

The effect of per os vs subcutaneous ¹²³I iodine administration on percentage thyroidal radioactive iodine uptake in normal cats

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Abstract

Background: Historical and recent literature disagree on whether a higher PO ¹³¹I dosage, compared to IV or SC routes, is required for successful resolution of spontaneous hyperthyroidism in cats, necessitating investigation into the effect of PO and injectable radioactive iodine administration on % thyroidal radioactive iodine uptake (RAIU).

Hypothesis/Objectives: To investigate the effect of PO and SC routes of ¹²³I administration on paired % thyroidal RAIU in euthyroid cats. Specifically, a 1.5-fold difference (50% relative change) was hypothesized, which in absolute terms can be expressed as a 3.25% increase in the mean %RAIU of 7.04% after PO ¹²³I administration to 10.56% after SC dosing.

Animals: Seven healthy euthyroid teaching-research colony cats.

Methods: A randomized, radiologist-blinded crossover study comparing %RAIU after PO and SC ¹²³I administration.

Results: Percentage thyroidal RAIU values (mean ± SD; 95% confidence interval) after PO (4.81% ± 1.63%; 3.30%-6.23%) and SC (5.26% ± 2.43%; 3.01%-7.51%) ¹²³I administration were associated with a median within-pair absolute difference of 0.2% (range: min, 0.1%-max, 4.9%). Statistical significance was not achieved (*P* = .45). Six of 7 cats had a within-pair absolute difference of 0.1% to 0.9% (relative change of 4%-20%), but a single outlier cat had a within-pair absolute difference of 4.9% (relative change of 108%).

Conclusions and Clinical Importance: This study did not detect an effect of ¹²³I administration route on paired % thyroidal RAIU in euthyroid cats. However, a type 2 statistical error due to small sample size is possible.

KEYWORDS

¹²³I thyroid scintigraphy, euthyroid cats, percentage thyroidal radioactive iodine uptake, route of iodine administration

Abbreviations: ¹²³I, radioisotope ¹²³I; ¹³¹I, radioisotope ¹³¹I; CI, confidence interval; RAI, radioactive iodine; RAIU, radioactive iodine uptake; ROIs, regions of interest.

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1 | INTRODUCTION

Radioactive iodine (RAI) ^{131}I therapy for hyperthyroidism in cats is widely accepted with success rates of 80% at 1 month and 95% at 6 months after treatment.¹ Subcutaneous and IV administration routes are typically used. Due to challenges procuring a sterile source of ^{131}I , RAI treatment centers in some countries, such as Australia and Canada, have had to consider administration of PO ^{131}I .^{2,3} The human medical community has no apparent need for sterile forms of ^{131}I as most diagnostic and therapeutic applications involve PO administration. In veterinary medicine, a single study demonstrated dosing equivalency with IV and SC ^{131}I , but relatively limited research has been done to directly compare PO iodine administration with injectable routes.⁴

Within the historical and recent literature, there appears to be disparity in ^{131}I dosing requirements between not only PO and injectable routes of RAI administration, but also PO dosing regimens over time.^{2,3,5-9} Earlier literature supported fixed-PO ^{131}I dosages of 5 or 6.8 mCi (range, 5.4-8.1 mCi).^{2,5} The median 6.8 mCi PO dose was 1.7 times the fixed 4 mCi IV dose used to attain similar treatment success rates in 2 separate studies from the same time period.^{2,6,7} These findings led to a perception that higher ^{131}I dosages were required with PO administration.² Recently, this historical literature has been challenged when treatment success was attained with a lower fixed-PO 3.7 mCi ^{131}I dose.³ Although the 3.7 mCi PO dosage resulted in treatment success rates similar to fixed- ^{131}I dosages of 3.35 mCi IV, and 4 mCi SC, this 3.7 mCi PO dose was still 1.9 times higher than a fixed 2 mCi SC dose, which also attained therapeutic success in mild to moderate cases of hyperthyroidism in cats.^{3,8,9}

A potential explanation for the outcome of these varied dosing requirements is the possibility that an inherent physiological difference in percentage thyroidal radioactive iodine uptake (%RAIU) occurs based on route of administration, particularly PO vs injectable. A direct comparison of the %RAIU attained with PO and SC dosing does not yet exist in the feline veterinary literature to the authors' knowledge. Ascertaining the role that administration routes have on iodine uptake within the context of normal physiology will directly address whether an innate difference in %RAIU exists between PO and SC administration.

