Potential Interference of Agents on Radioiodide Thyroid Uptake in the Euthyroid Rat

Ming-Der Yu, PhD[1]; and Stanley M. Shaw, PhD[2]

[1]*Department of Nuclear Medicine, Tri-Service General Hospital, Taipei, Taiwan; and* [2]*Division of Nuclear Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana*

The objective of this research was to investigate the merits of controlled studies with euthyroid rats as a means of determining the influence of dose and time after administration of agents that may interfere with radioiodide uptake in the thyroid. **Methods:** Potassium iodide (KI), propylthiouracil (PTU), diatrizoate meglumine, and iohexol were selected to represent interfering agents. Two dose levels per agent were investigated. Doses used were 1 and 2 mg/kg of body weight for KI, 3.5 and 7 mg/kg of body weight for PTU, 1 mL/kg (282 mg I/kg) and 2 mL/kg (564 mg I/kg) of body weight for diatrizoate meglumine, and 1 mL/kg (300 mg I/kg) and 2 mL/kg (600 mg I/kg) of body weight for iohexol. The 24-h radioiodide thyroid uptake was determined after ^{131}I was given at 1, 8, 15, and 22 d after administration of interfering agents. **Results:** The percentage radioiodide uptake value for the thyroid decreased significantly compared with controls for all agents and both doses on day 1 but returned to control levels by day 22 for all agents and both doses The time to return to normal varied between agents and doses. **Conclusion:** We conclude that the interfering agent, the dose given, and the length of time after administration influence the potential for an agent to affect radioiodide uptake in the thyroid. Further studies with the rat, preferably hyperthyroid, would be beneficial in generating data to reduce confusing contradictory information on the length and severity of interference of agents in radioiodide thyroid studies.

Key Words: euthyroid rat; radioiodide thyroid uptake; interfering agents

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It is well known that radioiodide and radioactive iodide uptake (RAIU) studies are important in nuclear medicine to aid in the diagnosis of hyperthyroid conditions. Also, the percentage uptake value is known to be important in the calculation of the radioiodide dose given to the patient for treatment of hyperthyroidism.

Various agents have been found to interfere with the RAIU study leading to a reduction in the percentage uptake value because of the presence of the agent. These potential problems have been documented (*1–10*), but data are conflicting in regard to the extent of the problem. The interference time of propylthiouracil (PTU) has been reported to vary from days to 1–2 wk. The interference time of diatrizoate meglumine has been reported to be from 2 wk to about 2 mo. The duration of interference from iodides has been noted as 1, 2, or 4 wk. Many reports on drug–radiopharmaceutical interactions are anecdotal and in situations that make comparisons between agents difficult.

It would appear beneficial to conduct controlled studies between agents and at various doses to gain additional knowledge about the length of time and degree of interference of agents on RAIU in the thyroid. The focus of this investigation was on the utilization of the euthyroid rat as a model for studies and to obtain data on the influence of several agents, each at 2 dose levels, on the degree and length of time of interference in radioiodide uptake in the thyroid. Agents were selected because of problems documented in the literature (*1–10*) and the continued utilization of the agents in medical practice. A dose representing a clinical situation, based on weight, was selected as well as a lower dose to ascertain a dose effect. The length of the study was based on documented reports, though variable, of the influence of the agents on radioiodide thyroid uptake in patients.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats weighing 220–240 g were obtained from Harlan Sprague–Dawley, Inc. (Indianapolis, IN). Five animals for each treatment or control group were housed together by random selection in stainless steel cages measuring 23.5 × 21 × 28 cm and maintained at a constant room temperature of 21°C–23°C with a 12:12 artificial lighting cycle (0600–1800 h). Each individual cage contained a steel food hopper and water bottle. Diet (Rodent Laboratory Chow no. 5001; Purina Mills, Inc., St. Louis, MO) and tap water were provided ad libitum during a 5-d acclimation period. The iodine content of the diet was approximately 0.6 mg/kg. Animals were housed in quarters approved by the American Association for Accreditation of Laboratory Animal Care. For each determination of the uptake of ^{131}I in the thyroid, the rats were fasted overnight and only water was supplied. Over the time of the entire study, the animals weighed 250–370 g. Each group remained together throughout the study. The study was

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For correspondence or reprints contact: Stanley M. Shaw, PhD, Division of Nuclear Pharmacy, Industrial and Physical Pharmacy, Purdue University, RHPH-308, 575 Stadium Mall Dr., West Lafayette, IN 47907-2051.

