

Potential cutaneous hypersensitivity reaction to an inactive ingredient of thyroid hormone supplements in a dog

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Background – Although discussions about allergic reactions to thyroid supplements abound on professional forums, there is almost no information in the literature on these specific idiosyncratic drug reactions.

Animal – A dog with a history of hypothyroidism-associated weight gain and mild lethargy was prescribed levothyroxine tablets (0.018 mg/kg twice daily). After 19 days the dog developed a severe skin condition that was responsive to levothyroxine withdrawal, and antibiotic and glucocorticoid therapy. Three weeks later a different levothyroxine tablet was prescribed. Within 48 h the dog developed a more severe cutaneous reaction that resolved with drug discontinuation and appropriate topical care.

Objectives – To confirm a possible hypersensitivity reaction and identify its chemical target.

Methods and results – The two prescribed levothyroxine formulations shared two inactive ingredients: magnesium stearate and polyvinylpyrrolidone. Nine months after discontinuation of thyroid supplement, a formulation without either of these two compounds was used for a second re-challenge. There was no recurrence of the drug reaction and after 1.5 years of treatment the dog remains normal.

Conclusions and clinical importance – These elements strongly suggest that this dog had an idiosyncratic reaction (likely immune-mediated) against one or both inactive ingredients in the first two formulations of levothyroxine. We are not aware of any previous confirmed delayed hypersensitivity to a thyroid supplement in a dog with the likely chemical trigger being an inactive ingredient rather than the therapeutic agent itself. We hope that this case will raise awareness about allergic reactions to thyroid supplements and allergic reactions to inactive formulation components.

Case description

A 5.5-year-old female spayed golden retriever dog was presented to a primary care veterinarian because of decreasing energy and a weight increase from 36.8 to 45.1 kg over 2 years despite any diet change. Physical examination was otherwise normal. Serum was sent to an external laboratory for thyroid hormone analysis. Results revealed abnormally low hormone levels: triiodothyronine (T3) < 35 ng/dL (normal 55–150 ng/dL) and thyroxine (T4) < 0.4 µg/dL (normal 0.9–3.9 µg/dL) (Table 1). Serum chemistry also showed increased

cholesterol [900 (112–328)] and blood urea nitrogen [48 (7–27)], and decreased creatinine [1.6 (0.4–1.8)] levels. Urinalysis revealed elevated red and white blood cells; the specific gravity was 1.025. Hypothyroidism was diagnosed and administration of levothyroxine (Thyrozone®, Phoenix Pharmaceuticals Inc.; Burlingame, CA, USA) 0.8 mg p.o. twice daily was initiated (Figure 1).

After 19 days of thyroid hormone supplementation the dog was re-examined because it had developed skin lesions that worsened over a 5 day period. A focal area of pyotraumatic dermatitis (10 cm in diameter) was present on the dorsal cervical region at the base of the skull. The dog had no known previous history of skin diseases. The hair was clipped and the lesions were cleansed with a povidone iodine solution. Triamcinolone acetonide (8 mg, Vetalog, Boehringer Ingelheim Vetmedica, Inc.; St. Joseph, MO, USA) and 400 mg ampicillin suspension (Polyflex, Boehringer Ingelheim Vetmedica, Inc.) were administered subcutaneously and amoxicillin (generic unknown brand) 500 mg p.o. twice daily was prescribed.

Five days later the lesions had worsened and involved the dorsal spine and the caudal legs (Figure 1). General-

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Table 1. Thyroid function and immunological assessments.