The primary goal of this study is to evaluate the effect of PO and SC ^{123}I administration on paired %RAIU in normal cats. Based upon the relative PO and injectable fixed-RAI dosing requirements (1.7- to 1.9-fold difference) reported in the veterinary literature, we hypothesized that a 1.5-fold difference (50% relative change) in paired %RAIU values might exist between PO and SC ^{123}I administration routes. Clinically, this represents an important difference in dosing requirements as higher PO RAI dosing can result in not only longer patient quarantines, and higher occupational exposures, but also possible dosing errors, thereby limiting treatment success. In absolute terms, the mean %RAIU (7.04%) and SD ($\pm 1.24\%$) reported in the literature after PO ^{123}I administration was hypothesized to increase by 3.52% to a value of 10.56% after SC dosing.¹⁰

2 | MATERIALS AND METHODS

2.1 | Study sample

Eight healthy, euthyroid domestic shorthair cats from a teaching and research colony at University of Saskatchewan participated in this study. Cats were determined to be euthyroid based on history, physical examination and baseline hematology (Advia 2120i; Siemens Healthcare Diagnostics Inc, Ireland), serum biochemistry profile (Cobas c311; Hitachi High-Technologies Corporation, Japan), urine specific gravity (Reichert VET360; Reichert technologies, Buffalo, New York), urine dipstick (Chemstrip9; Roche, Mississauga, ON, Canada), and serum total thyroxine (Immulite 1000; Siemens Healthcare Diagnostics, Inc, Los Angeles, California).

A sample size calculation was performed using a paired test comparing 2 correlated means and specifying SDs of the differences. The mean %RAIU (7.04%) and SD ($\pm 1.24\%$) reported in the literature after PO ^{123}I administration was hypothesized to increase by 3.52% to a value of 10.56% after SC dosing.¹⁰ Subsequently, a minimum sample size of 4 was calculated to attain a power of 0.8 and α of .05.¹⁰

All 8 cats were eating the same maintenance diet (Purina OM Overweight Management Dry Feline Formula, St. Louis, Missouri) containing 2.74 mg/kg iodine based on individualized resting energy requirements. The calculated daily energy requirements were divided into 2 feedings in the morning and evening for 6 months before the study. Each of the cats had access to their food ration via collar activated food dispensers. Ethical approval was granted by the University of Saskatchewan Animal Research Ethics Board (Animal Use Protocol Number 20190132). One cat was withdrawn from the study due to vomiting after PO ^{123}I administration, resulting in a final sample size of 7.

2.2 | Study protocol

The cats were randomly assigned to receive either a PO or SC dose of ^{123}I for the first arm of the crossover study. After a washout period of 7 days, each cat then received ^{123}I by the other route of administration for the second arm of the study. Each cat was individually housed during both arms of the study to allow for appropriate monitoring of drooling, and vomiting post PO ^{123}I administration.