E-mail: sshaw@pharmacy.purdue.edu

performed with appropriate animal care approved by the Purdue University Animal Research Council.

Agents and Experimental Design

Potassium iodide ([KI] lot no. 97012-1; Mallinckrodt Chemical Works, St. Louis, MO) was selected as 1 of the interfering agents because it is often used in nuclear medicine studies to block radioiodide uptake by the thyroid from ^{123}I- or ^{131}I-labeled radiopharmaceuticals. PTU (lot no. 76H2500; Sigma Chemical Co., St. Louis, MO) was selected because it inhibits the metabolic synthesis of thyroid hormones, and 2 radiopaque contrast agents were used in the study because of their high iodide content. Each treatment or control group was comprised of 5 animals. KI was given to 1 group of rats orally by intubation needle 2 h before the first administration of Na^{131}I solution, whereas PTU was administered orally once daily to another group for 5 d with the last dose given 2 h before the first administration of radioactive iodide. Two groups of 5 rats received 60% diatrizoate meglumine (Hypaque, lot no. M270LP; Sanofi Winthrop Pharmaceuticals, New York, NY) or iohexol (Omnipaque, lot no. B815NP; Nycomed Inc., New York, NY) intravenously 24 h before the first administration of ^{131}I. Doses investigated were 1 and 2 mg KI/kg of body weight, 3.5 and 7 mg/kg of body weight for PTU, 1 mL/kg (282 mg I/kg) and 2 mL/kg (564 mg I/kg) of body weight for diatrizoate meglumine, and 1 mL/kg (300 mg I/kg) and 2 mL/kg (600 mg I/kg) of body weight for iohexol. For each agent, a dose representing a clinical situation, based on weight, was selected as well as a lower dose to allow comparisons of dose on radioiodide uptake.

Twenty-four hours after the first administration of the Na^{131}I solution, percentage thyroid uptake values were determined by counting the neck region of the anesthetized rat with a shielding block (Lipowitz metal) to prevent the detection of radioactivity from other regions within the rat. To correct for geometry and attenuation, 0.6 cm of polyacrylamide was used to allow for accurate counting of the aliquot of radioiodide solution used to obtain the 100% dose counting rate administered to the rat. The percentage uptake values in the thyroid were based on relating thyroid counts to the counts from the 100% dose.

The 24-h radioiodide percentage uptake values obtained after cessation of the administration of interfering agents were considered as day 1 values. Seven days later each group received radioiodide solution as before and radioiodide uptake values were determined after 24 h (day 8). The procedure was repeated to obtain values at day 15 and day 22. Thus, the immediate influence of an agent was determined followed by reevaluation at several intervals over time to evaluate the length of interference from an agent. The 2 contrast agents were investigated with a control group. A second study was conducted with PTU- and KI-treated rats and another control group.

Radioactivity Measurement

Radioactivity measurements were accomplished with a NaI crystal scintillation system. The instrument was calibrated for the 662-keV γ-peak with a ^{137}Cs source. Counting was conducted for 0.5 min with the single-channel analyzer in the differential mode.

Radioiodide Dosing

Each animal received a volume of 0.2 mL of radioiodide solution for each 24-h radioiodide uptake study. To ensure continuity in radioiodide dosing, a 1-mL syringe with an intubation needle was used for dosing. Care was taken to ensure that radioiodide solution was in the intubation needle so that the 0.2 mL, as measured in the syringe, was truly administered. As measured by a dose calibrator, the average activity administered to the rats in the study was 148 $\pm$ 3.7 kBq. The 100% dose counting rate was determined for each radioiodide uptake study with three 0.2-mL radioiodide solution aliquots obtained in the same manner as the doses that were delivered to rats.

Shielding Block

To block radiation from regions other than the neck of the rat, a custom shielding block was prepared. The block was prepared with a low-melting-point alloy called a Lipowitz metal with a density of 9.4 g/cm^3 and consisting of 50% bismuth, 26.7% lead, 13.3% tin, and 10% cadmium. The block can be cast to custom fit a region by pouring melted Lipowitz metal into a polystyrene form. Calculations for the thickness of the shielding block were based on the activity administered to the rat and the mass attenuation coefficients for the materials in the Lipowitz metal. A conservative thickness of 1.5 cm was selected. The opening in the shielding block for the determination of activity from the thyroid in the neck of the rat was based on actual anatomic evaluations.

