GnRH Agonists – Their Role in Avian Reproductive Disease

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Introduction

Avian practitioners are regularly faced with reproductive disorders in their patients. Whether it is chronic egg laying, ovarian or oviductual disease or testicular neoplasia, these cases are becoming commonplace in avian practices throughout the world. Disorders of the reproductive tract of captive birds are well reported in the literature (Nemetz, 2010, 2012,; Keller et al., 2013, Mans and Sladky, 2013, Van Sant, 2013, Mans and Pilny, 2014) and are amongst the most commonly encountered reasons for birds presenting to veterinary practitioners. The disorders themselves are relatively easy to diagnose but their treatment remains a challenge despite significant medical advances based on a spate of recent publications (Rosen, 2012, Keller et al., 2013; Petritz et al., 2013; Mans and Pilny, 2014). The lack of scientific literature comparing medical and surgical management of reproductive conditions means that treatment recommendations are based largely on the clinician's preferences and not on scientifically sound analysis.

Surgical treatment options are complicated and carry a guarded prognosis in most cases, despite being curative for certain disease presentations, the inability to surgically remove the ovary leads to potential complications including yolk peritonitis from persistent ovarian activity. The advanced disease state and subsequent unstable nature of patients on presentation, can lead to a poor outcome following surgical treatment. Because of this, significant medical intervention is often required following surgical removal of reproductive pathology. In many cases, including ovarian neoplasia and ovarian cysts, surgical correction is currently not a feasible option. Techniques have been described for ovariectomy but the procedure carries with it a grave prognosis due to the ovaries close association with the aorta, caudal vena cava, common iliac vein, ovarian vasculature, the adrenal glands and kidney. The inability to achieve adequate haemostasis is compounded in neoplastic conditions as the ovarian arterial and venous supply increases in complexity. These factors, combined with the significant anaesthetic risk of coelomic surgery, particularly when dealing with smaller avian patients suggests that veterinarians and clients should consider medical management of such reproductive disorders in the first instance.

With the recent advancement in our understanding of the clinical applications of gonadotropin-releasing hormone (GnRH) agonists, medical management is now, more than ever a safe, effective, affordable and increasingly predictable option available to the veterinary clinician. It is critical to remember that neither surgical, nor medical management alone is curative. Management of these disorders is multifactorial and relies on modification of environmental factors, which may trigger ongoing reproductive activity, diet and social interactions in order to achieve a successful outcome.

Anatomy and Physiology – The Hypothalamic – Pituitary – Gonadal Axis

In birds, the reproductive physiology is under the control of the hypothalamic-pituitary-gonadal (HPG) axis. (Mans and Taylor, 2008) Many hormones are responsible for the reproduction in birds, the most significant being luteinizing hormone (LH), follicle-stimulating hormone (FSH) and GnRH. Short-lived GnRH is released in a pulsatile fashion from the hypothalamus and acts on the anterior pituitary gland where GnRH receptors control the synthesis and release of gonadotrophins (Fig. 1), which dictate gonadal function and therefore hormone production.

