Evaluation of the effects of a 4.7-mg deslorelin acetate implant on egg laying in cockatiels (Nymphicus hollandicus)

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OBJECTIVE  
To evaluate effects of administration of a 4.7-mg deslorelin acetate implant on egg laying in healthy cockatiels (Nymphicus hollandicus).

ANIMALS  
52 cockatiels.

PROCEDURES  
26 breeding pairs (a female and its respective male in each pair) were selected on the basis of their history of egg laying. Female birds were sedated and received a 4.7-mg deslorelin acetate implant (n = 13) or placebo implant (13) in the subcutaneous tissues between the scapulae. Male and female birds of each breeding pair were placed in separate but adjacent cages. Birds were exposed to 16 hours of light and 8 hours of darkness. A nest box was placed in cages of female birds to stimulate reproductive activity. Egg production and quality were monitored daily for 365 days.

RESULTS  
Deslorelin acetate implants significantly suppressed egg laying in cockatiels, compared with effects for the placebo implants. Eleven of 13 placebo-implanted birds laid eggs between 12 and 42 days after implantation. None of the deslorelin-implanted birds laid eggs within 180 days after implantation, and only 5 of 13 deslorelin-implanted birds laid an egg during the study period (first egg laid between 192 and 230 days after implantation). No differences in egg quality or number of eggs per clutch were observed between the 2 groups.

CONCLUSIONS AND CLINICAL RELEVANCE  
Insertion of a 4.7-mg deslorelin acetate implant suppressed egg laying in healthy cockatiels for at least 180 days. Studies are necessary to evaluate effects of a deslorelin acetate implant in other avian species or in association with reproductive disorders. (Am J Vet Res 2017;78:745–751)

Reproductive disorders are one of the most commonly diagnosed conditions in companion birds. These disorders include chronic egg laying, dystocia, ovarian and oviductal degenerative diseases, infections, and neoplasia as well as behavioral problems such as chronic feather-damaging behavior, aggression, or hypersexuality. Avian reproductive disorders can be treated medically and surgically. Surgical treatment may be recommended for dystocia, recurrent cloacal prolapse secondary to hypersexuality, neoplasia, or ovarian cysts. However, salpingo-hysterectomy is a technically difficult procedure, especially in small birds, and it can be associated with high morbidity and mortality rates. Thus, medical management is often preferred. The GnRH-receptor agonists are becoming the treatment of choice for medical management of chronic egg laying and chronic hypersexuality and have been reported anecdotally for the management of ovarian cysts and ovarian neoplasia in avian species.

The GnRH-receptor agonists have a wide range of applications in human and veterinary medicine for use in medically assisted procreation protocols and for sex hormone-related disorders (prostate cancer, mammary gland tumors, and endometriosis) in humans. They act through a 2-step mechanism. First, the pituitary gland is stimulated, which causes a marked increase in release of LH and follicle-stimulating hormone. This results in an initial increase of plasma sex hormone concentrations from the gonads. Continuous stimulation of the pituitary gland by GnRH-receptor agonists causes desensitization by internalization of GnRH receptors, which decreases release of follicle-stimulating hormone and LH and lowers plasma sex hormone concentrations.

In birds, GnRH-receptor agonists such as leupro-lide acetate and deslorelin acetate have become the treatments of choice for reproductive disorders.
prolide acetate, a synthetic GnRH-receptor agonist, has been widely used for the medical management of chronic egg laying, dystocia, ovarian cysts, and even ovarian adenocarcinoma. This drug is available as a depot formulation for humans. Investigators of a study of Hispaniolan Amazon parrots (Amazona ventralis) reported a decrease in fecal and plasma sex hormones for only 2 weeks after administration of a single dose (800 µg/kg). In another study, leuprolide acetate inhibited egg laying in cockatiels from 12 to 19 days after administration. Dose, frequency, and duration of treatment may differ among patients, which can represent financial and time constraints for owners and be a source of stress for birds because of frequent veterinary visits and restraint for injection.

