Acute Thyroid Hormone Supplement Overdosage

by
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Hypothyroidism occurs in many species, including people and dogs. Thyroid hormone supplements are indicated for treating hypothyroidism in all species. Both crude thyroid hormonal preparations and synthetic products are available. Between 1998 and 2000, the ASPCA Animal Poison Control Center (APCC) received approximately 275 calls on accidental ingestion of thyroid hormone preparations in domestic animals. Most calls were regarding dogs, but cases in cats and birds were also reported. To understand the toxicity associated with an acute thyroid hormone overdosage, you must know the physiological functions of the thyroid gland and its hormones.

The thyroid gland and thyroid hormones

The thyroid gland is composed of two lobes lying laterally and somewhat ventrally on either side of the proximal trachea. The lobes are occasionally connected by a narrow band of tissue called the *isthmus*. The cells of the thyroid gland are arranged circularly into follicles. Colloid, the main storage form of the thyroid hormones, fills the follicles (*Figure 1*).[1]

Thyroid hormone synthesis occurs through a series of steps. First, a large molecule, thyroglobulin, forms within the follicular cell and is secreted into the lumen of the follicle. Next, iodine that has been oxidized to iodide in the gastrointestinal tract and transported to the thyroid gland is trapped by the follicular cells through an active transport process. As iodide passes through the cell wall, it attaches to the tyrosine portion of the thyroglobulin molecule. Tyrosine can accommodate two iodide molecules. If one iodide attaches to the tyrosine, monoiodotyrosine (MIT) is formed. If two iodide molecules attach, diiodotyrosine (DIT) is formed. The main thyroid hormones are formed by the coupling of these iodinated tyrosines: two DITs form tetraiodothyronine (T_4, or thyroxine), whereas an MIT and a DIT form triiodothyronine (T_3).[1]

Once thyroid hormones are synthesized, they remain a part of the thyroglobulin molecules and are stored in the colloid within the follicles. This storage allows the thyroid gland to have a large reserve of hormone available when needed. For thyroid hormones to be released from the thyroid gland, the thyroglobulin molecules, with their attached T_3 or T_4 molecules, must be translocated into the follicular cells where cleavage occurs. The hormones are then released into the blood, and the thyroglobulin molecules are recycled.[1]

All T_4 is produced by the thyroid gland as described above. Thyroxine is the main secretory product of the thyroid gland. Most of T_3, however, is formed outside the thyroid gland by deiodination of T_4.[1] T_3 is considered the most important thyroid hormone at the cellular level; it is about three to five times more potent than T_4.[2] Thus, T_4 acts as a prohormone, allowing a large potential T_3 reservoir within the body. After the thyroid hormones are released into the circulation by the thyroid gland, about 99% become bound to plasma proteins. Only unbound T_3 and T_4 are available to interact with tissue receptors to induce a physiological effect.[3]

Thyroid hormones are vital for the normal functioning of many body systems and affect the rate of many physiological processes. They increase body temperature, oxygen consumption, cardiac output, heart rate, and blood volume. Thyroid hormones also promote the mobilization and utilization of glycogen stores and increase protein synthesis and gluconeogenesis. In addition, growth, maturation, and enzyme system activity depend on these hormones.[4] Thyroid hormones are especially important for adequate fetal and neonatal central nervous system development. And since people with hypothyroidism are mentally dull and lethargic, the maintenance of normal central nervous system function may also depend on adequate amounts of thyroid hormone.[1] Thyroid hormones (primarily T_3) exert their effects at the cellular level, but the exact mechanism is still not well-understood.[4]

