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*Elaboration of article in Dutch (1)

Practical points

In 2017 and 2018, the US Food and Drug Administration announced five recalls of petfoods due to high contents of thyroid hormones (2-7). The recalls involved canned dog foods and dog treats from three and two manufacturers. Each product was connected to observed toxic reactions in one to four dogs and demonstrated presence of active thyroid hormone. It was reasoned that the incriminated products contained livestock gullets with remnant thyroid tissue.

Intake of excessive amounts of thyroid hormones causes thyrotoxicosis. In dogs, the signs can include increased thirst and urination, weight loss, greater appetite, restlessness, hyperactivity, rapid heart rate and breathing, vomiting and diarrhea. Blood concentrations of thyroxine, a thyroidal hormone, are elevated. For the diagnosis of alimentary thyrotoxicosis, thyroid cancer must be ruled out and high dietary thyroid hormones made plausible. Within a few weeks after changing the food of affected dogs, clinical symptoms normally disappear and blood thyroxine returns to the reference interval.

In addition to the recalls-related cases (2-7), there are six further reports on diet-induced thyrotoxicosis (8-13). In all, the latter communications describe 35 hyperthyroxinemic dogs of which 21 also exhibited clinical signs. Eleven dogs had consumed home-made, bones-and-raw-food diets. Some of those formulations contained beef neck meat with thyroid tissue or ground head meat. Eight dogs received commercial food topped with dried or fresh gullets. Two dogs were fed commercial, deep-frozen food and 14 ate industrially-produced air-dried food and/or jerky treats. The recall announcements mention 8 thyrotoxic dogs fed canned food.

Alimentary thyrotoxicosis was recognized by high blood thyroxine without or with fitting clinical signs in the absence of thyroid cancer. In two case studies (8, 9) the rations clearly included thyroid tissue, while one report (12) shows increased thyroxine contents in the suspect foods. The return to health and normal blood thyroxine, after diet change, was taken as additional proof for alimentary thyrotoxicosis (8-13). None of the incriminated foods was fed to healthy dogs under controlled conditions to determine the effect on blood thyroxine.

Under controlled conditions, clinical exogenous hyperthyroidism has been induced in dogs by feeding dry food containing about 6% dried thyroid (14, 15). After two weeks, the dogs showed diarrhea, followed by increased urine excretion and accelerated heart rate. Supplying dry food with 1.8% thyroid powder for 18 weeks did not elicit clinical signs (14). This inclusion percentage is equivalent to 0.3 mg thyroxine/kg body weight per day, which induces serum total thyroxine concentrations higher than the upper limit of normal (16). In order to maintain serum total thyroxine within the reference range, which can be considered prudent, less than 0.07 mg thyroxine/kg body

weight per day appears required (Note 1). Thus, 0.4% dried thyroid tissue in dry food would be a safe upper limit.

Dog foods and treats with laryngeal tissue from which the thyroid glands are not completely removed, may contain hazardous amounts of thyroid hormones. Thyroxine is not significantly degraded during cooking (17), thus surviving thermal processing of ingredients and foods. Industrial products at risk are canned and pouched wet foods, deep-frozen and air-dried foods and also meat-infused and raw-included, extruded kibbles. As regular extruded foods are based on animal meals, they are at lower risk; during the rendering process of animal meal production, thyroid tissue is highly diluted by thyroidless slaughter byproducts. Petfood manufacturers should ensure that they are receiving animal materials that do not contain thyroid glands. The dry matter in complete dog foods must consist of less than 0.44% thyroid tissue.

Thyroid hormones

The thyroid glands of vertebrate animals have comparable structure and function. In the dog and cat, two thyroid lobes, which normally are impalpable, lie on either side of the trachea. The gland tissue secretes the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). The hormones contain iodine and are tyrosine-based. In blood, T4 is the major thyroid hormone. It is deiodinated to form T3 in peripheral tissues. T3 is the most active thyroid hormone. The thyroid hormones affect many aspects of bodily metabolism and development, but notably metabolic rate. Hyperthyroidism accelerates basal metabolism, which generates heat and leads to weight loss. Hypothyroid status has the opposite effects.

Hormone synthesis in the thyroid gland is controlled by thyroid-stimulating hormone (TSH) which is secreted by the pituitary in response to TSH-releasing hormone (TRH) from the hypothalamus. Higher blood TSH levels upregulate T3 and T4 production by the thyroid gland. The endocrine organ is subject to feed-back control. High blood concentrations of T3 and T4 diminish the release of TSH and vice versa. Hyperthyroxinemia can render blood TSH undetectable.

Thyrotoxicosis

Thyrotoxicosis refers to the clinical effects associated with increased metabolic rate caused by an excess of thyroid hormones in the bloodstream. In dogs, long-lasting high blood concentrations of thyroid hormones can damage the heart and lead to death. Overactivity of the thyroid gland due to functional thyroid tumors leads to hyperthyroxinemia and thyrotoxicosis. Thyroid cancer is uncommon in dogs compared with cats. Exogenous thyrotoxicosis results from ingestion of excessive amounts of thyroid hormones.