Test	Prior to 1st exposure to thyroid medication	Laboratory 1 Reference values	12 months after 2nd reaction (1st rechallenge, with excipients)	17 months after 2nd reaction (1st rechallenge, with excipients)	Before rechallenge (without suspected excipients)	Ten weeks of treatment (without suspected excipients)	Laboratory 2 Reference values
Total T4	<0.4	0.9–3.9 µg/dL	7	5.5	15	25	11–60 nM
Free T4			1	2	4	8	6–23 nM
Total T3	<35	55–150 ng/dL	0*	0.2*	0.5	0.9	0.8–2.1 nM
Free T3			5.3*	1.2*	3.3	3.4	1.2–8.2 nM
Canine TSH			1.11	0.94	0.47	<0.03	<0.52 ng/mL
T4 autoantibody			19%	13%	14	10	<20%
T3 autoantibody			15%*	7%	5	3	<10%
Thyroglobulin autoantibody			173%	190%	193	172	<25%

T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone

*Falsely decreased total T3 because of a falsely normal free T3 due to anti-T3 antibodies.

ized erythema and areas of epidermal desquamation were present; the hair coat was normal. The lesions were clipped and cleansed with a povidone iodine solution. The referring veterinarian suspected a potential adverse cutaneous reaction to the thyroid supplementation and discontinued it as a precaution. In addition, a generic ciprofloxacin 500 mg p.o. twice daily for 10 days was prescribed along with fish oil capsule 2000 mg twice daily (Aller G3®, Vetoquinol USA; Fort Worth, TX, USA).

Three weeks after levothyroxine discontinuation the skin lesions had completely resolved. Due to concern about a possible cutaneous reaction to a component in the first thyroid supplement, the primary care veterinarian prescribed a different formulation of levothyroxine (Synthroid®, AbbVie Inc.; North Chicago, IL, USA) 0.9 mg p.o. twice daily. Two days later, generalized erythema and desquamation reappeared. At this point the referring veterinarian again suspected a hypersensitivity reaction to the levothyroxine medication and discontinued it. Lesions were treated with topical therapy and resolved within a few days.

Because an adverse drug reaction was considered likely, the dog was referred to the Internal Medicine service at the University of Illinois-Urbana-Champaign to discuss treatment with a T3 supplement. The internist advised consultation with a veterinary pharmacologist because T3 and T4 have very similar structures, and T3 formulations often share similar inactive ingredients to T4 supplements. Thus, exposure to a T3 supplement could trigger a new and potentially more severe reaction. Based on this consideration, and the fact that hypothyroidism is not a life-threatening illness, a decision was made to temporarily avoid thyroid supplementation.

Over the next 9 months the dog's hypothyroidism was untreated and although no new skin lesions developed, the dog's energy level was low and its weight increased to 51.4 kg. Additional thyroid hormone assessments (Table 1) were performed and were compatible with primary hypothyroidism related to lymphocytic thyroiditis. Because of medical concerns regarding untreated clinical hypothyroidism, a drug challenge was discussed. The thyroxine tablets associated with both skin reactions shared two inactive ingredients: magnesium stearate and polyvinylpyrrolidone. The dog was treated with a levothyroxine supplement without these two ingredients

(Leventra®, Merck Animal Health; Summit, NJ, USA; 0.9 mg once daily). To closely monitor for a severe adverse drug reaction, the dog was hospitalized during the first day of dosing. The first treatment was well tolerated and the dog was discharged with instructions to observe the dog closely for adverse effects. No skin lesion developed, its weight decreased to 41.2 kg, and thyroid hormone panels normalized. After 1.5 years of treatment the dog continues to do well. The lack of reaction to the latest supplement suggests that the original cutaneous reactions mostly likely targeted one of the inactive ingredients rather than the thyroid hormone itself.

Discussion

Professional veterinary websites, such as the Veterinary Information Network, contain many discussions related to suspected hypersensitivity reactions to levothyroxine. However, only one publication (a conference abstract) is available in the veterinary literature on the subject.¹ In that case the dog apparently suffered an idiosyncratic reaction to one of the inactive ingredients of the thyroid supplement rather than the hormone itself. Despite numerous discussions of such a reaction on professional medical sites, the human literature contains a limited number of published cases.^{2–7} Interestingly, most human cases appear to be “immediate” reactions (i.e. Type I anaphylactic reactions happening within 24 h of exposure), whereas veterinary forums usually mention “delayed” reactions (i.e. Type II/III/IV hypersensitivity reactions after several days of exposure).⁸ In the present case the reaction also appeared to be “delayed” because the first clinical signs appeared after more than 2 weeks of thyroid supplementation.