The cats were fasted for 12 hours before receiving approximately 300 μCi of ^{123}I Sodium Iodide Solution (BWXT ITG Canada Inc, Cambridge, Canada) by either the PO or SC route of administration. Capsules were prepared by pipetting approximately 300 μCi of the sodium ^{123}I solution into a size #4 capsule (Capsuline, Dania Beach, Florida) and then sealing that capsule in a size #3 capsule of the same type to avoid leakage during the preimaging and administration period. For the SC doses, the stock solution was pushed through a 0.22 μm Millex-GS sterile filter (Merck Millipore Ltd, Cork, Ireland) and diluted with normal saline to allow for a fixed volume of 0.5 mL per 300 μCi of ^{123}I , which was administered with a BD 1 mL Tuberculin Slip Tip Syringe (Becton, Dickinson and Company, Franklin Lakes, New Jersey) and a

0.7 mm × 25 mm 22-Ga BD Precision Glide needle (Becton, Dickinson and Company).

The gamma camera (Millennium MRP, GE Medical Systems, Milwaukee, Wisconsin) was set up with a low-energy high-resolution collimator, a 20% energy window centered on the 159 keV photopeak of ^{123}I , and a 128 by 128 matrix with a 2.67 zoom. Before administration, the capsule or syringe of ^{123}I was imaged with the gamma camera for 2 minutes (approximately 200 000 counts). A 5 mm acrylic sheet was placed under the syringes and capsules to provide consistent imaging distance and attenuation between sources. After administration by both routes, the residual activity in the syringe, or an empty background image for capsules, was acquired using the same technique to account for background radiation and any residual volume in the syringe. After capsule administration, 4 to 6 mL of water was syringed PO to ensure passage into the stomach. The capsules were subsequently visualized in the region of the stomach by immediately placing the cats in sternal recumbency over the gamma camera and confirming the capsule location on the p-scope. A routine meal was fed 4 hours after iodine administration. The cats were then fasted for 12 hours before sedation, general anesthesia, and scintigraphy.

At 24 hours after iodine administration, the cats were sedated with a combination of 0.2 mg/kg butorphanol (Torbugesic, 10 mg/mL, Zoetis Canada Inc, Kirkland, Canada) and 0.008 mg/kg dexmedetomidine (Dexdomitor, 0.5 mg/mL, Zoetis Canada Inc) IM, 10 to 15 minutes before general anesthesia. General anesthesia was induced by mask with isoflurane ($^{PR}\text{AErrane}$ [isoflurane, USP], Baxter Corporation, Mississauga, Canada) at 0.5% to 2%, as needed, and oxygen at 1 L/min to facilitate 10-minute image acquisition times. Ventral planar images were acquired with the cat in sternal recumbency, and the head extended so that the ventral aspect of the neck was against the scan bed. These thyroid images were acquired over 10 minutes using the parameters previously described. Given that the thyroid gland is superficial relative to the cervical skin and situated directly over the gamma camera to acquire a planar ventral image, soft tissue attenuation correction was not considered necessary as determined to be appropriate in previous studies.¹¹⁻¹³

Image processing was done using purpose-built software (Thyroid Uptake Index Protocol for Xeleris, GE Healthcare). Isocontour regions of interest (ROIs) for each thyroid lobe, and then a suitable background region immediately below the thyroid ROIs, were generated semiautomatically. For each ventral planar image, the thyroidal percentage iodine uptake, also referred to as the radioactive iodine uptake (RAIU), was calculated by the software using the following equation:

$$\%RAIU = \frac{\text{Net counts per minute in thyroid}}{\text{Decay - corrected net counts per minute in the administered dose}} \times 100\%$$

The counts in each of the above factors were normalized for both the imaging acquisition time and the relative size of the background ROIs to the thyroid ROIs. For each image, a manual radiologist drawn ROI and %RAIU calculation was determined to confirm the software generated %RAIU. The scintigraphy scans and %RAIU values were reviewed by a board-certified radiologist who was blinded as to intervention. The reversal agent, 0.08 mg/kg

atipamezole (Antisedan, 5 mg/mL, Zoetis Canada Inc) IM, was administered after the scintigraphy was completed.

