Short Communication

Journal of Feline Medicine and Surgery
2022, Vol. 24(6) e138–e141

DOI: 10.1177/1098612X221091738
journals.sagepub.com/home/jfm

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS*

Evaluation of potential thiamazole exposure of owners of orally treated hyperthyroid cats

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Abstract

Objectives The objective of this study was to evaluate the presence of traces of thiamazole in the urine of owners of hyperthyroid cats treated with antithyroid drugs.

Methods Urine was collected from 24 owners of hyperthyroid cats, five human patients treated with thiamazole and five healthy humans without any contact with antithyroid drugs. All owners of hyperthyroid cats were asked to fill out a questionnaire. Urine of hyperthyroid cats was collected by spontaneous micturition. All urine samples were stored at −20°C until analysis by ultra-high-performance liquid chromatography coupled to high-resolution quadrupole Orbitrap mass spectrometry.

Results These owners were assessed to have a lot of contact with their cat. Adherence to antithyroid medication handling guidelines was rather poor. High concentrations of thiamazole were detected in all feline samples (median concentration 2818 ng/ml; range 104–15,127) and in the urine of all human patients treated with thiamazole (median concentration 4153 ng/ml; range 1826–5009). No thiamazole was detected in the urine of owners of hyperthyroid cats (limit of detection 3.88 ng/ml; limit of quantification 11.75 ng/ml).

Conclusions and relevance The results regarding the potential exposure of owners of hyperthyroid cats to antithyroid drugs are reassuring. Nevertheless, prudence is still warranted when administering antithyroid drugs. Whether these results can be extrapolated to the use of transdermal application requires further investigation.

Keywords: Hyperthyroidism; antithyroid; thiamazole; chromatography; teratogenic

Accepted: 15 March 2022

Introduction

Hyperthyroidism is the most frequently diagnosed feline endocrine disease worldwide, and is often treated with antithyroid drugs.[1] Thiamazole and its prodrug carbimazole are licensed for cats. In cats, antithyroid drugs are available for topical or oral administration. Antithyroid drugs are associated with side effects in both cats and humans.[2–8] Furthermore, antithyroid medication could be potentially teratogenic and, although owners should handle antithyroid medication with care, this recommendation does not always seem to be followed.[8–11] Currently, no studies have qualified and quantified the urinary excretion of thiamazole in cats in combination with a risk assessment of direct or indirect exposure for the owners. Nowadays, cats often live in close contact with their

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owners (rubbing, licking, sharing beds); hence, exposure of the cat owner to antithyroid medication should be evaluated.

The aim of this study was to investigate the presence of thiamazole in urine of owners of hyperthyroid cats treated with licensed oral antithyroid drugs.

Materials and methods

Samples

The owners of medically treated hyperthyroid cats presenting to the Small Animal Clinic (Faculty of Veterinary Medicine, Ghent University) and to a nearby private veterinary practice were asked to participate. Five people treated with antithyroid drugs presented at the endocrinology outpatient clinic (Ghent University Hospital) and five humans without exposure to thyroid medication were prospectively recruited as positive and negative control groups, respectively. Local ethical committee approval (UZ Gent, BC-06820) was obtained. All participants signed a written informed consent form. The owners of hyperthyroid cats completed a questionnaire related to the handling of the medication and contact with their cat.

Feline and human urine samples were collected by spontaneous micturition. In cats, a non-absorbent cat litter was used at home. A sample of at least 2 ml urine was requested. Urine samples were stored at −20°C within 24 h of collection. The samples were thawed prior to batch analysis.

Instrumentation

Chromatographic separation was achieved on an ultra-high-performance liquid chromatography (UHPLC) system (Dionex UltiMate 3000 XRS; Thermo Fisher Scientific), equipped with reversed phase chromatography column (Acquity UPLC HSS T3 C18 column; Waters) kept at a constant temperature of 25°C. Detection was performed on a standalone bench top quadrupole Orbitrap high-resolution mass spectrometer (Q-Exactive; Thermo Fisher Scientific), which was preceded by heated electrospray ionisation (HESI-II source) in positive ionisation mode. Of each sample, 10 µl was injected. Analysis was performed on two consecutive days. Targeted data processing was carried out with Xcalibur 3.0 software (Thermo Fisher Scientific).