Various algorithms have been developed to help establish a diagnosis of adverse drug reactions.^{9,10} Indeed, this can be challenging when the patient is treated with multiple medications at the same time as the reaction and/or the clinical signs also correspond to other aetiologies. Based on the clinical signs, timing, outcomes of de-challenges and re-challenges, this event would obtain a high score in all adverse drug reaction algorithms (ABON, RUCAM, Naranjo),¹⁰ making it a “very likely” drug allergic reaction. Furthermore, no lesions have been observed

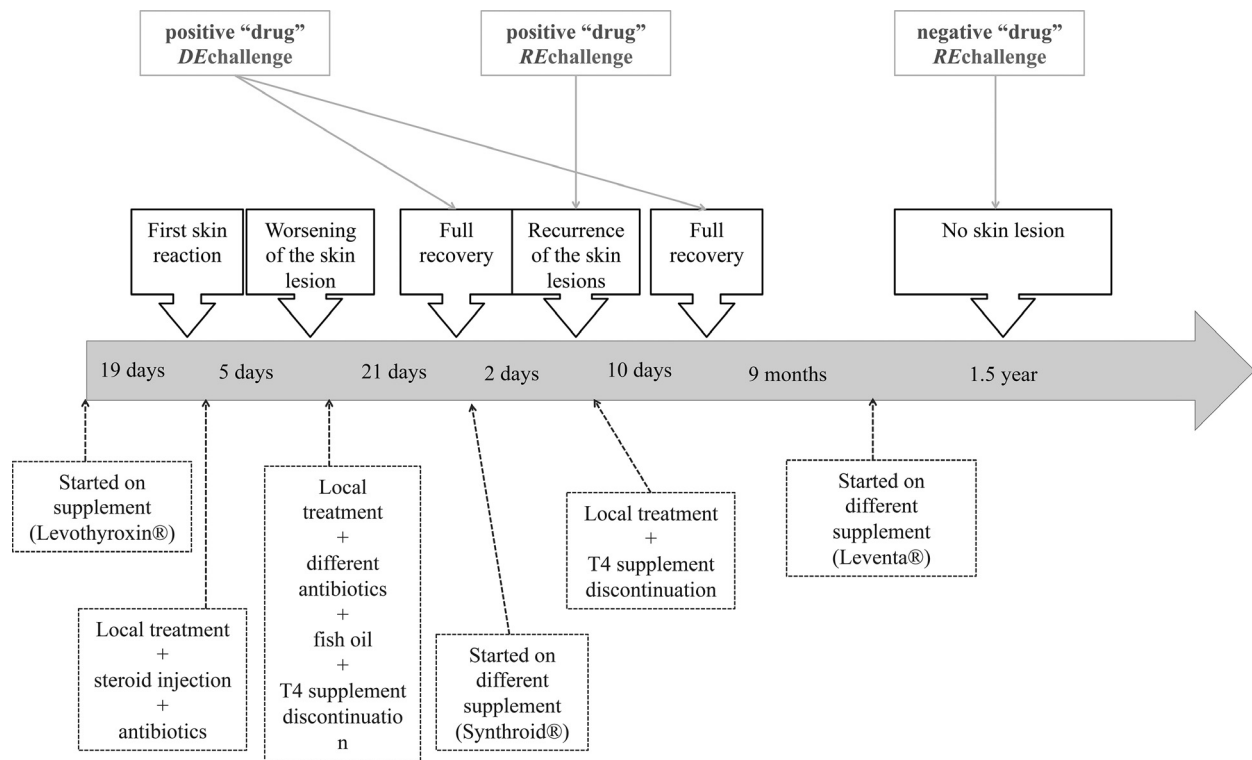


Figure 1. Timeline of events during treatment with and allergic reactions to thyroid supplements in a dog.

after treatment for 1.5 years with a thyroid supplement lacking the suspect inactive ingredients in the two previous medications associated with the clinical reactions. This clinical pattern strongly suggests that the delayed cutaneous hypersensitivity reaction to the thyroid supplements most probably targeted one of the inactive ingredients rather than the active ingredient (T4). Among the two inactive ingredients present in both formulations, only magnesium stearate has been associated with a drug allergic reaction in the literature, and this was in one human case report.¹¹ To date, there is no published report of reaction to the other inactive ingredient, polyvinylpyrrolidone. A re-challenge with each of the inactive ingredients would be needed to identify the one responsible for the reaction.