2.3 | Data and statistical analysis

The %RAIU values were assessed for normality with Shapiro-Wilk and normal probability plot testing. Parametric data were expressed as mean (SD) with a 95% confidence interval (CI), and nonparametric data expressed as median (min-max range). Matched pairs analysis was performed using a paired *t* test for parametric data and Wilcoxon signed-rank test for nonparametric data. An exact 95% CI was calculated for the proportion of cats with a difference in %RAIU of >1% between routes of ^{123}I administration. Statistical analysis and graphics were performed using commercially available software (GraphPad Prism 9, GraphPad Software, San Diego, California) and, for all analyses, statistical significance was set at $P \leq .05$.

3 | RESULTS

3.1 | Study sample

A single cat vomited after PO ^{123}I administration necessitating exclusion and reducing the sample size to 7. These 7 cats utilized in this study had a median age of 5 years (range, 4-8 years). The median body weight was 4.92 kg (range, 4.54-6.18 kg). Three of the cats were neutered males and 4 of the cats were spayed females. No significant abnormalities were identified upon review of history, physical examination or baseline hematology, serum biochemistry profile, urine specific gravity, urine dipstick, and serum total thyroxine levels. Relevant clinicopathological results are summarized in Table 1.

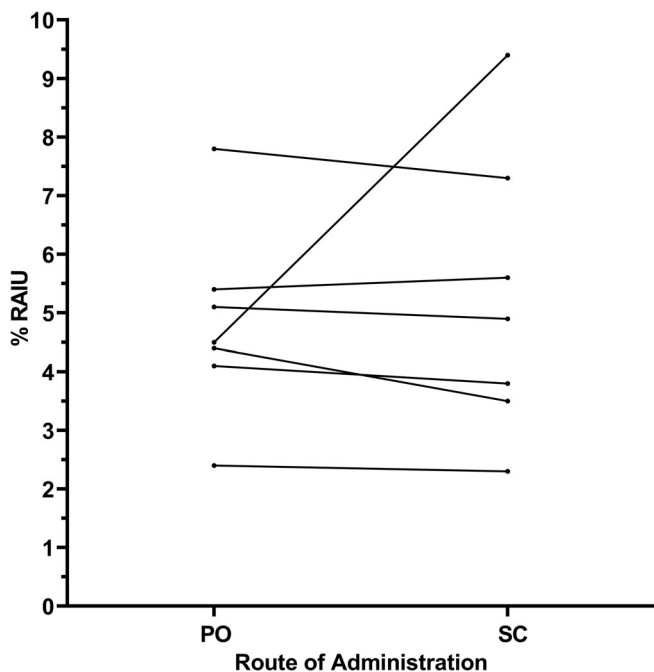
3.2 | Percentage RAIU associated with PO and SC ^{123}I administration

A Shapiro-Wilk normality test identified parametric distribution of the %RAIU values associated with both PO and SC routes of ^{123}I administration. PO and SC ^{123}I administration was associated with a mean %RAIU of 4.81% (SD = 1.63; 95% CI = 3.30-6.23) and 5.26% (SD = 2.43; 95% CI = 3.01-7.51), respectively. The within-pair absolute differences between PO and SC administration had a nonparametric distribution. The median within-pair absolute difference was 0.2% (range: min, 0.1%-max, 4.9%), ($P = .45$).

The paired %RAIU associated with PO and SC routes of ^{123}I administration are summarized as a paired dot plot (Figure 1). Five of 7 cats had higher PO and lower SC %RAIU values. For these 5 cats, the within-pair absolute difference between PO and SC %RAIU values for 4 of 5 cats was 0.1% to 0.5% (relative change of 4%-7%), and for 1 of 5 cats was 0.9% (relative change of 20%). Two of 7 cats had lower PO and higher SC %RAIU values. For these 2 cats, the within-pair absolute difference between PO and SC %RAIU values was 0.2%

TABLE 1 Select clinicopathological parameters in seven healthy euthyroid colony cats

