random effect and period (two levels: before and after MPA treatment) as categorical fixed effect.

In order to assess the overall effect of aglépristone on the plasma GH and IGF-I concentrations, a mixed model was fitted with dog as random effect and period (three levels: immediately before aglépristone, during aglépristone, and 3.5 and 5.5 weeks after the last aglépristone treatment) as categorical fixed effect. The three periods were compared pair wise using Tukey's multiple comparisons technique.

To study the evolution of the GH and IGF-I concentrations during the aglépristone period, a mixed model was fitted with dog as random effect and time since start of aglépristone treatment as continuous fixed effect at a global significance level of 5%.

The plasma GH and IGF-I concentrations before MPA treatment were compared with the concentrations 3 days after the last aglépristone treatment (i.e. at day 25) using a mixed model with dog as random effect and period (two levels: before MPA treatment and 3 days after the last aglépristone treatment) as categorical fixed effect.

To evaluate the effect of withdrawal of aglépristone treatment, the two last measurements during aglépristone treatment (days 22 and 25) were compared with the two measurements after aglépristone treatment (days 46 and 60) using a mixed model with dog as random effect and period (two levels: days 22 and 25, and days 46 and 60) as categorical fixed effect.

The 6-h plasma profiles of GH were analyzed by means of the Pulsar program developed by Merriam and Wachter [26]. The program identifies secretory peaks by height and duration from a smoothed baseline, using the assay SD as a scale factor. The cut-off parameters G1–G5 of the Pulsar program were set at 3.98, 2.40, 1.68, 1.24, and 0.93 times the assay SD as criteria for accepting peaks 1, 2, 3, 4, and 5 points wide, respectively. The smoothing time, a window used to calculate a running mean value omitting peaks, was set at 5 h. The splitting cut-off parameter was set at 0.5 and the weight assigned to peaks was 0.05. The *A*-, *B*-, and *C*-values of the Pulsar program, used to calculate the variance of the assay, were set at $A = 0$, $B = 7.2$, and $C = 5$. The values extracted from the Pulsar analysis included the mean of the smoothed baseline, the pulse frequency, and the area under the curve (AUC). The AUC for GH was calculated above the zero-level (AUC_0) as well as above the baseline (AUC_{base}). The difference in variables before MPA treatment, before aglépristone administration, and 1 week after the last aglépristone treatment (i.e. at day 28) were analyzed by the signed rank test with dog as block.

All values are expressed as mean ± S.E.M. or median. Statistical significance was defined at $P \leq 0.05$. Analyses were performed with SAS Version 9.1 for Windows (Insightful Corp., Seattle, USA).

2.6. Ethics of the study

This study was approved by the Ethics Committee of the Faculty of Veterinary Medicine, Ghent University.

3. Results

During MPA administration none of the dogs showed signs of estrus and the mean plasma progesterone

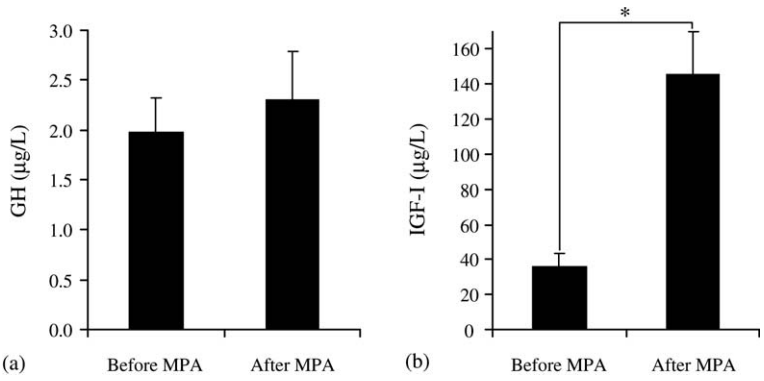

Fig. 1. Mean (±S.E.M.) plasma concentrations of GH (a) and IGF-I (b) in five Beagle dogs before administration of MPA (before MPA) and after 1 year treatment with MPA (after MPA). Significant differences between periods are indicated with an asterisk.

concentration was low 5 months (0.2 ± 0.2 ng/L) and 12 months (0.2 ± 0.1 ng/L) after the start of the MPA treatment. The mean body weight of the dogs on the day of the last administration of MPA (12.4 ± 0.7 kg) was significantly higher ($P < 0.02$) than that on the day of the first MPA administration (9.5 ± 0.3 kg) (paired Student's *t*-test). Signs of acromegaly became apparent in three of the five dogs after 6 months of MPA treatment and consisted of prominent skin folds especially on the head, an increase in the interdental spaces, inspiratory stridor, and snoring.