Thyroid hormone supplements
Thyroid hormone preparations are classified into four groups: 1) crude hormones prepared from animal thyroid, 2) synthetic levothyroxine (L-thyroxine) sodium, 3) synthetic liothyronine (L-triiodothyronine) sodium, and 4) synthetic combinations of L-thyroxine and L-triiodothyronine. L-thyroxine, the levo isomer of thyroxine, is the compound of choice when treating most cases of hypothyroidism. Administering L-thyroxine allows normal conversion by the body to T_3. The therapeutic goal is to achieve normal concentrations of T_3 and T_4 in both tissue and serum, and this is best accomplished by administering exogenous T_4.[2] Additionally, there is less variability in bioavailability in the synthetic preparations compared with crude products, and L-thyroxine is less expensive than other synthetic preparations.[2]

Pharmacokinetics
Most thyroid hormone overdosage calls received by the ASPCA APCC relate to the ingestion of L-thyroxine products. Clinically, a remarkably normal physiological state can be maintained in dogs in the face of a massive L-thyroxine overdosage.[5] This phenomenon can be explained in part by pharmacokinetics. L-thyroxine is poorly absorbed in dogs. Only 10% to 50% of an orally administered dose is absorbed in dogs[5] as compared with 48% to 80% absorption in people.[6] Peak plasma concentrations in dogs are expected four to 12 hours after oral dosing.[4]

In plasma, most of the T_3 and T_4 is reversibly bound to plasma proteins (>99%). Bound T_3 and T_4 are unable to interact with tissue receptors. Only the small amount of free hormone is able to diffuse into tissues, penetrate cell membranes, and interact with target tissue receptors to induce a physiological effect. Yet, only 1% to 30% of available serum protein binding sites are occupied at normal serum T_4 concentrations in dogs.[7] Since these sites are not already occupied, in an oral L-thyroxine overdosage excess T_4 may be bound and, thus, unable to either cause a physiological effect itself or be converted to T_3.

In addition to thyroid hormones being highly protein-bound, certain organs (particularly the liver and kidneys) can concentrate thyroid hormones intracellularly, thereby rendering these hormones unavailable to bind to tissue receptors and induce a physiological effect.[2] Thus, the liver and kidneys can act as buffers by releasing small or large amounts of hormones back into the plasma, depending on what the body needs. In an overdose situation, the buffer organs can concentrate the extra hormone and not release the already stored hormone.

Thyroid hormone metabolism is accomplished in two ways: deiodination and glucuronidation. As previously mentioned, most of T_3 formation occurs outside the thyroid gland by deiodination of T_4. But if further deiodination of T_3 occurs, the hormone is deactivated. The tissues that have the highest concentration of deiodinating enzymes, and are thus able to metabolize thyroid hormones in this way, are the liver and kidneys.[3] Metabolism of thyroid hormones by glucuronidation may also occur in the liver.[3] So in an L-thyroxine overdosage, deiodination can be used to metabolize the hormone instead of converting it to active T_4, or glucuronidation can occur in the liver at an increased rate.

Although the total daily production of thyroid hormones by thyroid glands in dogs may exceed that of thyroid glands in people by twofold or threefold, comparatively larger fecal excretion helps explain dogs' lower normal serum concentrations and the substantially greater amounts of thyroid supplements required to establish euthyroidism in hypothyroid dogs.[3] Thyroid hormones are excreted in the bile, but less than 15% of excreted T_4 undergoes enterohepatic recirculation in dogs.[3] Of the thyroid gland hormones produced each day, dogs excrete more than 50% of the T_4 and about 30% of the T_3 in their feces.[3] This greater potential for biliary excretion and fecal loss in dogs helps explain why dogs appear to be resistant to the signs of thyrotoxicosis during both thyroid hormone supplementation and accidental overdosage.[3]

In dogs, the plasma half-life of T_4 is about 10 to 16 hours. In contrast, T_3 has a much shorter plasma half-life of five to six hours.[2] Thus, in an overdosage situation the serum T_4 concentration may stay elevated for many days (15 to 36 days in one case report), whereas the T_3

concentration should return to normal within a few days (three to six days in the same case report).[5]

Clinical signs of acute overdosage
A single acute overdose is less likely to produce severe thyrotoxicosis than a chronic overdosage is. In an acute overdosage situation, the clinical signs are extensions of the hormone's physiological effects. In dogs and cats, acute overdosage of L-thyroxine may produce vomiting, diarrhea, hyperactivity, hypertension, lethargy, tachycardia, tachypnea, dyspnea, and abnormal pupillary light reflexes. In one dog, serum alanine transaminase activity was elevated six days after L-thyroxine ingestion.[5] The most common signs reported to the ASPCA APCC in acute ingestions in dogs are mild to moderate hyperactivity and tachycardia (ASPCA APCC Database: Unpublished data, 2001).