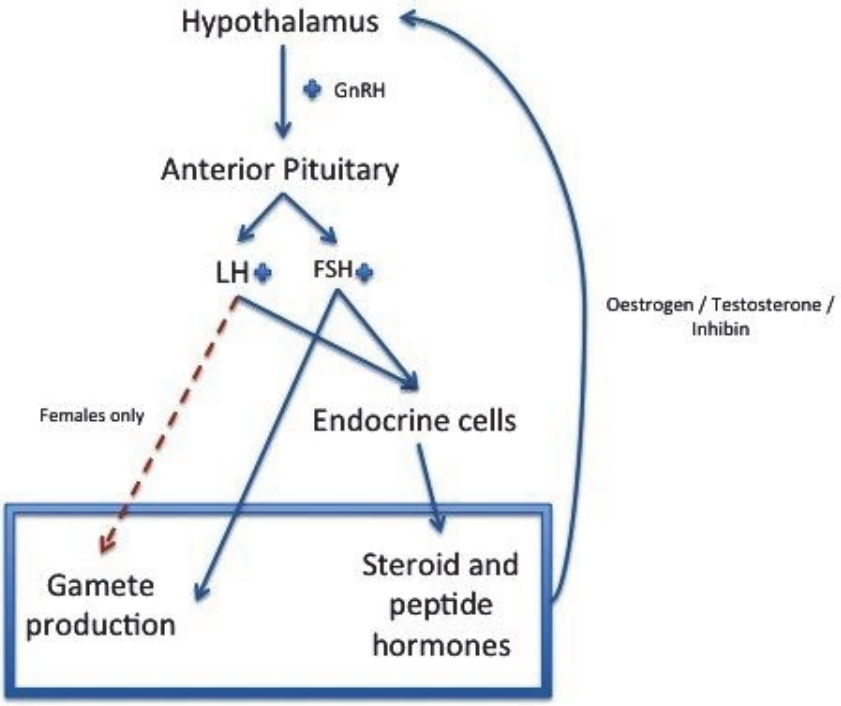

Figure 1. Short-lived GnRH is released in a pulsatile fashion from the hypothalamus and acts on the anterior pituitary gland where GnRH receptors control the synthesis and release of gonadotrophins through the action of LH and FSH on endocrine cells and gametes.

In birds there are currently three known forms a GnRH: avian GnRH-1(King and Millar, 1982), avian GnRH-2 (Miyamoto et al., 1984) and avian GnRH-3 (Bentley et al., 2004). It is avian GnRH-1 that is believed to control LH release from the anterior pituitary. When Sharp et al (Sharp et al., 1990) immunised chickens against avian GnRH-1 but not against avian GnRH-2, the result was complete suppression of egg production combined with a significantly lower LH plasma concentration. Immunisation against avian GnRH-2, in the same study, had no effect on LH concentrations or egg production (Sharp et al., 1990). However avian GnRH-2 has been shown to control behaviours such as copulation and courtship (Mans and Pilny, 2014). It is widely accepted in the avian veterinary community that mammalian GnRH supra-agonists (eg. Lurprolide acetate or deslorelin acetate) are far less efficacious in birds than in their mammalian counterparts. The reason for this remains unknown, but is likely to be the result of variation in avian GnRH or the expression of GnRH receptors in avian species. The variation in efficacy between avian species is also widely accepted amongst avian clinicians and is becoming better documented in the recent literature (Keller et al., 2013; Petritz et al., 2013).

GnRH Analogues to Stimulate Reproduction

The synthetic GnRH used in veterinary medicine has a longer half-life and a higher affinity for GnRH receptors than endogenously produced GnRH (Wilson et al., 2007). Short acting GnRH agonist, buserelin, was used by Lovas et al (Lovas et al., 2010) to assess testosterone secretory capacity and resulted in a significant increase in plasma testosterone 60-90 minutes after administration of 8 µg/kg buserelin intramuscularly. Costantini et al (Costantini et al., 2009) reported using buserelin acetate, a slow release GnRH agonist to stimulate a higher rate of egg production and excreted sex hormone metabolites in a breeding colony of budgerigars (*Melopsittacus undulatus*). Unfortunately there is no information provided by the authors regarding the formulation of buserelin acetate used in this study. It is possible that this was a compounded formulation but attempts to confirm this with the authors have been unsuccessful. There are similar reports of GnRH agonists in canaries (Serinus canaria) where administration of transdermal cream containing lecirelin between 5-21 µg/kg, was shown to significantly increase egg production and fertility and decrease the time between pairing and egg laying (Robbe et al., 2008).

GnRH Analogues to Down-Regulate Reproduction and Control Reproductive Disease

Because of the pulsatile nature of endogenous GnRH release, prolonged administration of synthetic GnRH, either through sustained release implants or via serial administration, leads to negative feedback and an anti-gonadotropic effect. The result is a decrease in the synthesis and release of gonadal hormone. In mammals a period of stimulation shortly after implantation, but before down regulation has occurred is reported. This same phenomenon has not been evaluated in birds, but anecdotally clinicians using GnRH analogue implants have been unable to appreciate this stimulation phase. There are a number of publications evaluating the efficacy of long-acting formulations of GnRH agonists either as injections (ie. Luprolide acetate)(Millam and Finney, 1994; Klaphake et al., 2009; Nemetz, 2010; Keller et al., 2013; Mans and Sladky, 2013) or implant (ie. Deslorelin acetate)(Nemetz, 2012, Nooan, 2012, Petritz et al., 2013, Petritz, 2013, Van Sant, 2013).

Clinical Application

Deslorelin Acetate

Deslorelin acetate is available in two sizes, 4.7mg and 9.5mg and both are available under the trade name Suprelorin (Peptech Animal Health Pty Ltd, Macquarie Park, NSW, Australia) in Australia. There are multiple case reports and retrospective studies that illustrate the species-specific response to deslorelin. A study of layer chickens (Gallus g. domesticus) implanted with suprelorin (4.7mg and 9.5mg) resulted in 100% cessation of egg laying, with the size of the implant affecting the length of time egg laying was suppressed (180 days and 319 days respectively). This is in contrast to other studies looking at the same implants in japanese quail (*Coturinx japonica*)(Petritz et al., 2013; Petritz, 2013) and domestic pigeons (*Columbria livia*), (Cowan, 2014) which saw a significant reduction in egg production in both species but neither was 100% effective.