Extraction

The thawed samples (n = 57) were centrifuged (4–25°C) for 10 mins at 4000 *g*. Fifty microlitres of propylthiouracyl–d5 (PTU-d5, internal standard; 1 ng/µl) was added to 1 ml urine before vortexing for 30 s, followed by 15 mins of equilibration. Subsequently, 1 ml phosphate buffered saline was added to each sample. The samples were vortexed for 1 min and heated for 30 mins at 65°C. Ethyl acetate (5 ml) was added to the mixture, followed by manual shaking for 1 min, after which the supernatant was removed. The latter was performed twice, employing 10 ml ethyl acetate in total.

The extracts were transferred to plastic tubes and evaporated to dryness at 60°C under a gentle stream of nitrogen. Two hundred microlitres of 0.1% of aqueous formic acid was added to each residue and vortexed for 30 s. Finally, 200 µl was transferred to a liquid chromatography mass spectrometry vial for analysis.

Quantification

To prepare a calibration curve for quality assurance of the procedure, 1 ml of two blank urine samples (one from a healthy cat and one from a healthy human) was placed five times in a sample tube. In each sample, 1 ng/µl internal standard PTU-d5 was added. The samples were spiked by adding increasing amounts of a standard solution. Based on the calibration curve, the limit of detection (LOD; 3.88 ng/ml) and the limit of quantification (LOQ, 11.75 ng/ml, LOQ 11.75 ng/ml) were determined.

The method described has been extensively validated by Vanden Bussche et al.[12]

Results

Twenty-four owners of a total of 23 hyperthyroid cats were included. Thiamazole was administered to 12 cats in syrup form (median daily dosage/cat 5 mg; range 2.5–7.5) and to 11 cats in tablet form (median daily dosage/cat 5 mg; range 2.5–15 mg). The cats had been treated for varying lengths of time (median of 11 months; range 1 week–5 years).

Most owners (22/24) reported living in close contact with their cat. Fourteen cats lived mainly or exclusively indoors. Twenty-one owners were the person responsible for administering the medication at home. One cat received medication from both owners, as such, they both participated in the study. Sixteen owners were the primary person responsible for cleaning the litter box. Two cats had no litter box as they were urinating and defecating outside, and one response was missing. Two of 24 owners were splitting the tablets without using gloves. Two people wore gloves to administer the tablets; one person used fingertip protectors. Of the other 21 owners, nine washed their hands after giving the medication, eight did not and four responses were missing.

High concentrations of thiamazole were detected in all feline samples (median concentration 2818 ng/ml; range 104–15,127) and in the urine of all human patients treated with antithyroid drugs (median concentration 4153 ng/ml; range 1826–5009). No traces of thiamazole were detected in the urine of owners of hyperthyroid cats (LOD 3.88 ng/ml) or in the urine of the negative control group.

Discussion

No thiamazole was found in the urine of owners of hyperthyroid cats treated with antithyroid drugs after urinalysis by UHPLC coupled to high-resolution quadrupole

Orbitrap mass spectrometry. These results are quite reassuring, as the owners described having close contact with their cat. Owner exposure to thiamazole occurs not only while administering the medication, but could also be indirect, especially through contact with urine and faeces when cleaning the litter box.

Thiamazole is the only registered antithyroid drug for cats in Belgium. Consequently, only cats treated with this molecule were included. However, as carbimazole is a prodrug of thiamazole similar results would be expected. As in humans, oral thiamazole is rapidly and well absorbed from the gastrointestinal tract in cats.[13–17] Excretion of unchanged thiamazole and its metabolites occurs mainly in urine in human patients, with only a small percentage in faeces.[13–15] Urine is also the major route of excretion in rats.[14,18] No specific study has been conducted on the excretion of thiamazole in cats. In a previous unpublished study by our group, high concentrations of thiamazole were detected in all urine samples of 20 client-owned cats treated with thiamazole (range 1166–31,303 ng/ml).