MPA administration for over 1 year resulted in a higher mean plasma GH concentration (2.3 ± 0.5 μg/L) compared to that before MPA treatment (1.9 ± 0.3 μg/L), although this difference did not reach statistical significance (Fig. 1a). However, the mean plasma IGF-I concentration after 1 year of MPA administration (146 ± 25 μg/L) was significantly ($P = 0.003$) higher compared to that before MPA treatment (36 ± 6 μg/L) (Fig. 1b). Analysis of the pulsatile plasma GH profiles after 1 year of MPA administration revealed a trend ($P = 0.06$) for a higher mean basal plasma GH concentration and a higher mean AUC_0 for GH compared to these values before MPA treatment (Table 1; Fig. 2).

The administration of aglépristone caused no side effects except a short-term skin irritation at the site of the injection in one dog. The mean plasma GH concentration immediately before aglépristone administration (2.3 ± 0.5 μg/L) was significantly higher than that during (1.7 ± 0.3 μg/L; $P < 0.0001$) and 3.5 and 5.5 weeks after (1.8 ± 0.3 μg/L; $P = 0.018$) the last administration of aglépristone (Fig. 3a). Also the mean plasma IGF-I concentration immediately before aglépristone administration (146 ± 25 μg/L) was significantly higher than that during (108 ± 27 μg/L; $P < 0.0001$) administration of aglépristone (Fig. 3b). In the weeks when aglépristone was administered, analysis of the course of the circulating hormone concentrations indicated a significant decrease in plasma GH ($P = 0.005$) and IGF-I ($P < 0.0001$) concentrations (Fig. 4a and b, respectively).

The plasma GH and IGF-I concentrations before MPA treatment did not differ significantly from these concentrations 3 days after the last aglépristone treatment (i.e. day 25).

Analysis of the pulsatile plasma GH profiles revealed a trend ($P = 0.06$) for a lower mean basal plasma GH concentration and a lower mean AUC_0 for GH 1 week after the last aglépristone administration (i.e. day 28) compared with these concentrations before aglépristone treatment. The AUC_{base} for GH increased again after the last aglépristone treatment compared with this concentration before aglépristone administration, although

Table 1
Area under the curve for GH above the baseline (AUC_{base}) (μg/L × 6 h), AUC for GH above the zero-level (AUC_0) (μg/L × 6 h), GH pulse frequency (peaks per 6 h), and basal plasma GH concentration (μg/L) in five Beagle dogs before MPA administration (before MPA), after 1 year of MPA administration (=before aglépristone administration) (before A), and 1 week after the last aglépristone administration (after A)

	AUC_{base} (mean ± S.E.M.)	AUC_0 (mean ± S.E.M.)	GH pulse frequency (median)	Basal GH (mean ± S.E.M.)
Before MPA	1 ± 0.4	11.3 ± 1.1	1	1.7 ± 0.1
Before A	0 ± 0.0	17.0 ± 3.6	0	2.8 ± 0.6
After A	0.3 ± 0.2	8.8 ± 0.7	0	1.4 ± 0.1

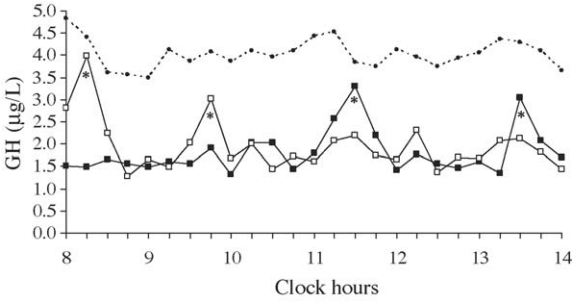

Fig. 2. The plasma profiles of GH in a 4-year-old Beagle bitch. Blood samples were collected at 15-min intervals between 08:00 and 14:00 h, before MPA administration (□), after 1 year of MPA administration (=before aglépristone administration) (dotted line), and 1 week after the last aglépristone treatment (■). Significant pulses, calculated by the Pulsar program, are indicated by an asterisk.

this difference did not reveal statistical significance (Table 1; Fig. 2).