In male quail the level of circulating testosterone, size of the cloacal gland and various other parameters were measured and it was found that the duration of effect ranged from 2 – 13 weeks and testosterone levels, in all male birds implanted, were significantly reduced within three days of implantation, suggesting a rapid onset of action. (Mans, 2013) Based on the current literature, it can be concluded that the duration of action, in chickens, is related to the size of the implant used to suppress gonadal function. It can also be concluded that there are significant species differences with regards to efficacy and duration of action regardless of implant size.

Much of the literature assessing deslorelin use in psittacine birds is non-peer reviewed but is useful nonetheless. (Nemetz, 2012; Straub, 2013; Van Sant, 2013) Van Sant treated 32 psittacine birds for chronic egg laying and a 4.7mg deslorelin implant suppressed egg laying for approximately 3 months in 100% of the birds. The use of deslorelin implants to medically manage gonadal neoplasia that are either inoperable or carry a poor prognosis for surgical correction is becoming widely accepted as gold standard. Reports in budgerigars with hormone producing gonadal tumors (Straub, 2013) showed a response to treatment based on cere colour (brown to blue) being reported in 7 of 9 cases. There is a report in an adult cockatiel with ovarian neoplasia (Nemetz, 2012) highlighting the management of her condition for approximately 2 years using 4.7mg deslorelin implants after the neoplasm became refractory to treatment with luprolide acetate. These implants saw an abatement of clinical signs and radiographic evidence of neoplastic proliferation for an average of 5 months per implant.

In all of the literature reviewed, no significant side effects were reported in any study. Weight loss was considered one of the most likely sequelea to deslorelin implantation because sex steroid production is inhibited, reducing anabolism. Other possible adverse effects include swelling at the site of implantation, self-mutilation at the implant site (psittacine birds) and implant removal by the patient. (Van Sant, 2013) Based on the available literature and anecdotal reports, there are no indicators that would prevent recommendation of the treatment.

Luprolide acetate

Luprolide acetate is available in different formulations. Slow-release depot formulations will produce a steady, non-pulsatile release and so suppress the reproductive system, whilst short-acting injectable formulations will stimulate the release of LH and FSH from the pituitary.

A wide range of dose rates are reported ranging from 100-1200 µg/kg (Hawkins, 2012) with most clinicians preferring doses between 400 and 1000 µg/kg (Nemetz, 2010; Keller et al., 2013). Administration to psittacines is recommended every 2-3 weeks to control reproductive pathology. Luprolide acetate has been used clinically for a variety of applications including malignant ovarian neoplasia, macro-orchidism of various aetiologies and management of chronic egg layers.

Implant Technique

It is the author's opinion that all avian patients undergoing implantation should be anaesthetised briefly to prevent stress or trauma associated with movement during implantation. If the patient is unsuitable for an anaesthetic, local infusion with lignocaine (4mg/kg) and sedation with intranasal midazolam has been reported as being successful. (Van Sant, 2013; Mans and Pilny, 2014) Once the patient is anaesthetised sterile surgical preparation of the pectoral muscle should take place. Implantation using the delivery syringe should be directed cranially to caudally to prevent the implant from falling out through the skin incision should it break down. The implant should sit subcutaneously or shallow beneath the superficial pectoral muscle. There are potentially fewer possible complications with subcutaneous implants and so many clinicians prefer this technique. To close the incision, tissue glue is used. The removal of old implants is not necessary but may be requested by some owners as treatment progresses to prevent unsightly buildup of implants. Post-operative pain relief; Meloxicam (Boehringer Ingelheim Pty Limited, North Ryde, NSW 2113, Australia) (0.8 – 1mg/kg PO) is given before the patient is returned to the owner.

Conclusion

The use of GnRH agonists in clinical practice is becoming more common. As their use filters from specialist avian and exotics practices into general practitioners, it is essential that their application remains evidence based. As highlight, GnRH agonists are not a suitable treatment for all reproductive disease, nor are they equally efficacious in all avian species. They do however provide a treatment option for reproductive disease where surgery is not deemed suitable and are a valuable tool in prolonging both length and quality of life in these cases.

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