Patients with autoimmune diseases, like the dog in this report, are thought to have a higher incidence of immune-mediated drug reactions although the connection has mainly been evaluated for systemic autoimmune diseases rather than localized disorders like hypothyroidism.^{12,13} These immune systems might have a lower threshold for immune reactivity over tolerance. Some major histocompatibility complex (MHC) II genetic predispositions have been studied in human drug allergy.^{12,14,15} Adult-onset canine hypothyroidism is an immune-mediated disease for which some genetic predispositions, including MHC II, have been suggested.^{16–18} Reported cases of allergic reactions to thyroid supplements in human medicine have included no, or limited, investigations of the specific target ingredient or its exact pathogenesis.^{2–5,7}

The skin is the most common target of delayed drug immune hypersensitivity in humans and one of the most common in canine cases.⁸ However, drug hypersensitiv-

ity reactions commonly target other organs, especially the liver and blood cells.⁸ Interestingly, thyroid diseases themselves are often associated with cutaneous problems in humans and dogs.^{19,20} The pre-existing thyroid disease might have predisposed the dog to develop cutaneous signs as the manifestation of its hypersensitivity reaction. Unfortunately, skin biopsy findings were not available for this case. Most of the few cases of thyroid hormone allergy in humans also had cutaneous clinical signs, but the liver was targeted in one of them.^{2–5,7}

It is dangerous to reintroduce a drug suspected to be responsible for an allergic reaction without a careful step-by-step approach under medical supervision. Most desensitization protocols in human medicine have been developed for nonbiological drugs.²¹ However, there are some reports of desensitization for insulin allergy^{22–24} and two reports of desensitization in levothyroxine-allergic human patients.^{4,6} Until now, no desensitization has ever been investigated to address any type of drug allergy in veterinary medicine. This presently renders attempting such desensitization process hazardous or potentially unethical.

Although it would have been very interesting to have access to skin biopsies, rechallenges with each inactive ingredient separately and some *ex vivo* testing for antigen-specific immune markers, this case does provide several valuable points for the veterinary literature. The authors could find no other report in the veterinary literature describing a delayed cutaneous hypersensitivity reaction to a thyroid supplement in a dog with no prior evidence of allergic disease, confirmed by drug discontinuation and drug provocation tests. In addition, this is the first case report with strong evidence for an immune-mediated reaction against the inactive ingredients of a

drug preparation rather than its active component. Finally, this dog had a delayed hypersensitivity reaction rather than an immediate reaction to a thyroid supplement.

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Résumé

Contexte – Bien que des discussions sur les réactions allergiques aux suppléments thyroïdiens soient fréquentes sur les forums professionnels, il n'y a presque pas d'information dans la littérature sur ces réactions médicamenteuses spécifiques idiosyncrasiques.

Sujet – Un chien avec une prise de poids associée à une hypothyroïdie et une léthargie modérée a reçu des comprimés de lévothyroxine (0.018 mg/kg deux fois par jour). Après 19 jours le chien a développé des lésions cutanées sévères répondant à l'arrêt de la lévothyroxine et un traitement corticoïde et antibiotique. Trois semaines plus tard, des comprimés différents de lévothyroxine ont été prescrits. En 48h le chien a développé une réaction cutanée plus sévère qui s'est résolue à l'arrêt du traitement et avec des soins topiques appropriés.

Objectifs – Confirmer la possible hypersensibilité et identifier ses cibles chimiques.

Méthodes et résultats – Les deux formules de lévothyroxine partageaient deux composants inactifs : le stéarate de magnésium et la polyvinylpyrrolidone. Neufs mois après l'arrêt de la supplémentation thyroïdienne, une formulation sans aucun de ces deux composants a été utilisée pour une provocation. Il n'y a eu aucune récurrence de réaction médicamenteuse et après 1.5 ans de traitement le chien est resté normal.