The mean plasma GH concentration at the end of the period of aglépristone administration (i.e. days 22 and 25) (1.5 ± 0.1 μg/L) did not differ significantly from that at 3.5 and 5.5 weeks (i.e. days 46 and 60) after withdrawal of aglépristone (1.8 ± 0.3 μg/L). However, the mean plasma IGF-I concentration at the end of the period of aglépristone administration (88 ± 22 μg/L) was significantly ($P < 0.0001$) lower compared with that 3.5 and 5.5 weeks after withdrawal of aglépristone (124 ± 29 μg/L).

In the two control dogs that did not receive aglépristone after the 14th MPA administration, the mean plasma concentrations of GH and IGF-I before the 14th administration of MPA (1.6 ± 0.1 and 105 ± 28 μg/L, respectively) were not different from those before the 15th administration of MPA (1.7 ± 0.1 and 116 ± 26 μg/L, respectively).

4. Discussion

In three of the five Beagle dogs, signs of acromegaly became apparent after 6 months of MPA administration. In line with these changes, the mean plasma IGF-I concentrations were raised. Moreover, analysis of the pulsatile plasma profile showed a trend for a higher mean basal GH concentration and a higher mean AUC_0 for GH in the five Beagle dogs. These findings are consistent with progestin-induced hypersecretion of GH [3,27–29].

Previous studies identified foci of hyperplastic ductular epithelium of the mammary gland as the site of origin of GH excess induced by progestins [2,4]. The expression of the gene encoding GH has been

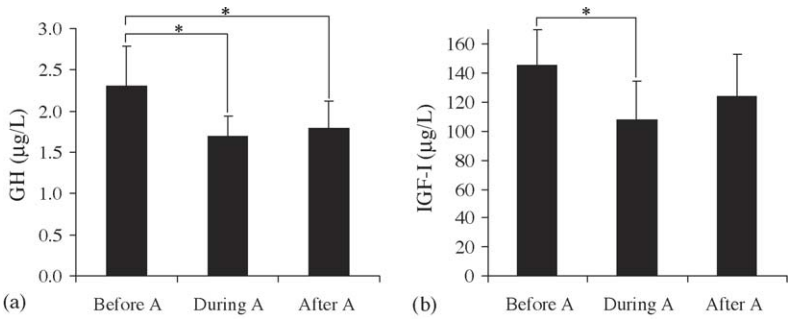

Fig. 3. Mean (±S.E.M.) plasma concentrations of GH (a) and IGF-I (b) in five Beagle dogs immediately before aglépristone (before A), during aglépristone (during A), and 3.5 and 5.5 weeks after the last aglépristone administration (after A). Significant differences between periods are indicated with an asterisk.

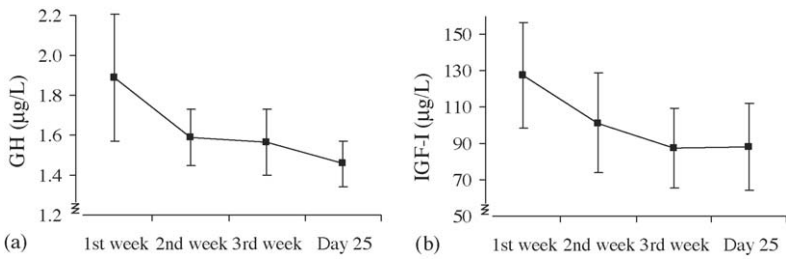

Fig. 4. Mean (±S.E.M.) plasma concentrations of GH (a) and IGF-I (b) in five Beagle dogs at 1 week, 2 weeks, 3 weeks, and at day 25 during aglépristone administration.

demonstrated in canine mammary gland tissue, and sequence analysis has revealed that this gene is identical to the pituitary GH gene [30,31]. Immunohistochemical studies have demonstrated the intracellular co-localization of both the progesterone receptor and GH in progestin-exposed, hyperplastic canine mammary epithelial tissue, whereas immunoreactive GH could not be demonstrated in progesterone receptor-negative epithelial cells [23]. These observations are consistent with the central role of progestins in GH gene expression in the canine mammary gland and allow for a targeted endocrine therapy with progesterone receptor blockers in dogs with progestin-induced mammary-derived GH hypersecretion.