Variable	Median	Range	Reference interval	Units
Red blood cell count	9.09	6.94-10.33	6.20-10.60	× 10 ¹² /L
Alkaline phosphatase	28	22-42	11-56	IU/L
Alanine aminotransferase	52	45-62	22-90	IU/L
Total thyroxine	26	23-38	13-50	nmol/L
Creatinine	92	75-124	78-178	μmol/L
Urine specific gravity	1.060	1.050-1.074	>1.035	

**FIGURE 1** Paired dot plot for 24-hour %RAIU after PO and SC ¹²³I administration. The median within-pair differences were associated with a *P* value of .45. RAIU, radioactive iodine uptake

(relative change of 4%) and 4.9% (relative change of 108%). This single cat had a substantially lower %RAIU value after PO administration (4.5%) compared to SC administration (9.4%). This proportion of cats in the study sample, 1/7 (14%), is consistent with an estimated population proportion, 95% CI, of 0.004 to 0.58 (4%-58%).

Subanalysis of only the 6 cats with 0.1% to 0.9% within-pair absolute differences was performed. A parametric distribution was identified for both the %RAIU after PO and SC dosing and the within-in pair absolute differences. PO and SC ¹²³I administration was associated with a mean %RAIU of 4.87% (SD = 1.78%; 95% CI = 3.00-6.73) and 4.57% (SD = 1.76%; 95% CI = 2.72-6.42), respectively. The within-pair absolute differences were associated with a mean of 0.3% (SD = 0.37%; 95% CI = -0.09 to 0.69) (*P* = .11).

4 | DISCUSSION

This randomized, single-blinded crossover study did not find an effect of PO and SC ¹²³I administration on paired % thyroidal RAIU in

euthyroid cats. Absolute differences between paired %RAIU after PO and SC ¹²³I administration were as follows: 5 of 7 cats, 0.1% to 0.5% (relative change 4%-7%); 1 of 7 cats, 0.9% (relative change 20%); and 1 of 7 cats, 4.9% (relative change 108%). For the 6 of 7 cats that had within-pair absolute differences of 0.1% to 0.9% (relative change of 4%-20%), these findings likely represent normal sampling variation as opposed to evidence for unique iodine uptake and metabolism associated with route of ¹²³I administration. However, the expected 1.5-fold difference (50% relative change) hypothesized to be clinically relevant was not observed except for a single cat with a 2-fold difference (108% relative change) in %RAIU after SC-dosing compared to PO-dosing. This makes a type 2 statistical error due to lack of power both a possibility and an important limitation of this study.

The results of this study must be cautiously extrapolated to geriatric hyperthyroid cats, but are most consistent with literature identifying that similar PO and injectable fixed ¹³¹I dosages can be used to successfully treat hyperthyroidism.^{3,8} In addition, a 2005 human clinical trial also reported the use of identical PO and IV mean therapeutic ¹³¹I dosages to successfully treat both Graves' disease and toxic nodular goiter.¹⁴ Older literature supporting the use of higher PO ¹³¹I dosages for the successful treatment of feline hyperthyroidism may not be accurate.^{2,5}

This study has some important limitations. The hypothesis that a 1.5-fold difference (50% relative change) in %RAIU exists between PO and SC ¹³¹I dosing regimens was drawn from comparisons of successful fixed-dose PO and injectable RAI-treatment protocols described in the literature.^{2,5-7} This assumption is problematic as many factors likely influenced the dosages and treatment successes observed in these studies: disease severity and volume of hyperplastic adenomatous tissue; balancing resolution of the hyperthyroid state while minimizing iatrogenic hypothyroidism and CKD progression; concurrent disease states; hyperthyroidism's effects on the gastrointestinal tract; and attempts to limit both occupational radiation exposures and duration of isolation in the RAI ward.^{2,3,5-9,15}