Conclusion et importance clinique – Ces éléments suggèrent fortement que ce chien a présenté une réaction idiosyncrasique (à médiation immune) contre un ou deux composants actifs dans les deux premières formulations de lévothyroxine. A notre connaissance aucune autre réaction d'hypersensibilité retardée à un supplément thyroïdien chez un chien dont le déclencheur chimique serait un composant inactif plutôt que l'agent thérapeutique lui-même. Nous espérons que ce cas permettra d'améliorer la sensibilisation des réactions allergiques aux suppléments thyroïdiens et aux réactions allergiques aux composants inactifs des formulations.

Resumen

Introducción – aunque las discusiones acerca de las reacciones alérgicas a los suplementos tiroideos son numerosas en los foros profesionales, no existe apenas información en la literatura de estas reacciones idiosincráticas específicas

Animales – un perro con historia de aumento de peso asociado con hipotiroidismo y ligera letargia fue tratado con tabletas de levotiroxina (0,018 mg/kg dos veces al día). Tras 19 días el perro desarrolló una condición de la piel severa que respondió a la retirada del tratamiento con levotiroxina, y a terapia con glucocorticoides y antibióticos. Tres semanas más tarde se administró una tableta diferente de levotiroxina. En menos de 48 horas el perro desarrolló lesiones cutáneas más severas que se resolvieron con interrupción del tratamiento y con terapia tópica apropiada.

Objetivos – confirmar una posible reacción de hipersensibilidad e identificar su diana química.

Métodos y resultados – las dos formulaciones de levotiroxina prescritas compartían dos ingredientes inactivos: estearato de magnesio y polivinilpirrolidona. Nueve meses tras la discontinuación de la suplementación tiroidea se utilizó una formulación sin ninguno de estos compuestos para intentar otra reexposición. No hubo recurrencia de la reacción de hipersensibilidad y tras 1,5 años de tratamiento el perro permanece normal

Conclusión e importancia clínica – los resultados sugieren que este perro tuvo una reacción idiosincrática (posiblemente inmunomediada) contra uno o ambos ingredientes inactivos en las dos primeras formulaciones de levotiroxina. No conocemos ninguna otra reacción de hipersensibilidad retardada confirmada a un suplemento tiroideo con la diana química siendo posiblemente un ingrediente inactivo en lugar del agente terapéutico en sí mismo. Esperamos que este caso incremente la atención acerca de las reacciones alérgicas a los suplementos tiroideos y las relaciones alérgicas a componentes inactivos de las formulaciones.

Zusammenfassung

Hintergrund – Obwohl die Diskussionen über allergische Reaktionen auf Schilddrüsenpräparate in professionellen Foren reichlich vorkommen, gibt es in der Literatur fast keine Information über diese speziellen idiosynkratischen Reaktionen.

Tiere – Einem Hund mit der Anamnese einer mit Hypothyreose-assoziierten Gewichtszunahme und geringer Lethargie wurden Levothyroxin Tabletten (0,018mg/kg zweimal täglich) verabreicht. Nach 19 Tagen entwickelte der Hund eine starke Hautreaktion, die sich auf das Absetzen des Levothyroxins sowie auf eine Therapie mit Antibiotikum und Kortison besserte. Drei Wochen später wurde eine andere Levothyroxin Tablette verschrieben. Innerhalb von 48h entwickelte der Hund eine schwerwiegendere Hautreaktion, die nach Absetzen der Medikamente und einer entsprechenden topischen Behandlung verschwand.

Ziele – Das Ziel war es eine mögliche Hypersensibilitätsreaktion zu bestätigen und ein chemisches Target zu identifizieren.

Methoden und Ergebnisse – Die beiden verschriebenen Levothyroxinformulierungen hatten einen gleichen inaktiven Inhaltsstoff: Magnesium Stearate und Polyvinylpyrrolidone. Neun Monate nach Beendigung der Schilddrüsenpräparate wurde eine Formulierung zur neuerlichen Provokation verwendet, die keinen der beiden Stoffe beinhaltete. Diesmal traten keine Nebenwirkungen auf und nach 1,5 Jahren mit dieser Behandlung ist der Hund normal.