The petfood recalls (2-7) were dictated by protection of dogs against dietary thyrotoxicosis. High amounts of thyroid hormones, administered by various routes, have been shown to induce thyrotoxicosis in dogs (14, 15, 18-22). Accidental ingestion of thyroid hormone preparations occurs regularly (23). Acute and chronic, inadvertent overdosing situations in a healthy dog (24) and dogs with hypothyroidism (25) have been reported. A coprophagic dog contracted thyrotoxicosis as a result of consuming the feces from a thyroxine-treated housemate (26).

Fate of oral thyroxine

The efficiency of intestinal thyroxine absorption in dogs is unknown. In thyroidectomized dogs given thyroxine orally, steady-state concentrations of serum thyroxine were dose-dependent (27). In overnight-fasted dogs, orally dosed with thyroxine, serum thyroxine peaked after 4 hours (28). Absorption of thyroxine in dogs was markedly lowered by concomitant food intake (29). When thyroxine was ingested together with food, bioavailability was 12% of that when thyroxine was administered intravenously (29). Percentage thyroxine absorption is higher than 12% of intake. Part of the thyroxine that crosses the gut wall into the portal vein is lost by hepatic uptake and subsequent conversion (cf. 30-32) before reaching the systemic circulation. The mechanism of thyroxine absorption is poorly understood and so is the role, if any, of intestinal lymphatic transport.

Two days after intravenous administration of ^{131}I-labeled thyroxine in dogs, 40% of the dose was recovered in feces and 41% in urine (31). Fecal radioactivity was associated with thyroxine, while urinary radioactivity was about 90% iodide and 10% glucuronosylated thyroxine. A mixture of thyroxine and its glucuronide represented most bile radioactivity. The urinary excretion of thyroxine conjugated with glucuronic acid (31) concurs with the 7% of administered radioactivity found in dogs' urine after intravenous injection of ring-labeled ^{14}C-thyroxine (32).

Owing to its lipophilic nature, thyroxine is converted to water-soluble derivatives, which are then excreted in bile and urine. This mechanism is operative in dogs as indicated by the studies with radiolabeled thyroxine (30-32). Tiny amounts of absorbed thyroxine may be neutralized by the hypothalamus-pituitary-thyroid axis. Higher amounts lead to increased blood thyroxine concentrations, without or with harmful effects. Within a certain range of thyroxine intakes, excretion mechanisms appear to allow for differential planes of steady-state concentrations of serum thyroxine (16).

Challenge studies

In 1895, Lanz reported about feeding dogs with dried porcine thyroid gland mixed into the diet (33). Intakes of 30 g/day for months were well tolerated. However, pulse rate became faster and some weight was lost while appetite and thirst were increased. Four years later, Cunningham published (34) that dogs gained weight when fed a mixture of chopped thyroids of the ox, calf and sheep as sole nourishment for six days. The dogs were lively, while pulse rate, temperature and feces quality were undisturbed.

Dogs have been challenged with pure, synthetic thyroxine preparations. Oral administration of 1 mg thyroxine/kg body weight per day (kg bw.day) increased body temperature, heart and respiratory rates in dogs, but allowed a gradual increase in body weight (20, 21). Thyroxine was given to those dogs in two equally divided doses 12 hours apart for 60 days. Feeding L-thyroxine mixed with the diet (1.6 mg thyroxine/kg bw.day) for 150 days accelerated metabolic rate and markedly lowered body weight (19). Similar effects were seen with 2 mg oral thyroxine/kg bw.day (22).

Piatnek and Olson (14) stated that to achieve a persistent hyperthyroid state in the dog over several months, the oral dose of desiccated thyroid powder must be greater than 300-400 mg/kg bw.day. The powder used met the requirements of the United States Pharmacopeia (USP). In two healthy

dogs, 70 mg USP desiccated thyroid/kg bw.day, for periods of two or four months, did not systematically affect body weight and oxygen consumption (18).

Piatnek and Olson (14) increased the initial dose of 500 mg to the final dose of 1000 mg by three to four weeks. During the 14-weeks feeding period, the challenged dogs developed diarrhea, polyuria and tachycardia. The investigators have induced hyperthyroidism not only by feeding desiccated thyroid (1 g/kg bw.day), but also by subcutaneously injecting thyroxine (0.6 -1.2 mg/kg bw.day) (14, 15). There were 50 thyroxine-treated dogs, including 8 with salivariectomy and 7 with surgically-induced cardiac valvular lesions. Sixteen dogs developed cardiac failure, three of which had pre-existing valvular lesions.