Deslorelin acetate is available as controlled-release implants (4.7 or 9.4 mg) for SC administration and is commercially available for use in ferrets (Mustela putorius furo) in the United States. Although this product cannot be used in an extralabel manner in other species, it is available in other regions (eg, Europe, Australia, and New Zealand). It was originally designed for use as an ovulation-inducing agent in mares. In dogs, contraceptive effects last approximately 6 months for the 4.7-mg implants and 12 months for the 9.7-mg implants. Deslorelin acetate has also been administered to several other mammalian species, including horses, ferrets, domestic cats, nondomestic cats, rats (Rattus norvegicus), flying foxes (Pteropus spp), eastern grey kangaroos (Macropus giganteus), tammar wallabies (Macropus eugenii), sea otters (Enhydra lutris), red pandas (Ailurus fulgens), and boars (Sus scrofa).

There is an increasing amount of information on the use of deslorelin acetate implants in birds, In a recent study of female Japanese quail (Coturnix coturnix japonica), one 4.7-mg deslorelin acetate implant prevented egg laying in 6 of 10 quail for approximately 70 days. In another recent study of female Japanese quail, two 4.7-mg implants halted egg production in 7 of 10 quail for 100 days, and the 9.4-mg implant halted egg production in 7 of 10 quail for at least 182 days. Female pigeons implanted with a 4.7-mg deslorelin implant laid significantly fewer eggs than did pigeons in the control group and did not produce any eggs for at least 49 days after implantation. In chickens (Gallus gallus), 4.7- and 9.4-mg deslorelin implants inhibited egg laying for 180 days (range, 125 to 237 days) and 319 days (range, 229 to 357 days), respectively. Anecdotally, deslorelin implants have been used in several avian species to decrease egg production, dystocia, cloacal and oviductal prolapse, ovarian neoplasia, metabolic bone disorders secondary to hyperestrogenism, hyperlipidemia, feather-damaging behavior, self-mutilation, recurrent dermatitis, and aggression. Substantial variability among species and individual birds has been described with the use of deslorelin implants in avian species; thus, it is challenging to make direct extrapolations from one avian species to another. To our knowledge, no controlled study has been published on the use of deslorelin acetate in psittacine birds.

The objective of the study reported here was to evaluate the efficacy and duration of action of a 4.7-mg deslorelin acetate implant on egg laying in cockatiels (Nymphicus hollandicus). We hypothesized that a 4.7-mg deslorelin implant would stop egg laying in at least 80% of the implanted females and that effects would last approximately 120 days, as determined on the basis of previous anecdotal reports for cockatiels. Efficacy of a 4.7-mg deslorelin acetate implant in birds has been reported to range from 60% to 100%; therefore, we elected to use 80% as the mean of this range.

Materials and Methods

Birds

Thirty-seven breeding pairs of adult wild-phenotype cockatiels from a breeding flock were evaluated on the basis of their history of egg laying to determine possible pairs for use in the study. Each breeding pair was housed in the same cage and exposed to a constant photoperiod (16 hours of light and 8 hours of darkness) via standard lighting for 90 days. Birds were fed ad libitum a commercial diet formulated for cockatiels. A nest box with aspen wood shavings was provided for each breeding pair, and egg laying was monitored. Twenty-six females and their respective males were then selected for the study on the basis that there was no evidence of egg-laying abnormalities. Cockatiels ranged from 1 to 15 years of age, and body weight ranged from 80 to 131 g. Results of physical examination of the birds were unremarkable. The study was conducted at the University of California-Davis, and the study protocol was approved by the University of California-Davis Institutional Animal Care and Use Committee (No. 17910).

Study design

After the initial 90-day evaluation period was completed, the amount of light was decreased (12 hours of light and 12 hours of darkness), and nest boxes were removed for a second 90-day period in an attempt to stop egg laying. During this second 90-day period, the birds were simultaneously provided 2 diets (the original commercial diet and a custom-formulated diet based on corn, rice, and soybean protein that exceeded all nutrient requirements for growing or reproducing cockatiels) as part of a concurrent study (unpublished data). Male and female birds from each breeding pair were separated and placed individually in adjacent cages.

