Is it in, is it not or is it just on top
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Abstract
Breeders, owners and practitioners tend to believe that medications, parasiticides applied topically have no effect on reproduction and pregnancy. In fact, many of these products can be and are absorbed systemically and have either direct or indirect effects on the reproductive system and the endocrine systems. Topical medication can have either a temporary or a more long-term effect depending upon the length of administration and the age of the animal being treated.

Keywords: Topical medications, hypothalamic pituitary axis, reproductive toxicants, steroids, endocrine disruptors

Today many practitioners and owners prefer topical medications as an alternative to oral or injectable products. As with any medication, there are risks, benefits and contraindications for these products. It is very important that label directions and recommended applications be considered when making product selection. Equally important is addressing the potential reproductive status of any animal being treated with a topical medication as some of these products can have a negative effect on future reproductive ability.

Endocrine disrupting chemicals have major risks for humans by targeting different organs and systems in the body. Multiple mechanisms are involved through estrogen receptors, nuclear receptors and steroidal receptors activation. Xenobiotics are compounds with pharmacologic, endocrinologic or toxicologically active substance which are not produced within the animal and are therefore foreign to the organism. Endocrine disturbances in humans result in breast cancer, ovarian problems, thyroid disease, testicular carcinoma, Alzheimer’s, schizophrenia, nerve damage and obesity. These endocrine disrupting chemicals are present in pesticides, fuels and many elements that are in routine daily use.

Topical preparations such as antibiotic preparations, antifungals (zinc undecyclenate), antivirals, capsaicin, sunscreens, topical corticosteroids, tanning lotions and vitamin A or E all have potential for toxicity. When using any topical preparations the package labeling and packaging insert require investigation. Of particular importance are the precautions and animal safety indications.

The hypothalamic-pituitary axis (HPA) of healthy dogs can be readily suppressed with any form of glucocorticoid. The HPA axis controls development, reproduction and aging in animals. Ocular, otic and other topical products containing any glucocorticoid can be absorbed systemically and result in suppression of the HPA for weeks. The duration of action of many glucocorticoids administered either intravenously or orally is well documented however this information is scarce as it relates to topical usage. In a study published in Endocrinology, Beagle dogs were administered an otic preparation containing dexamethasone for twenty-one days. The treatment resulted in a marked suppression of resting plasma concentration within the first eleven days of treatment and these levels remained reduced during the entire treatment up to nineteen days. Additionally, significant increases in serum activities of alkaline phosphatase, gamma-glutamyl transferase, alanine transaminase and aspartate transaminase were detected. Eosinophils and lymphocytes were reduced. In this study cortisol levels and hematologic parameters returned to baseline seven days after treatment cessation while liver enzymes remained elevated.

One of the important functions of the HPA axis is to regulate reproduction. The hypothalamus is located in the brain and secretes gonadotropin releasing hormone (GnRH). In females follicle stimulating hormone (FSH) and luteinizing hormone (LH) activate the ovaries to produce estrogen and inhibit. In female dogs the positive feedback loop between estrogen and LH help to prepare the follicle in the ovary and the uterus for ovulation and implantation. Once ovulation occurs the ovary begins to produce progesterone to inhibit the hypothalamus and the anterior pituitary thus stopping the estrogen-LH positive feedback loop. In males the production of these hormones are similar but the effects are different.
Follicle stimulating hormone acts on Sertoli cells of the testicle to stimulate spermatogenesis. Luteinizing hormone acts on Leydig cells to stimulate steroidogenesis. The testosterone produced works on the Sertoli cells to stimulate spermatogenesis and on the hypothalamus and anterior pituitary to inhibit GnRH, LH and FSH secretion.

Glucocorticoids affect both gonadotropin and gonadal function. Administration of corticosteroids to male dogs inhibits gonadotropin secretion as evidenced by decreased circulating testosterone concentrations and testicular atrophy. Blood levels of testosterone are two to three times lower than the levels of testosterone required for sperm production. Thus you cannot give enough systemic testosterone or any other anabolic steroid to improve sperm production. Instead any exogenous steroid including topically applied but systemically absorbed corticosteroid will interfere with the HPG axis causing a decrease in hypothalamic activity and less testosterone in the testicle itself even though libido may be enhanced.\(^3\) Prednisone has been shown to have deleterious effects. It may impair spermatogenesis resulting in decreased sperm numbers and motility which appears to be dose related.

In female dogs, the same corticosteroids can suppress the HPA access as evidenced by interruption of estrous cycle activity. Glucocorticoid administration topically and systemically absorbed can be considered one of many xenobiotic compounds. A xenobiotic compound by definition is a pharmacologically, endocrinologically or toxicologically active substance which is not produced endogenously and is therefore foreign to an organism. The effects of these compounds can range from no effect to irreversible sterility. Other possible outcomes included premature reproductive aging and possibly increased neoplasia. In a mature female the effects are more likely to be temporary. Exposure prepuberally can disrupt reproductive function either by delaying or accelerating puberty.

When selecting topical preparations for use in our patients, reproductive status and potential reproductive demand should be considered. In patients with reproductive futures, topical preparations that contain a corticosteroid with the least potency and the shortest duration of action after withdrawal should be selected. Dexamethasone, flumethasone, betamethasone and cortisone administration to dams has been associated with increased incidence of cleft palate and other congenital malformation and may induce premature labor and abortion in dogs.

For topical parasiticides, it is important to read the package insert and to identify those the products which have been tested safe for breeding animals. The indications, safety and precautions areas of the package insert are the most informative portion of the insert. Selamectin (Revolution®, Zoetis, Florham Park, NJ) is one product that has many applications that are useful in reproducing animals. It has limited efficacy against several tick species but is very effective for control of heartworm, roundworm, hookworm and fleas. While many other products may be safe even if not labeled for use in reproducing animals, the clinician recommending these products assumes responsibility for any extra-label usage.

Many of the oral medications prescribed for dogs and cats have not been tested for their effect on pregnancy or for the effect on fetal development. Antifungal drugs are known to be teratogenic, fluoroquinolones can inhibit cartilage formation, tetracyclines and inhibit dental enamel production, chloramphenicol can suppress bone marrow, and aminoglycosides may be neurotoxic. As would be expected chemotherapeutic agents can be teratogenic or induce abortion. Cimetidine can decrease androgen production which may contribute to cryptorchidism. Exogenous hormone administration by any route may affect sexual development. Glucocorticoids may cause fetal anasarca, cleft palates and may induce abortion. Pain medications should be used with caution - opioids are the analgesics of choice during pregnancy. The US Food and Drug Administration have developed a table which categorizes drugs into five categories based on the effects of each on pregnancy in women. Whenever a drug choice is made the risk versus benefit ration should be considered.\(^4\)

References