Geometry and Attenuation Correction

Because the percentage uptake of ^{131}I in the thyroid of the rat was calculated based on the relative counts using a sample of the radioactive solution administered to the rat, the attenuation of radiation by tissue and the influence of geometry were considered. A 0.6-cm thickness of polyacrylamide was used to correct for geometry and attenuation when obtaining the 100% dose counting data. The selection of polyacrylamide was based on the mass attenuation coefficient of the material for the 364-keV γ-energy from ^{131}I being somewhat equal to tissue. Calculations were confirmed by actual measurements with tissue covering the thyroid of the rat. Additionally, the thickness of the hairy skin and other tissue covering the thyroid was measured to determine the influence of geometry.

Preliminary Study

A preliminary study was performed to assess the accuracy of determining the actual thyroid uptake by measuring radioactivity in the neck region. The study was designed to determine the influence of time and tissue background radioactivity in the assessment of the percentage uptake of ^{131}I in the thyroid in the intact rat. Sixteen rats were divided into 4 groups. ^{131}I was administered orally with an intubation needle. Rats were anesthetized and the neck region was counted. Animals were euthanized and the thyroid was removed and counted with geometry equal to that of the intact rat. Percentage uptake values were obtained using counting data from the 100% dose counting-rate aliquots. The neck uptake was 16.6% at 6 h after ^{131}I administration. However, the actual thyroid uptake was only 8.1% at the same time interval. Thus, the background activity was about 8.5%. At 12 h the neck uptake was 13.4% and the actual thyroid uptake was 12.5%. By 24 h the percentage uptake in the neck was 10.1% and 10.5% in the isolated thyroid. Values at 48 h were similar. Thus, 24 h after administration of radioiodide was selected for the determination of percentage radioiodide uptake for the remaining studies.

RESULTS

KI and PTU

As may be observed in Table 1, on day 1 radioiodide thyroid uptake was reduced in comparison with that of the

TABLE 1
Effect of KI and PTU on Radioiodide Thyroid Uptake

Group	Day 1*†	Day 8*†	Day 15*†	Day 22*†
Control	9.9 ± 0.7	12.0 ± 1.2	10.9 ± 0.5	10.8 ± 1.3
KI				
1 mg/kg	4.0 ± 0.7	11.2 ± 1.8	15.2 ± 0.6	9.8 ± 1.0
2 mg/kg	2.8 ± 0.4	11.6 ± 1.1	14.7 ± 0.5	9.9 ± 1.0
PTU				
3.5 mg/kg	2.9 ± 0.8	7.4 ± 1.2	11.5 ± 0.5	11.2 ± 1.6
7 mg/kg	2.8 ± 0.6	8.3 ± 1.5	10.9 ± 0.5	9.9 ± 1.1

*Radioiodide administered 24 h before determination of thyroid uptake.

†Time after termination of administration of interfering agent.

Data are expressed as percentage radioiodide thyroid uptake (mean ± SD; $n = 5$ rats per group).

control group for both KI and PTU at both dose levels. The reductions were statistically significant ($P < 0.01$) according to the ANOVA statistical test. The Student–Newman–Keuls test showed that the thyroid uptake values on day 1 could be placed into 3 groups (Table 2). Radioiodide uptake in the thyroid of rats that received KI at 2 mg/kg or either dose level of PTU (group C) was statistically lower than that of animals receiving the 1 mg/kg KI dose (group B) or control animals (group A). On day 8, the percentage radioiodide thyroid uptake value for both doses of KI was the same as that of control animals (group A), whereas the values for both doses of PTU remained statistically lower (group B). By day 15, the percentage radioiodide values in the thyroid of PTU-treated animals were the same as those of control animals (group B), whereas the percentage radioiodide uptake was higher in KI-treated animals (group A) than that of control animals. By day 22, all animals exhibited the same percentage of radioiodide in the thyroid at 24 h after administration of ^{131}I.