Schlussfolgerungen und klinische Bedeutung – Bei diesem Hund liegt ein deutlicher Hinweis auf eine idiosynkratische Reaktion (am wahrscheinlichsten immun-vermittelt) gegenüber einem oder beiden inaktiven Inhaltsstoffen in den beiden ersten Formulierungen des Levothyroxins vor. Es ist uns nicht bekannt, dass bisher eine verzögerte Hypersensibilität auf ein Schilddrüsenpräparat bei einem Hund beschrieben ist, bei dem der vermutlich auslösende Stoff ein inaktiver Bestandteil und nicht der chemische Bestandteil war. Wir hoffen, dass dieser Fall das Bewusstsein bezüglich allergischer Reaktionen auf Schilddrüsenpräparate, sowie bezüglich allergischer Reaktionen auf inaktive Komponenten der Formulierung steigern wird.

要約

背景 – 多くの専門家の公開討論会で、甲状腺製剤のアレルギー反応が議論されているが、これらの特定の特異的な薬物反応は論文にはほとんど記載がない。

供与動物 – 甲状腺機能低下症と関連した体重増加および軽度の元気消失の病歴のあるイヌに、レボチロキシン錠 (0.018 mg/kg 1日2回) を処方した。19日後、そのイヌはレボチロキシンの休薬および抗菌薬とグルココルチコイド療法に反応する重度の皮膚症状を示した。3週間後、異なるレボチロキシン錠が処方された。48時間以内にそのイヌは休薬と適切な外用療法によって治癒する、さらに重度の皮膚反応を発症した。

目的 – 可能性のある過敏症反応を確認することおよび、その薬物ターゲットを特定すること。

方法と結果 – 2種類の処方済みレボチロキシン錠にステアリン酸マグネシウムおよびポリビニルピロリドンの2つの非活性原材料が共通していた。甲状腺製剤の中止から9ヶ月後、これらの2つの化合物を含まない製剤を2度目の再投与試験として使用した。薬物反応は再発せず、治療の1.5年後もイヌは正常であった。

結論および臨床的な重要性 — これらの要素は、このイヌが最初の2種類のレボチロキシン製剤に含まれる非活性原材料の1つ、あるいは両方にたいして特異的な反応(免疫介在性の様な)を示していたことを強く示唆する。筆者らはイヌにおける今までに立証された甲状腺製剤に対する遅延型過敏症は治療薬そのものよりむしろ、非活性原材料が薬剤トリガーになることに気づいていなかった。筆者らは、この症例が甲状腺製剤に対するアレルギー反応および非活性製剤成分に対するアレルギー反応に関する認識を高めることを望んでいる。

摘要

背景 — 虽然在专业论坛上有对于甲状腺补充剂过敏的讨论,但几乎没有这类专属性药物反应的具体文献信息。

动物 — 一只犬有体重增加和轻度嗜睡这类甲状腺功能减退相关病史,口服左旋甲状腺素片(0.018 mg/kg一日两次)。19日后该犬出现严重的皮肤问题,停用左旋甲状腺素以及使用抗生素和糖皮质激素后症状消失。三周后使用另一种左旋甲状腺素片。48小时内该犬表现出更严重的皮肤反应,停药和局部护理后症状消失。

目的 — 确定可能的过敏反应并识别其化学靶点。

方法与结果 — 这两种左旋甲状腺素片都有两种惰性材料:硬脂酸镁和聚乙烯吡咯烷酮。停药九个月后,使用另一种左旋甲状腺素片。没有再发生药物反应,1.5年后该犬无异常。

总结与临床意义 — 这些表现足以证明:该犬对前两种左旋甲状腺素片的一种或两种惰性材料有特异性反应(可能为免疫介导性)。对于确定为甲状腺素补充剂引起的犬迟发型过敏反应,我们之前并不知道化学靶点可能是惰性材料而非药物本身。希望这个病例能提高我们的意识,来甄别是甲状腺素补充剂引起的过敏反应还是惰性配方成分。