

Comparative Pharmacotherapy of Thyroid Diseases in Dogs and Cats--- What Should the Retail Pharmacist Filling Pet Prescriptions Understand?

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Abstract

Community pharmacies are increasingly receiving prescriptions from veterinarians for dogs and cats to receive human medications. However, retail pharmacists are not routinely trained in relevant aspects of veterinary-specific pharmacotherapy, such as, signs of improvement, time to improvement, drug administration techniques and potential adverse effects. Thyroid diseases in dogs and cats are treated with human-approved drugs that may be referred to pharmacies. Hypothyroidism is far more frequent in dogs, while hyperthyroidism is far more frequent in cats.

Important comparative aspects of canine hypothyroidism pharmacotherapy can be summarized as follows:

- 1) Canine hypothyroid disease is similar to Hashimoto's thyroiditis in humans in many of its signs and is treated using levothyroxine;
- 2) The doses of levothyroxine given to dogs are strikingly higher than in people;
- 3) A reasonable therapeutic goal is resolution of symptoms in two weeks to two months and a normal total T4 value ($\approx 0.4\text{-}3.7 \mu\text{g/dL}$).

Important comparative aspects of feline hyperthyroidism pharmacotherapy are:

- 1) Cats usually have a functional thyroid adenoma, while people usually have an autoimmune condition referred to as Grave's disease;
- 2) Common signs noticed by cat owners are weight loss and increased appetite;
- 3) Methimazole is used for therapy as it often is in people;
- 4) Clinical improvement follows in approximately 3-4 weeks;
- 5) Adverse reactions occur and are most often vomiting, anorexia, and lethargy;
- 6) Transdermal methimazole from a compounding pharmacy will be a consideration for some cats.

Keywords: Veterinary pharmacy; Hypothyroid; Hyperthyroid; Levothyroxine; Methimazole; Dog; Cat

Abbreviations: T4: Thyroxine; T3: Triiodothyronine; TSH: Thyroid Stimulating Hormone; TBG: Thyroid Binding Globulin; CIS: Client Information Sheets

Introduction

Retail pharmacies are receiving an increasing number of prescriptions for pets, primarily dogs and cats, to receive human-approved medications. Retail pharmacists are not routinely trained by pharmacy schools in veterinary-specific pharmacotherapy, yet they have a duty to provide necessary counselling. They may need to help the pet client with questions regarding signs of therapeutic efficacy, time from initiation of therapy until clinically noticeable improvement, remedies to drug administration difficulties and potential adverse effects. Pharmacist-to-client counselling should take into account differences in pet vs. human behaviors. This article will cover the most common endocrine diseases of dogs and cats—thyroid diseases. While diabetes is by far the most common endocrine disease in people, in dogs and cats, diseases of the thyroid are the most frequent endocrinopathies. For dogs, hypothyroidism is far more frequent than hyperthyroidism, while in cats, the opposite is true. As with people, thyroxine (T4) and triiodothyronine (T3) exist both in bound-to-plasma-protein and in unbound, free states, and only the free molecules have biological effects and can be readily metabolized.

Hypothyroidism

Background

In dogs, hypothyroidism is usually primary, i.e., due to atrophy of the thyroid gland. In the majority of cases, this atrophy is associated with acquired autoimmune lymphocytic thyroiditis, similar to Hashimoto's thyroiditis in humans, as both are characterized by cellular lymphocytic, as well as humoral autoantibodies against thyroglobulin, T4 and T3 in the thyroid gland [1]. The remainders of canine hypothyroid causes are non-inflammatory or of unknown etiology; congenital hypothyroidism is rare [2].

Hypothyroidism is most often diagnosed in middle-aged dogs (approximately 7-8 years old) and is more likely in pure breeds

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such as Golden and Labrador Retrievers, Doberman Pinschers, and Irish Setters. It is also more common in neutered and spayed dogs [3]. In people, hypothyroidism is more frequent in women; however, female dogs do not appear to be at greater risk.

Hypothyroidism symptoms and diagnosis

Signs that the client notices in dogs have usually developed over time and are similar to those observed in people. These dogs have dry and brittle hair with poor growth progressing to symmetrical alopecia. Hypothyroid people also develop dry, thinning hair. Hypothyroid dogs have dry skin, which may have dark pigmentation and, like people with chronic severe hypothyroidism, dogs can progress to dermatologic myxedema. Both hypothyroid people and dogs show fatigue, weight gain and exercise intolerance. However, in dogs, neurologic deficits are uncommon [2]; while in people hypothyroidism is associated with memory deficits [4]. Hypothyroidism is one of the few disease conditions in dogs that can result in hypercholesterolemia and even coronary artery disease.

