

Topical Review

Treatment of Canine Pyometra With the Gonadotropin-Releasing Hormone Antagonist Acyline: A Case Series

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To describe the effect of the third-generation gonadotropin-releasing hormone antagonist acyline in the treatment of 4 diestrous bitches with the cystic endometrial hyperplasia-pyometra complex. The 4 bitches were treated with 330 µg/kg of subcutaneous acyline on day 0 and antibiotics, and followed up for 2 weeks. One closed-cervix case showed cervical dilatation 36 hours after treatment, and all the 4 animals showed resolution of clinical signs starting on day 3 posttreatment. Ultrasonographic uterine diameters and luminal contents decreased in the bitches having high progesterone serum concentrations before treatment but not in those with low levels. Serum progesterone importantly decreased from high to basal concentrations in the 3 “ultrasonographically cured” animals. No local or systemic side effects related to the treatment were observed. The gonadotropin-releasing hormone antagonist acyline may have a promising place for the medical treatment of cystic endometrial hyperplasia-pyometra complex in dogs.

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Introduction

Cystic endometrial hyperplasia-pyometra complex (CEH-P) is the most common uterine disorder of intact bitches. Pathophysiology of CEH-P includes bacterial infection of an endometrium that is under the influence of progesterone. Unlike most other female mammals, the bitch secretes ovarian progesterone for approximately 60–70 days after ovulation (diestrus) irrespective of whether she is pregnant. Progesterone secretion is maintained by secretion of the hypothalamic peptide gonadotropin-releasing hormone (GnRH).¹ Bitches with CEH-P may be classified as having a closed cervix (accumulation of purulent material in the uterus without a purulent vulvar discharge) or open cervix (presence of a purulent vulvar discharge). CEH-P can be a life-threatening condition that must be managed expeditiously. Treatment of CEH-P in most bitches includes ovariohysterectomy; however, medical treatment is desirable for bitches intended for breeding.²

Peptide analogues of GnRH are used in a variety of clinical applications for suppression of the reproductive endocrine axis in both humans^{3,4} and dogs.⁵ GnRH antagonists bind to and block gonadotropin GnRH receptors from binding to endogenous GnRH, thereby suppressing the pituitary-gonadal axis.⁶ Acyline is a potent and safe third-generation GnRH antagonist which, in dogs, has been shown to rapidly decrease gonadotropins and (male) testosterone for 9 days after a single subcutaneous administration.⁷ No hematologic, serum biochemical, local, or systemic side effects have been attributed to acyline treatment in the dog.⁸

When acyline was administered to bitches in midpregnancy, gestations were terminated after a mean of 6 days and serum

progesterone concentrations decreased to basal levels (< 1 ng/mL).

Rate of progesterone decrease varied among animals and was temporally related to abortion when serum progesterone reached basal.⁹ GnRH antagonists have not been reported for use in the treatment of progesterone-dependent CEH-P; the objective of this report is to describe the effect of acyline in the treatment of 4 cases of CEH-P in the female dog.

Clinical Cases*Patients*

Four purebred diestrous bitches (Table 1) diagnosed with CEH-P were referred to our service. Uterine enlargement was confirmed by ultrasonography in all of the cases (Day 0).¹⁰ The bitches were slightly febrile and dehydrated and had decreased appetite. Mean serum urea and creatinine concentrations for all of the bitches were < 60 mg/dL and 1.5 mg/dL, respectively, after rehydration. This medical trial to decrease serum progesterone with acyline was approved by the Institutional Animal Care and Use Committee of the University of La Plata, and consent forms were signed by all of the owners.

Treatment Protocol

After the diagnoses were confirmed and uterine measures taken (described later), the bitches were treated with 330 µg/kg of subcutaneous acyline (Day 0). Acyline was provided in a

Table 1
Signalment of Bitches With Cystic Endometrial Hyperplasia-Pyometra Complex Treated With Acyline

Bitch Breed	Age (y)	Body Weight (kg)	Time After Estrus (d)	Cervix ^a
Miniature Poodle	7	7.3	26	Closed
Shar-pei	6	18	15	Open
Canary Dog	2	37	33	Open
Giant Schnauzer	8	39	66	Open

* Open: purulent vulvar discharge. Closed: no vulvar discharge.

lyophilized powder that was suspended in sterile distilled water at a concentration of 2 mg/mL. The dosage was selected based on a previous report.⁹ Amoxicillin-clavulanate administered twice a day at 12.5 mg/kg orally (Clavamox, Pfizer, Argentina) was administered for 7 days, and rehydration was accomplished in the first 24 hours.

Follow-Up

On day 0 (before treatment) and day 7, blood samples were collected for serum progesterone determination by electrochemiluminescence immunoassays (Elecys Progesterone II, Roche Diagnostics, Mannheim, Germany).

On days 3, 7, and 14 following treatment, the bitches were clinically and ultrasonographically evaluated. Clinical examination included body temperature, hydration, presence of vulvar discharge if any, and appearance of clinical local or systemic side effects. Total external and luminal maximal uterine diameters were measured by transabdominal ultrasonography (Toshiba Core Vision Pro, Shimoishigami, Otawara-Shi, Tochigi-Ken, Japan) using an 8-MHz linear-array transducer.¹⁰ For imaging, the bitches were positioned in lateral recumbency and the ventral abdomen shaved. Acoustic gel was applied to the transducer and coupled directly to the skin. Additionally, 2-dimensional ultrasound was used to identify the uterine body in a transverse axis.