After the second 90-day period was completed, female cockatiels were randomly assigned by use of an automated computer software program to a control (n = 13) or treatment (13) group. The control group ranged from 2 to 11 years of age, and the deslorelin
Acetate group ranged from 2 to 13 years of age. Each female was sedated with midazolam (2 mg/kg) and butorphanol tartrate (1 mg/kg) administered IM in the pectoral muscle for implant placement. Females of the treatment and control groups received a 4.7-mg deslorelin acetate implant or placebo implant, respectively (day 0). Implants were inserted in the subcutaneous tissues between the scapulae by use of a disposable applicator syringe and sterile 14-gauge needle provided by the drug manufacturer. Deslorelin acetate and placebo implants were provided by the manufacturer, and each of the implants was from the same lot. The dose of deslorelin acetate ranged from 35.8 to 58.8 mg/kg. The skin was apposed and closed with tissue adhesive. Each female cockatiel received an injection of meloxicam (1 mg/kg, IM in the pectoral muscle) for pain management and flumazenil (0.05 mg/kg, IM in the pectoral muscle) to reverse the midazolam. All cockatiels recovered uneventfully from sedation.

The site of implant placement for each bird was evaluated the following day, and it was found that 3 females (2 in the control group and 1 in the treatment group) had removed the implant. These 3 birds were sedated as previously described, and a new implant was inserted. It was determined during recheck examinations that none of the birds subsequently removed their implants. Two days after implants were initially inserted in all 26 birds, a nest box was placed in the cage of each female, and the following day, the amount of light was increased (16 hours of light and 8 hours of darkness).

Egg production was monitored daily for 365 days. A 365-day period was chosen on the basis of anecdotal reports of cockatiels and companion birds of similar size for which investigators evaluated the duration of the effects of deslorelin acetate implants. Eggs were left in the nest box until a full clutch (from 3 to 11 eggs, depending on the bird) was laid. Shape, color, and shell quality of each egg was evaluated and recorded. Basic health assessments of all birds (observations of eating, drinking, and fecal production and consistency) were performed daily.

Statistical analysis
The Kaplan-Meier method was used to graphically determine time to commencement of egg laying in control and deslorelin acetate groups while accounting for censoring (ie, did not lay eggs by the end of the study period). A log-rank test was used to non-parametrically compare the 2 groups. A multivariable Cox proportional hazards regression model was used to estimate the incidence rate of egg laying between the 2 groups while controlling for bird age and cage position. Statistical analysis was performed by use of commercially available software. Values of \( P < 0.05 \) were considered significant.

Results
Transient mild cutaneous erythema was observed after implantation in the placebo and deslorelin acetate groups and resolved within 72 hours. No other effects were associated with implant placement.

All females maintained typical behavior and were healthy over the 1-year duration of the study, except for 2 birds. A 6-year-old female in the placebo group (laid 12 eggs beginning on day 7 after implantation) was euthanized at 317 days after implantation because of failure of medical management to resolve severe crop distension. Necropsy and histologic examination revealed a colloid goiter compressing the esophagus. A 2-year-old deslorelin acetate–treated female (laid no eggs) had a severe traumatic injury of the gnathotheca and was euthanized at 322 days after implantation. Necropsy results for the reproductive tract were unremarkable for both birds.

Deslorelin acetate implants significantly \( (P < 0.001) \) prevented egg laying in cockatiels, compared with effects of placebo implants (Figure 1). Of the 13 placebo-treated birds, 11 (age range, 2 to 11 years) laid eggs between 12 and 42 days (median, 19 days) after placebo implantation. The 2 placebo-treated birds that did not lay eggs were each 2 years old. None of 13 deslorelin acetate–treated birds laid eggs within the first 180 days after deslorelin acetate implantation, and only 5 deslorelin acetate–treated birds (age range, 2 to 6 years old) laid an egg during the study period (first egg laid between 192 and 230 days after implantation). The 8 deslorelin acetate–treated birds that did not lay an egg by day 365 ranged from 2 to 13 years of age.

Number of eggs laid per clutch did not differ significantly \( (P = 0.072) \) between the 2 groups. Median number of eggs per clutch for the 11 birds that laid eggs in the placebo group was 12 (range, 3 to 29), whereas the median number of eggs per clutch for the 5 birds that laid eggs in the deslorelin acetate group was 15 (range, 9 to 19). No differences in egg shape, color, or shell quality were observed between the placebo and deslorelin acetate groups. Age of bird did not significantly affect the number of eggs laid per clutch.