The use of a research colony of euthyroid cats with young adult cats (median age of 5 years [range, 4-8 years]) reflects normal feline physiology with respect to iodine metabolism and thyroidal uptake. Important differences likely exist in the target patient population of senior hyperthyroid cats, including but not limited to dietary iodine, gastrointestinal transit times, variability in the volume of the abnormal thyroid tissue, and concurrent or occult gastrointestinal disease. It has been proposed that RAI absorption is affected by the hyperthyroid state, particularly its effect on the gastrointestinal system.² Despite

limitations regarding extrapolation of these findings to hyperthyroid cats, the primary aim of this study was to initially investigate whether an intrinsic physiological difference in iodine uptake might exist between PO and SC routes of administration in euthyroid cats. It should also be noted that early, subclinical hyperthyroidism, although unlikely, could have been further addressed in this study by performing technetium pertechnetate imaging, serum-free thyroxine concentrations, and serum thyroid-stimulating hormone concentrations.

SC dosing did result in a %RAIU value approximately twice that associated with the PO route in a single cat (1 of 7). This observation may suggest that a subpopulation of cats do take up smaller percentages of iodine after PO consumption compared to SC injection. Unfortunately, this study does not address this possibility, as a much larger sample size would be needed to further identify if a subgroup of cats with unique iodine metabolism truly exists, which introduces the possibility of a type 2 error. This represents an important limitation of the current study. Alternative explanations for this individual cat might include dosing or administration errors, such as loss of a proportion of the dose through unobserved salivation or vomiting, capsule defectiveness, delayed gastric emptying, or undiagnosed enteropathy affecting intestinal absorption.

A sample size of 8 was initially chosen, but 1 cat vomited up the RAI within 2 hours of oral administration as confirmed with the use of a gamma counter held over the vomitus. Vomiting after RAI administration remains a concern with the use of this route of administration.^{2,3} Twelve-hour fasting, 1 mg/kg maropitant SC or both have been described by some authors before routine PO ¹³¹I administration for RAI treatment of feline hyperthyroidism.^{2,3} In retrospect, maropitant could have been utilized in this study to minimize vomiting and maximize the sample size.

Thyroidal RAIU can be determined by scintigraphy at different times post ¹²³I administration with 8 and 24 hours being most common.¹⁶ It is believed that the 8-hour time point reflects the activity of sodium iodine/iodide pumps, which transport iodine from blood into the thyroidal colloid.¹⁶ The 24-hour measurement is presumably indicative of organification and coupling.¹⁶ The 24-hour time point was believed to serve as the ideal indicator for this study as it represents the iodine incorporated into the thyroid gland that ultimately serves as the source of therapeutic radiation. In this study, we chose not to use an 8-hour assessment of %RAIU because of the potential effects of sedation and general anesthesia on gastrointestinal mobility, transit times, absorption, and bioavailability.

Ninety percent of iodine consumed orally is rapidly absorbed from the gastrointestinal tract within 60 minutes, and then 20% of iodide in the blood is taken up by the thyroid, making 8-hour %RAIU a well-accepted time point for thyroid scintigraphy using PO ¹²³I.¹⁶ However, there was a concern that if a poorly understood innate difference in iodine uptake and metabolism was truly occurring between PO and SC administration, then sedation and general anesthesia at the 8-hour time point might decrease %RAIU after PO but not SC administration. A systematic error might then be introduced into the study design resulting in a type 1 error and incorrectly supporting the hypothesis that innate differences exist between PO and SC RAI administration. In addition, a paucity of literature exists on the effects

of various anesthetic drug protocols on ¹²³I thyroid scintigraphy, but ^{99m}Tc scans are affected by such drugs, albeit injectable and not PO administration was described in that study.¹⁷

In conclusion, this study did not detect an effect of PO and SC ¹²³I administration routes on paired % thyroidal RAIU in euthyroid cats. However, a small sample size and low statistical power make a type 2 statistical error possible.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approval by the University of Saskatchewan Animal Research Ethics Board (Animal Use Protocol Number 20190132).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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