Outcome of the Clinical Cases

The Miniature Poodle (closed cervix, Table 1) showed cervical dilatation 36 hours after treatment, as evidenced by a heavy purulent vulvar discharge. By day 3, all 4 animals were afebrile and hydrated and had normal appetite. Vulvar discharges were copious in the Miniature Poodle, Shar-pei, and Canary Dog and mild in the Giant Schnauzer. Uterine diameters and luminal contents importantly decreased throughout the trial in the in the first 3 bitches but not in the Giant Schnauzer (Table 2). Serum progesterone levels importantly decreased from high to basal concentrations in the 3 “ultrasonographically cured” bitches (Table 2). On days 7 and 14, all 4 bitches appeared clinically healthy and had no vulvar discharge. The Giant Schnauzer bitch was ovariectomized immediately after ultrasound on day 14. No local or systemic side effects related to the treatment were observed in any of the bitches at any time during the follow-up period.

Discussion

In women, third-generation GnRH antagonists have been shown to be useful in the medical management of nonmalignant uterine conditions such as endometriosis and uterine fibroids.^{3,4} If treatment success is defined as uterine diameter within normal limits and absence of luminal fluids in the ultrasound examination of clinically healthy bitches, the response to this treatment

Table 2
Ultrasonographic and Hormonal Data in Four Bitches With CEH-P After Acyline Treatment

Bitch	Day	Uterine Diameter (mm)	Uterine Luminal Diameter (mm)	Serum Progesterone (ng/mL)
Miniature Poodle	0	46.2	35	22.1
	3	20.6	10	
	7	15.8	3	1.5
	14	13.6	3	
Shar-pei	0	46.3	36.5	18.5
	3	21.1	12.1	
	7	16.3	2.9	3.5
	14	15.6	1.3	
Canary Dog	0	28	22	25.2
	3	21.5	3	
	7	16.5	2	1.7
	14	14.9	2	
Giant Schnauzer	0	67	49	3
	3	54.6	43	
	7	63	51	2
	14	65.1	55	

appeared to vary with progesterone concentrations when treatment was administered. Canine luteal function is known to be independent of gonadotropins during the early luteal phase, whereas corpora lutea depends on luteotrophic hormones as diestrus progresses. Serum progesterone concentrations decrease to basal levels by approximately day 75 when anestrus commences.¹

In the late diestrus Giant Schnauzer, serum progesterone concentration was already low at treatment onset and treatment did not appear to reverse the already established pathologic condition. Conversely, the other 3 bitches treated during high progesteronemia, showed decrease in uterine diameters by approximately 50% a week after a single acyline administration. In the Miniature Poodle, the cervix opened in 36 hours, causing a dramatic improvement in the patient's condition. No adverse effects were observed in association with the acyline treatment.

These results contribute to the understanding of the role of the gonadotropin, luteinizing hormone, in maintaining the mid-diestrus canine corpus luteum. Similar findings previously were reported in pregnant (days 25–35¹; day 30 onward¹¹); and non-pregnant¹² diestrus bitches using second- and third-generation GnRH antagonists.

GnRH antagonists may have promise in the medical treatment of the CEH-P complex in high progesterone bitches. This report provides preliminary data for further studies that may define the window of efficacy, effect on CEH, and future fertility and recurrence rate, if any, before GnRH antagonists can be recommended for this hormone-dependent uterine condition of female dogs.

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References

1. Concannon PW. Endocrinologic control of normal canine ovarian function. *Reprod Domest Anim* **44**:3–15, 2009
2. Smith FO. Canine pyometra. *Theriogenology* **66**:610–612, 2006
3. K pker W, Felberbaum RE, Krapp M, et al. Use of GnRH antagonists in the treatment of endometriosis. *Reprod Biomed Online* **5**:12–16, 2002
4. Britten JL, Malik M, Levy G, et al. Gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate and GnRH antagonist cetrorelix acetate directly inhibit leiomyoma extracellular matrix production. *Fertil Steril* **98**:1299–1307, 2012
5. Gobello C. New GnRH analogs in canine reproduction. *Anim Reprod Sci* **100**:1–13, 2007
6. Gobello C. Effects of GnRH antagonists vs. agonists in domestic carnivores. *Reprod Domest Anim* **47**:373–376, 2012
7. Garc a Romero G, Valiente C, Aquilano D, et al. Endocrine effects of the GnRH antagonist, acyline, in domestic dogs. *Theriogenology* **71**:1234–1237, 2009
8. Valiente C, Corrada Y, De La Sota PE, et al. Effect of the GnRH antagonist, acyline, on canine testicular characteristics. *Theriogenology* **68**:687–692, 2007
9. Valiente C, Corrada Y, De La Sota PE, et al. Comparison of two doses of the GnRH antagonist, acyline, for pregnancy termination in bitches. *Reprod Domest Anim* **44**:156–159, 2009 (suppl)
10. Yeager AE, Concannon P. Ultrasonography of the reproductive tract of the female dog and cat. In: Bonagura JD, Kirk KW, editors. *Current Veterinary Therapy XII*. Philadelphia: W.B. Saunders; 1995. p. 1040–1052
11. Vickery BH, Mcrae GI, Goodpasture JC, et al. Use of potent LHRH analogues for chronic contraception and pregnancy termination in dogs. *J Reprod Fertil Suppl* **39**:175–187, 1989
12. Vickery BH, Nestor JJ. LHRH analogues, development and mechanism of action. *Semin Reprod Endocrinol* **5**:353–570, 1987