In dogs, signs of acute L-thyroxine overdosage develop within one to nine hours after ingestion (ASPCA APCC Database: Unpublished data, 2001). L-triiodothyronine overdosage would be expected to induce a more rapid onset of clinical signs and a shorter duration of effects compared with L-thyroxine ingestions as a result of immediate cellular availability of T_3.[8] In L-thyroxine overdosages in people, signs of toxicosis may be delayed as long as five to 11 days after ingestion, with an apparently symptom-free interval between ingestion and toxicosis.[9] This phenomenon has not been noted in dogs.

In one case study of acute L-thyroxine overdosage in a dog (10 mg/kg), a serum T_4 concentration measured three to nine hours after ingestion was 4,900 nmol/L (normal = 5.3 to 26.7 nmol/L). The T_4 concentration decreased slowly and was not normal until 36 days after ingestion. However, the T_3 concentration returned to normal by Day 6. During this time, the owner reported no detectable alterations in the dog's behavior.[5] Per the ASPCA APCC Database, signs of mild hyperactivity and tachycardia have developed in dogs at L-thyroxine oral doses as low as 0.2 mg/kg.

Treatment and prognosis
In dogs and cats, treatment of thyroid hormone supplement overdosage is aimed at preventing and managing clinical signs. Inducing emesis in an asymptomatic patient is recommended if the ingestion occurred within two hours and no contraindications to emesis exist. After emesis, administer activated charcoal (1 to 2 g/kg orally) and a saline cathartic (250 mg/kg magnesium sulfate or sodium sulfate orally).[10] Since only a small amount of enterohepatic recirculation occurs, multiple doses of activated charcoal are not indicated.

Because mild signs of hyperactivity and tachycardia were seen in dogs at doses as low as 0.2 mg/kg, this may be used as a trigger dose to begin decontamination. However, you must consider many factors before deciding how to proceed with each case. These factors include the patient's health before ingestion (underlying diseases, concurrent medications, recent surgeries), what other products might have also been accidentally ingested, the time since ingestion, and the patient's present state (symptomatic vs. asymptomatic).

Of course, underlying health problems, including heart disease, seizure disorders, and, possibly, liver disease (since the liver is involved in metabolizing the thyroid hormone) increase the risks associated with thyroid hormone overdosage. Also because thyroid hormones are highly protein-bound, they could displace other highly bound drugs (e.g. phenobarbital) and increase the amount of drug available to exert clinical effects.

Monitor a patient by observing an electrocardiogram, measuring blood pressure, and obtaining complete blood counts, serum chemistry profiles (including electrolytes), and serum thyroid concentrations. Treatment is supportive and symptomatic. Provide fluid therapy in patients with vomiting and diarrhea and those needing cardiovascular support. Monitor fluid rates with caution, since hypertension may be present. Use thermoregulation, oxygen, and antiemetics as needed. Diazepam (0.5 to 1 mg/kg intravenously[4]) can be used for hyperactivity, tremors, or seizures. A β-blocker such as propranolol hydrochloride (0.02 to 0.06 mg/kg intravenously slowly[4]) can be used

for tachycardia, and lidocaine hydrochloride (2 to 4 mg/kg intravenous bolus slowly[4]) may be indicated if ventricular arrhythmias develop.

The prognosis for full recovery is good as long as the clinical signs are managed and there are no underlying risk factors. Continue therapy and monitoring until the clinical signs have resolved and the serum thyroid hormone concentration has returned to normal.

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