![Figure 1](image-url)
per clutch for the placebo (P = 0.056) or deslorelin acetate (P = 0.628) groups. Similarly, position and height of the bird cage did not significantly affect the number of eggs per clutch for the placebo (P = 0.118 and P = 0.915, respectively) or deslorelin acetate (P = 0.085 and P = 0.744, respectively) group. The difference in latency of egg laying between groups remained significant (P = 0.001) after correction for age and placement of the cage. Two deslorelin acetate–treated birds visited the nest box at > 180 days after deslorelin acetate implantation but did not lay any eggs during the study period.

**Discussion**

In the study reported here, a 4.7-mg deslorelin acetate implant significantly prevented egg laying in adult female cockatiels. None of the 13 females from the deslorelin acetate group laid eggs within 180 days after implantation, and only 5 of 13 deslorelin acetate–treated birds laid eggs during the study. Variable efficacy of deslorelin implants has been reported for avian species. In Japanese quail, 6 of 10 and 7 of 10 females ceased laying eggs after receiving 4.7 and 9.4 mg of deslorelin acetate, respectively. Administration of a 4.7-mg deslorelin implant to 10 pigeons and 20 chickens caused a complete cessation of egg production in all treated birds (49 to 65 days and 125 to 237 days after implantation, respectively). For the present study, it was hard to determine whether the absence of egg laying after administration of a deslorelin acetate implant was strictly attributable to a drug effect because only 11 of 13 control birds laid eggs during the same period. However, there was a significant effect of the 4.7-mg deslorelin acetate implant on egg laying in cockatiels for at least 180 days after implant placement.

Duration of the deslorelin acetate effect in the present study was longer than expected, as determined on the basis of anecdotal reports for cockatiels or birds of similar size. In 1 case report, an ovarian adenocarcinoma in a 13-year-old cockatiel was successfully managed for approximately 4 months by use of a 4.7-mg deslorelin acetate implant. Effects of 4.7-mg deslorelin implants reportedly lasted for approximately 70 days in Japanese quail, 5 weeks in pigeons, 6 weeks in mallard ducks (*Anas platyrhynchos*), 4 to 5 months in cockatiels, 6 months in chickens, 9 months in budgerigars (*Melopsittacus undulatus*), and 10 months in a sun conure. Doses of deslorelin used in the study reported here ranged from 35.8 to 58.8 mg/kg because of variation in body weight among females of the treatment group. These doses are higher than those reported for Japanese quail (31.5 to 37.3 mg/kg), dogs (0.15 to 0.76 mg/kg), and ferrets (3.0 to 4.41 mg/kg). In dogs, increasing the dose of deslorelin from 3 to 12 mg prolonged the suppressive effects of the GnRH-receptor agonist by several months and resulted in a delay until recovery from suppression. Variations among Japanese quail were also observed because only 6 of 10 quail ceased laying after insertion of a 4.7-mg deslorelin implant. Various causes have been hypothesized for the shorter duration or decreased efficacy of deslorelin acetate in avian and mammalian species; these include species variation in the pituitary gland response to exogenous GnRH, pituitary gland resistance to desensitization, or a higher metabolic rate in birds. For example, 1 mammalian GnRH-receptor antagonist may have an agonist effect on GnRH receptors of chickens, and 3 forms of avian GnRH have been identified. These differences may be responsible for the variable response to deslorelin acetate in birds. Some avian species, such as Japanese quail, lay eggs daily, whereas other species, such as cockatiels, lay 1 or 2 clutches/y, which could also have an impact on the effect of deslorelin acetate implants. For seasonal breeders receiving appropriate husbandry and care, insertion of a deslorelin acetate implant before the breeding season could potentially prevent reproductive behaviors for a longer period, possibly until the following breeding season a year later.

Eight of 13 deslorelin acetate–treated birds had not laid eggs by the end of the study 1 year after implant placement. The effect of deslorelin acetate implants reportedly is completely reversible in Japanese quail. Stress related to procedures or environmental changes can prevent egg laying in birds. Reversibility of drug effects was not evaluated in the study reported here; thus, reversibility of effects of a 4.7-mg deslorelin acetate implant in cockatiels remains to be determined. In addition, because of the study design, we did not evaluate effects of deslorelin acetate implants on egg fertility, which could have important impacts for breeding flocks.