To the authors' knowledge, treatment of acromegalic dogs with the progesterone receptor antagonist aglépristone (RU 46534) has not been reported before. The results of the present study demonstrate that progestin-induced elevations in circulating GH and IGF-I concentrations decrease significantly during treatment with aglépristone. At the end of the aglépristone treatment period the plasma GH and IGF-I concentrations did not differ significantly from those before MPA administration. Our findings are in agreement with those of Watson et al. [8] who found that administration of the antiprogestin mifepristone (RU 38486) resulted in a decrease of plasma GH concentrations and normalization of plasma IGF-I concentrations in bitches with progestin-induced acromegaly.

The mean basal plasma concentrations of GH and IGF-I in the two control dogs that did not receive aglépristone after the 14th MPA administration remained high and did not decrease. This indicates that indeed aglépristone is responsible for the lowering of the plasma GH and IGF-I concentrations in the dogs treated with the progesterone receptor blocker, and that this lowering is not due to, for example, a waning effect of MPA on GH and IGF-I secretion.

The 6-h pulsatile plasma profile of GH represents a more sensitive way of analyzing the effects of different treatments on the secretion of GH than the plasma GH concentration itself. Analysis of the plasma GH profiles revealed that the mean basal plasma GH concentration and AUC_0 for GH tended to decrease at the end of the treatment with the progesterone receptor blocker compared with these values before aglépristone administration. In addition, the AUC_{base} for GH, i.e., the amount of GH secreted in pulses, increased again during aglépristone treatment, although this difference did not reveal statistical significance. Thus, treatment with aglépristone resulted in partial restoration of the normal pulsatile GH secretion. Higher dosages of aglépristone may result in complete normalization of the secretion pattern of GH.

Plasma IGF-I concentrations are generally regarded as more sensitive indicators of the GH status than plasma GH concentrations [32]. Consequently, the significantly higher plasma IGF-I concentrations at days 46 and 60 compared with those at days 22 and 25 therefore suggest increased GH exposure, despite the fact that analysis of the plasma GH concentrations did not reveal a significant increase. The recurrence of IGF-I hypersecretion after withdrawal of aglépristone treatment is not surprising as all dogs received a depot progestin preparation for a period of 1 year, and the progestin effect of this depot preparation is much longer than the duration of aglépristone treatment in the present study. Similarly, in a cat with fibroadenomatous mammary hyperplasia due to treatment with a depot progestin preparation hyperplasia recurred 8 days after discontinuation of aglépristone administration [19]. This indicates that treatment with an antiprogestin is required as long as the action of the synthetic progestin is present. Also in our three dogs with acromegalic signs, no physical changes were visible during or after treatment with aglépristone.

Due to the insulin-antagonistic action of GH, progestin-induced hypersecretion of GH may also result in hyperglycemia and eventually manifest diabetes mellitus may ensue [11,29]. Disappearance of these catabolic abnormalities depends on the functional status of the pancreatic β-cells. If an adequate population of functional β-cells is present at the time the progestin effect is blocked, hyperinsulinemia, carbohydrate intolerance, and hyperglycemia may be reversible after correction of the hypersomatotropism [13]. If the population of functional β-cells is severely decreased, permanent diabetes mellitus can be anticipated. Because the effects of depot progestins may persist for several months, prevention or reversal of the catabolic effects of progestin-induced GH excess is especially important when, in case of hyperglycemia, the depot progestin has been administered only recently. The results of the present study illustrate that in these cases aglépristone offers an effective treatment option.

In conclusion, administration of aglépristone significantly decreases plasma GH and IGF-I concentrations in dogs with progestin-induced hypersomatotropism.

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