Thiamazole readily crosses placental membranes and is potentially teratogenic, particularly when administered in the first trimester of pregnancy.[19,20] Reported thiamazole-related embryofetopathies include aplasia cutis, craniofacial birth defects, defects of the abdominal wall and gastrointestinal tract, and ventricular septal defect.[21] Two recent meta-analyses confirmed that the use of thiamazole during pregnancy was associated with an increased risk of congenital anomalies.[22,23] A systematic review and meta-analysis of observational studies with methodological considerations published in 2021 reached the same conclusion, and the absolute risk difference of a congenital defect vs the unexposed comparison group per 1000 live births was estimated to be 17.8 in women treated with thiamazole or carbimazole.[24]

Although uncommon, the described congenital anomalies can be severe. This underscores the importance of prudent handling of antithyroid medication in veterinary medicine, especially by women who are pregnant or are intending to become pregnant. Worryingly, owners' responses to the questionnaire indicated that compliance with precautions when administering antithyroid drugs was rather poor. Indeed, 2/24 owners were splitting the tablets without using gloves, 8/17 did not wash their hands after giving the medication and only 3/24 were using protection (gloves or fingertip protectors) while administering the medication. The latter could be due to insufficient instructions from their veterinarian regarding the use of the medication. Another explanation would be that these instructions were communicated to, but not followed by, the owners. In the veterinarian–owner relationship, transparency about possible side effects of veterinary drugs on pet and human health is essential in caring for animals and the trust of the owner in the professional. Some people may be worried and reluctant to use the medication after having read the handling guidelines. This study can contribute to reassuring overworried owners.

Although participants described living in close contact with their cat, thiamazole was not detected in their urine. In this study, a LOD of 3.88 ng/ml was achieved. Therefore, it is possible that very small amounts of thiamazole were present but could not be detected in human urine. However, such a low concentration may appear to be harmless. There is currently no information on the minimum dose of thiamazole that might induce teratogenic effects.

This study did not include cats treated with carbimazole orally or thiamazole as a transdermal gel. Transdermal formulations are not approved for veterinary use and therefore do not necessarily have the same standards or data as veterinary-approved oral formulations. When applying the gel, protection with gloves or finger cots is mandatory, but it is not known whether these guidelines are actually followed. It is possible that the exposure of this population to antithyroid drugs is higher than following oral dosing.

Conclusions

No thiamazole was detected in the urine of owners of hyperthyroid cats treated with oral antithyroid drugs. These results regarding the potential exposure of owners of hyperthyroid cats to antithyroid drugs are reassuring. However, caution is still warranted. Whether these results can be extrapolated to the use of transdermal application should be further investigated.

Acknowledgements The authors would like to thank Dr Ingrid De Beleyr and the endocrinology service of Ghent University Hospital for their assistance with this study.

Author note This paper was presented as a poster at the 2021 ECVIM-CA congress.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental

animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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References