Cockatiels were selected for use in the present study because they are overrepresented as companion birds and in the number of reproductive disorders seen by avian veterinarians. Other contributing factors for the selection of this species were the abundant amount of information on reproductive physiology of cockatiels, their small size, and accessibility to a controlled and successful breeding colony.

Egg production has been described as a useful measure of the effects of deslorelin acetate on the reproductive tract for previous studies in birds, therefore, it was used to assess the effect of deslorelin acetate implants in the present study. Birds from each breeding pair were placed in separate cages adjacent to each other. Photoperiod, introduction of a nest box, number of eggs in the nest, and degree of mate access may affect egg production in cockatiels. In 1 study, females allowed only auditory contact with their mates had significantly longer latencies until they inspected the nest and formed nest bowls, had significantly lower LH values, and were less likely to lay eggs than were females that had physical contact with males. Despite the absence of full contact with males, 11 of 13 females of the control group laid eggs. This number could have been improved by housing breeding pairs together in the same cage.
Other possible causes for decreased reproductive function in avian species include systemic illness, genetics, heat stress, toxins and chronic and acute stress. No signs of systemic illness, heat stress, or toxicoses were observed during the study. Furthermore, most of these birds had been exposed to similar protocols to stimulate egg production in the past, which potentially decreased risks associated with stress related to the present study protocol.

Hormonal plasma concentrations have been used to evaluate the effect of deslorelin implants on egg production. Plasma androstenedione, estradiol-17β, and testosterone concentrations of Japanese quail were not correlated with efficacy of deslorelin acetate. Deslorelin administration to female pigeons significantly reduced serum LH concentrations at 7, 28, 56, and 84 days, compared with pretreatment concentrations. In the present study, LH concentrations were not evaluated because there currently were no commercial assays or laboratories performing plasma measurements of avian LH concentrations. Direct visualization of the ovaries via endoscopy before or after deslorelin acetate implantation was not performed because of concerns about negative effects on egg laying.

Mild erythema and soft tissue swelling were observed after implant placement in both the control and the treatment group, but they resolved within 72 hours after implantation. Adverse effects secondary to GnRH-receptor agonists are uncommon. No adverse effects were observed histologically in Japanese quail after administration of one 4.7-mg, two 4.7-mg, or one 9.4-mg deslorelin implant, and no effect on body weight was observed in female pigeons and Japanese quail following administration of deslorelin implants. Death secondary to a suspected anaphylactic shock was reported for 2 elf owls (Microtus whitneyi) following administration of a leuprolide acetate (a short-acting GnRH-receptor agonist), despite the fact the birds had received this medication for several years. Adverse effects in mammalian species include mild edema at the injection site and increased body weight in felids, injection site discomfort and lameness in California sea lions (Zalophus californianus) and Southern sea otters (Enhydra lutris nereis), and prolonged estrus and follicular stasis in a dog. No adverse effects related to deslorelin acetate were observed in the cockatiels of the present study.

In the study reported here, a single 4.7-mg deslorelin acetate implant significantly prevented egg laying in healthy cockatiels for at least 180 days, with unknown reversibility. These results can have a direct clinical impact by providing additional information about effects of a drug frequently used in one of the most common pet bird species. Further studies are needed to evaluate the effects of a 4.7-mg deslorelin acetate implant in birds with reproductive disorders such as chronic egg laying.

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**Footnotes**


b. Roudybush Inc, Woodland, Calif.


d. Midaazolam hydrochloride injection, West-Ward Pharmaceuticals, Eatontown, NJ.

e. Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa.

f. Suprelorin, Virbac (Australia) Pty Ltd, Milperra, NSW, Australia.

g. Surgi-lock 2oc, Meridian Animal Health, Omaha, Neb.

h. Loxicom, Norbrook Laboratories Ltd, Newry, County Down, Northern Ireland.

i. West-Ward Pharmaceuticals Corp, Eatontown, NJ.

j. Stata IC/13, StataCorp LP, College Station, Tex.

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