Toxic and safe doses

In one case study of acute toxicity, a dog had ingested levothyroxine sodium tablets (24). The intake was about 10 mg thyroxine/kg body weight. Within 9 hours, the overdose induced an episode of vomiting and pupillary spasm with a serum thyroxine level of 4,900 nmol/l. Petfood contaminated with thyroid hormones rather leads to chronic toxicity. There are no longer-term, dose-response studies that span oral thyroxine amounts from harmless to toxic. Furthermore, the older studies reported clinical signs and serum protein-bound iodide (14, 18) or triiodothyronine (22) rather than serum total thyroxine. The more recent studies (16, 35-37) describe serum thyroxine concentrations, but focused on lower thyroxine intakes that did not elicit clinical signs.

Chronic toxicity with clinical signs has been induced by daily oral intakes of 1-2 mg thyroxine (19-22) or 1 g dried thyroid powder (14, 15) per kg body weight. Treatment with 300 mg thyroid powder/kg bw.day for 18 weeks did not induce clinical signs in dogs (14). USP-grade, dried and powdered porcine or bovine thyroid glands for therapeutic use can be put at 0.63 mg T4 plus 0.15 mg T3 per gram (38-40). When assuming twofold greater toxicity of T3 versus T4 (cf. 41, 42), then 1 g thyroid powder is equivalent to about 1 mg thyroxine. Thus, prolonged intakes of 0.3 mg thyroxine/kg bw.day may not evoke clinical symptoms in dogs.

Healthy euthyroid dogs orally given 0.022 mg thyroxine/kg bw.day for 8 weeks did not show changes in echo- and electrocardiographic measurements while serum T4 concentrations remained within the normal range (35). In healthy euthyroid dogs, dosed with 0.024 mg oral thyroxine/kg bw.day for 8 or 16 weeks, no clinically relevant abnormalities were identified (36). Euthyroid dogs with congestive heart failure received oral thyroxine (0.02 mg/kg bw.day for two months and then 0.04 mg) as an adjunct to medication (37). Thyroxine treatment reduced median survival time; the effect was not statistically significant. After two months, mean plasma thyroxine concentration in the hormone-treated dogs (n =5) was 63 nmol/l.

Hare et al. (16) has studied the impact of relatively low doses of synthetic levothyroxine tablets in young, healthy euthyroid Beagle dogs. For 26 weeks, dogs received single daily oral doses of 0, 0.044, 0.132 or 0.22 mg levothyroxine sodium/kg body weight. Serum total thyroxine and TSH concentrations increased and decreased, respectively, in a dose-dependent fashion. Severe adverse reactions were not seen. Clinical signs of thyrotoxicosis were sporadic and dose independent. The results corroborate the above inference that 0.3 mg thyroxine/kg bw.day leaves dogs practically symptom-free.

The reference ranges used for serum thyroxine concentrations in dogs vary across publications (8-13, 16, 23), but 10-40 nmol/l seems reasonable. Then, as a rough guide, 0.07 mg thyroxine/kg bw.day would be the safe upper limit of oral intake according to the data published by Hare et al. (16, Note 1). For a 20-kg dog consuming 333 g dry food/day, the dose of 0.07 mg thyroxine/kg bw.day is equivalent to about 4 mg thyroxine or 4 g dried thyroid tissue per kg dry food. Thus, the dry matter in complete dog foods must contain less than 4.4% thyroid tissue.

In the study of Broome et al. (12), 10 out of 14 dogs with thyrotoxicosis had clinical signs. Thyroxine immunoreactivity was analysed in dog food samples. The suspect treats and complete foods had a median concentration of 1.52 µg of immunoreactive T4/g, whereas the value for the control samples was 0.38. This outcome supports the authors' diagnosis of exogenous thyrotoxicosis. The incriminated air-dried, complete foods would contain about 1.5 mg thyroxine/kg, which is below the above-mentioned safe level of 4 mg thyroxine/kg dry food. As suggested by the authors, the concentration of immunoreactive T4 may be an underestimate of the true content of thyroid hormones in food. Furthermore, the T4 contents of individual samples point at 1.5 µg of immunoreactive T4/g as an analytical upper bound.

Note 1

For the concentration of serum total thyroxine in dogs, different reference intervals are in use (8-13, 16, 23), but 10-40 nmol/l seems fair. Maximum serum total thyroxine levels in dogs (n = 8/dose) were 30 and 61 nmol/l after oral administration of 0.044 and 0.132 mg thyroxine/kg bw.day during a period of 26 weeks (16). It follows that a maximum level of 40 nmol/l would be induced by 0.072 mg thyroxine/kg bw.day.

Note 2

Cats have been made hyperthyroid by the intraperitoneal injection of 0.75 mg L-thyroxine/kg bw.day (43). After 10-17 days, the cats, with mean initial body weight of 3.1 kg, had lost 750 g body weight while serum protein-bound iodine and serum cholesterol were increased and decreased.

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