In people, a rise in thyroid stimulating hormone (TSH) is the first suggestive diagnostic of hypothyroidism, as the free T4 levels remain normal initially [5]. In dogs, TSH is not the initial diagnostic, total T4 is. A low total T4 in a dog is highly suggestive of hypothyroidism. In people, >95% of T4 levels are regulated by TSH, therefore, an elevated TSH strongly suggests hypothyroidism. In dogs however, T4 is only regulated approximately 70% by TSH because growth hormone regulates the remainder; thus, as opposed to human medicine, TSH levels in dogs usually play little or no role in routine diagnosis. In people, diagnosis is often made using TSH in combination with free T4 measurements. In dogs, total and free T4 measurements correlate in >95% of suspected canine hypothyroid cases and therefore, the routine testing of both total and free T4 in dogs provides no significant added benefit in the general diagnostic setting [6]. Only in select circumstances is a free T4 assay useful to differentiate dogs with, for instance, non-thyroidal illness or atypical clinical signs [6]. The common-place diagnosis of canine hypothyroidism is based on a low T4 with clinical symptoms followed by a positive response to therapy.

Hypothyroidism therapy

Thyroid hormone replacement, levothyroxine, is usually administered once a day and adjusted frequently early in treatment. Dogs may be given levothyroxine as a trial to rule out other non-thyroid illnesses. In this case, levothyroxine is administered over approximately 2 months, and if symptoms resolve, the drug is withdrawn over 4-6 weeks. Re-appearance of symptoms indicates hypothyroidism. Ideally, as with people, thyroid replacement should be administered without food, but in the home setting, clients may need to provide a small meatball of food with the oral tablets so that their dog takes the pill. It is important for the client to be reminded to develop a consistent time and method of administering levothyroxine to their pet so that plasma concentrations and drug effects are also consistent on a daily basis. A Client Information Sheet (CIS) on levothyroxine is available on-line at: <https://sites.google.com/site/vetpharmacis/home>, and this CIS can be used to assist with client counseling. This CIS is part of a series written by Marshall University School of Pharmacy students taking a veterinary pharmacy elective.

In people, a treatment goal is maintenance of the patient's TSH and free T4 within normal range. This is not the goal with dogs. For dogs, resolution of symptoms and normal total T4 values often suffice. The client can be counseled that successful treatment is demonstrated by

the return of normal energy levels and a healthier hair coat. Loss of the extra body weight the dog has gained will follow. These responses can occur over 2 weeks to 2 months, with anticipated resolution of most symptoms in 4 weeks [7]. There are no particular adverse reactions associated with levothyroxine therapy at the recommended dosage levels; however, over dosage will result in the signs of thyrotoxicosis, not dissimilar from people. Symptoms of levothyroxine overdose may include excitability, dizziness and fainting, increased thirst, urination and hunger, and panting [8].

The doses of levothyroxine given to dogs are strikingly higher than those doses typically administered to people, and to an unaccustomed pharmacist, they may appear incorrect. While the dose for an adult person can be 75 to 125 µg a day, a medium-sized (25 kg) dog would begin therapy at ≈500 µg a day (assuming a dose of 20ug/kg/day [8]) and half of dogs may need an upward adjustment of this dose and/or frequency [7]. Cats rarely develop hypothyroidism; however, in those that do, the levothyroxine dose is one-half the dog dose. Human-labeled products, such as Synthroid are sold in tablet strengths from 25 micrograms to 300 micrograms; however to accommodate medium and large dogs, veterinary-labeled products such as Soloxine are available in strengths up to 1 mg [8]. Clients should be encouraged not to switch between different brands of levothyroxine due to some reports of bioavailability differences.

The dramatic difference in comparative dosing levels is partially explained by the different plasma levels of thyroid binding globulin (TBG). Dogs have only one-fourth the amount of TBG as people, while cats have no detectable TBG [9]. The lower level of plasma protein-bound T4 leads to T4 half-lives in dogs and cats that is much shorter than in people. The half-life of canine T4 is approximately 12h [7]; feline T4 is approximately 10h, compared with people, who have a T4 half-life of approximately 7 days [5]. In addition, the oral bioavailability of levothyroxine is much lower in dogs than humans [8].

In summary, hypothyroidism is very similar in dogs and humans in its pathophysiology, symptoms and drug therapy. The difference most relevant to pharmacy staff is the large dosing necessary in dogs. Pharmacy staff should readily contact the referring veterinarian regarding answers to questions or concerns they or their clients have about the therapy of hypothyroidism in dogs or cats.

Hyperthyroidism

Background

Hyperthyroidism is the endocrine disease most frequent in cats. Feline thyroid disease is primarily caused by a functional thyroid adenoma (adenomatous hyperplasia). A similar adenomatous condition, toxic adenoma, also occurs in people; however, in people, the most frequent cause of hyperthyroidism is an autoimmune syndrome referred to as Grave's disease, which occurs rarely, if ever, in cats [10]. Hyperthyroid dogs most often have thyroid carcinoma [11]; therefore this article will focus on the treatable disease in the cat.

Feline hyperthyroidism occurs primarily in middle-aged and older cats (between 10 and 13 years of age [12] with no gender predisposition [10]; in contrast, Grave's disease usually develops in people under 40 years of age and is diagnosed eight times more commonly in women [5].