1 Peterson M. **Hyperthyroidism in cats: what's causing this epidemic of thyroid disease and can we prevent it?** *J Feline Med Surg* 2012; 14: 804–818.
2 Mooney CT. **Feline hyperthyroidism. Diagnostics and therapeutics.** *Vet Clin North Am Small Anim Pract* 2001; 31: 963–983.
3 Daminet S, Kooistra HS, Fracassi F, et al. **Best practice for the pharmacological management of hyperthyroid cats with antithyroid drugs.** *J Small Anim Pract* 2014; 55: 4–13.
4 Peterson ME, Kintzer PP and Hurvitz AI. **Methimazole treatment of 262 cats with hyperthyroidism.** *J Vet Intern Med* 1988; 2: 150–157.
5 Ducornet B and Duprey J. **Side-effects of synthetic antithyroid drugs** [article in French]**.** *Ann Med Intern* 1988; 139: 410–431.
6 Meyer-Gessner M, Benker G, Olbricht T, et al. **Side effects of antithyroid therapy of hyperthyroidism. A study of 1256 continuously treated patients** [article in German]**.** *Dtsch Med Wochenschr* 1989; 114: 166–171.
7 Cooper DS. **The side effects of antithyroid drugs.** *Endocrinologist* 1999; 457–478.
8 Cooper DS. **Antithyroid drugs.** *N Engl J Med* 2005; 352: 905–917.
9 Mandel SJ, Brent GA and Larsen PR. **Review of antithyroid drug use during pregnancy and report of a case of aplasia cutis.** *Thyroid* 1994; 4: 129–133.
10 Di Gianantonio E, Schaefer C, Mastroiacovo PP, et al. **Adverse effects of prenatal methimazole exposure.** *Teratology* 2001; 64: 262–266.
11 Diav-Citrin O and Ornoy A. **Teratogen update: antithyroid drugs-methimazole, carbimazole, and propylthiouracil.** *Teratology* 2002; 65: 38–44.
12 Vanden Bussche J, Vanhaecke L, Deceuninck Y, et al. **Development and validation of an ultra-high performance liquid chromatography tandem mass spectrometry method for quantifying thyreostats in urine without derivatisation.** *J Chromatogr A* 2010; 1217: 4285–4293.
13 Alexander WD, Evans V, MacAulay A, et al. **Metabolism of 35S-labelled antithyroid drugs in man.** *Br Med J* 1969; 2: 290–291.
14 Pittman JA, Beschi RJ and Smitherman TC. **Methimazole: its absorption and excretion in man and tissue distribution in rats.** *J Clin Endocrinol Metab* 1971; 33: 182–185.
15 Marchant B, Lees JFH and Alexander WD. **Antithyroid drugs.** *Pharmacol Ther Part B Gen Syst* 1978; 3: 305–348.
16 Trepanier LA, Peterson ME and Aucoin DP. **Pharmacokinetics of methimazole in normal cats and cats with hyperthyroidism.** *Res Vet Sci* 1991; 50: 69–74.
17 Trepanier LA, Peterson ME and Aucoin DP. **Pharmacokinetics of intravenous and oral methimazole following single- and multiple-dose administration in normal cats.** *J Vet Pharmacol Ther* 1991; 14: 367–373.
18 Sitar DS and Thornhill DP. **Methimazole: absorption, metabolism and excretion in the albino rat.** *J Pharmacol Exp Ther* 1973; 184: 432–439.
19 Yoshihara A, Noh J, Yamaguchi T, et al. **Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation.** *J Clin Endocrinol Metab* 2012; 97: 2396–2403.
20 Andersen SL, Olsen J, Wu C Sen, et al. **Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study.** *J Clin Endocrinol Metab* 2013; 98: 4373–4381.
21 Seo GH, Kim TH and Chung JH. **Antithyroid drugs and congenital malformations: a nationwide Korean cohort study.** *Ann Intern Med* 2018; 168: 405–413.
22 Li H, Zheng J, Luo J, et al. **Congenital anomalies in children exposed to antithyroid drugs in-utero: a meta-analysis of cohort studies.** *PLoS One* 2015; 10: e0126610. DOI: 10.1371/journal.pone.0126610.
23 Song R, Lin H, Chen Y, et al. **Effects of methimazole and propylthiouracil exposure during pregnancy on the risk of neonatal congenital malformations: a meta-analysis.** *PLoS One* 2017; 12: e0180108. DOI: 10.1371/journal.pone.0180108.
24 Morales DR, Fonkwen L and Nordeng HME. **Antithyroid drug use during pregnancy and the risk of birth defects in offspring: systematic review and meta-analysis of observational studies with methodological considerations.** *Br J Clin Pharmacol* 2021; 87: 3890–3900.