Hyperthyroidism symptoms and diagnosis

The signs of hyperthyroidism in cats that are most noticed by the owner are weight loss and increased appetite. Owners may also observe

their cats to be hyper-excitabile, to have polydipsia and polyuria, and to have gastrointestinal signs including vomiting, diarrhea, and increased fecal volume [11]. People with Grave's disease share the signs of weight loss and increased appetite, along with diarrhea and anxiety. They also have an exophthalmos that cats do not [5]. As is the case with free T4 assay in the hypothyroid dog, free T4 analysis in the cat adds little benefit to the accuracy of the total T4 alone; therefore, feline hyperthyroidism is presumptively diagnosed by a high T4 and accompanying clinical signs [10,11]. People suspected of hyperthyroidism are diagnosed through elevated serum free T4, total T3 and low TSH levels [5].

Hyperthyroidism therapy

Pharmacologic therapy for both cats and people involve the administration of thiourea drugs. Methimazole is most often the drug used to treatment of feline hyperthyroidism. Propylthiouracil, a second-line therapy in people, is rarely used in pets because of its greater adverse effects [8]. Mechanistically, methimazole and propylthiouracil inhibit the enzyme thyroid peroxidase. To form natural thyroid hormones, iodide is oxidized by this enzyme and then incorporates onto tyrosine amino acid residues. The thioureas also inhibit other steps in thyroid hormone synthesis [5].

In the cat, therapy begins with 2.5-10mg methimazole total dose per animal, which is administered 2-3 times daily for a trial period of approximately 3 weeks. After this trial period, the veterinarian will likely re-assess total T4 levels and clinical response by improvement in signs. The methimazole dose will then be adjusted with the ultimate goal of reaching just once daily administration. Up to 50% of cats receiving methimazole over 6 months will require a dose reduction due to the production of antinuclear antibodies. In comparison with cats, adult humans receive methimazole in dose ranges from 5mg given three times daily for mild hyperthyroidism to 20mg given three times daily. In terms of dosing equivalency per mg body weight, cats will typically receive about twice the dose level as people. A cat client can expect to see clinical improvement in their pet in approximately three weeks [12], while people with Grave's disease expect to benefit in 4-8 weeks [5]. If severe tachycardia has developed, a beta blocker such as propranolol, may be prescribed as adjunctive therapy as in people to reduce palpitations and anxiety. The cat client should be counseled on the importance of consistently administering the methimazole in order to control symptoms, since the disease is not itself cured [8]. A Client Information Sheet (CIS) on methimazole is available on-line at: <https://sites.google.com/site/vetpharmacis/home>.

Administering oral medications to cats can be challenging in general and methimazole presents an additional problem since it has a bitter taste. Because it is critical for the drug to be taken consistently, methimazole is a favorite medication referral by veterinarians to compounding pharmacies where it can be reformulated and dispensed as a transdermal gel [13]. A variety of applicators for dispensing the transdermal methimazole compound are available [14,15]. The typical point of application is inside the inner ear pinna every 12 hours. If applying by hand, the client should be counseled to wear a glove. Reported disadvantages of the transdermal formulation are that it is more expensive, less effective in some cats, and that it has a shorter shelf life (approximately 2 weeks) [8].

As opposed to the treatment of dogs for hypothyroidism, adverse reactions are not uncommon in the cat treated for hyperthyroidism. Any concerns from the client or pharmacist should be referred back to the veterinarian. Most adverse reactions, if they occur, occur early in treatment and may warrant a dosage adjustment to reduce the

severity of adverse symptoms. These are most frequently vomiting, anorexia, lethargy and depression. A rare, yet relevant adverse reaction by some cats, is pruritus and self-induced facial excoriation. In people, methimazole is also associated with pruritic rashes, as well as occasional nausea, vomiting, epigastric distress, and a more common adverse effect, benign transient leukopenia, which occurs in up to 12% of adult people [5]. Agranulocytosis is a less frequent, yet serious effect in people with incidences from 0.5 to 6% [5]. Cats (approximately 15%) also develop transient leukopenia within the first 2 months of therapy, and less frequently, approximately 4% of cats also show the more severe agranulocytosis [8]. Key counseling points to give to clients on adverse effects are to observe for lethargy, vomiting, anorexia or pruritus and to contact their veterinarian if adverse reactions occur. Reasons to consider a switch to transdermal methimazole are difficulty in administering the oral drug to defiant cats and/or frequent vomiting with the tablet form [8].

In summary, feline hyperthyroidism arises through a different etiology than the most frequent cause of human hyperthyroidism, Grave's disease; yet both are treated pharmacologically with methimazole. The relative dose is much higher in cats, yet consistent, chronic administration is essential in both cats and people to ensure effective reduction in thyroid hormone levels and signs of clinical pathology. Drug-related adverse effects are similar, but their relative frequencies differ between the two species with vomiting more common in cats. A pet-owner can often administer a pill by hand to a dog if the dog does not take the pill with food; however, cats are difficult for most clients to pill by hand, especially if it must be done daily. Therefore, in consultation with the referring veterinarian, a transdermal delivery option should be considered for cats that do not take oral methimazole well.

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