Diatrizoate Meglumine and Iohexol

The results of the study of the interference of the 2 contrast agents on radioiodide uptake in the thyroid are presented in Table 3. On day 1, radioiodide thyroid uptake was reduced for both interfering agents at both dose levels in comparison with control animals. The reductions were statistically significant ($P < 0.01$) according to the ANOVA statistical test. Percentage uptake values could be placed into 4 groups as indicated by the Student–Newman–Keuls test (Table 4). On day 1, radioiodide uptake values in animals receiving diatrizoate meglumine at 282 mg I/kg (group B) were statistically lower than those of control animals (group A) but higher than those of animals receiving diatrizoate meglumine at 564 mg I/kg (group C) as well as those of animals receiving either dose of iohexol (group D). These results illustrate both a dose effect for a specific agent and the influence of different agents on the thyroid radioiodide uptake. On day 8, animals receiving either diatrizoate meglumine (group B) or iohexol (group C) had lower percentage thyroid uptake values than those of control animals (group A). Statistically lower percentage uptake values were observed for both doses of iohexol (group C) as compared with diatrizoate meglumine (group B) on day 8. Thus, a greater interference of 1 agent compared with the other was observed. On day 15, the percentage uptake values for both doses of diatrizoate meglumine and the smaller dose of iohexol were the same as those of control animals (group A). The percentage uptake values for the 600 mg I/kg dose of iohexol (group B) were statistically different from those of control animals, both dose levels of diatrizoate meglumine and the 300 mg I/kg dose of iohexol (group A). The influence of the dose of an agent (iohexol at

TABLE 2
Student–Newman–Keuls Test of Repeated Measurement Studies for KI and PTU

Group	Day 1*†	Day 8*†	Day 15*†	Day 22*†
A	Control	Control KI, 1 mg/kg KI, 2 mg/kg	KI, 1 mg/kg KI, 2 mg/kg	Control KI, 1 mg/kg KI, 2 mg/kg PTU, 3.5 mg/kg PTU, 7 mg/kg
B	KI, 1 mg/kg	PTU, 3.5 mg/kg PTU, 7 mg/kg	Control PTU, 3.5 mg/kg PTU, 7 mg/kg	
C	KI, 2 mg/kg PTU, 3.5 mg/kg PTU, 7 mg/kg			

*Radioiodide administered 24 h before determination of thyroid uptake.

†Time after termination of administration of interfering agent.

Student–Newman–Keuls test controls type I experiment-wise error rate ($\alpha = 0.05$) under complete null hypothesis but not under partial null hypotheses.

TABLE 3
Effect of Diatrizoate Meglumine and Iohexol on Radioiodide Thyroid Uptake

Group	Day 1*†	Day 8*†	Day 15*†	Day 22*†
Control	10.1 ± 0.5	10.2 ± 1.0	10.2 ± 0.7	9.8 ± 0.8
Diatrizoate meglumine				
1 mL/kg (282 mg I/kg)‡	4.5 ± 0.4	7.2 ± 0.7	9.6 ± 0.8	9.1 ± 1.0
2 mL/kg (564 mg I/kg)‡	3.9 ± 0.3	6.6 ± 0.6	9.9 ± 0.8	10.0 ± 1.8
Iohexol				
1 mL/kg (300 mg I/kg)‡	3.2 ± 0.2	5.0 ± 0.7	9.4 ± 1.0	9.4 ± 0.4
2 mL/kg (600 mg I/kg)‡	3.0 ± 0.3	4.6 ± 0.6	7.6 ± 0.6	9.2 ± 1.2

*Radioiodide administered 24 h before determination of thyroid uptake.
†Time after termination of administration of interfering agent.
‡Milligrams of organic iodide.
Data are expressed as percentage radioiodide thyroid uptake (mean ± SD; n = 5 rats per group).

600 mg I/kg vs. at 300 mg I/kg) can be observed. All groups of animals exhibited the same radioiodide thyroid uptake on day 22.

DISCUSSION

The percentage thyroid uptake in an RAIU study has been shown to be influenced by the dose of stable iodide (Table 5). In 1940, Hamilton and Soley (*11*) reported the results of the first in vivo radioiodide thyroid uptake study in healthy persons and patients with thyroid disorders. A solution containing 888–3,700 kBq of radioiodide and a total of 14 mg of iodide in the form of NaI was administered orally to each subject. In 5 healthy control subjects, the average percentage thyroid uptake value at 24 h was 3.0%, whereas the value for 10 adults with thyrotoxicosis was 6%, and the value for 1 child with hypothyroidism was 2.5%. In 1942, Hamilton (*12*) reported observations using healthy individuals and hyperthyroid patients who received radioiodide with 0.1 μg of stable iodide orally. In 3 healthy control subjects, the average ^{131}I 24-h percentage thyroid uptake value was 18.5%, whereas the value for 3 adults with thyrotoxicosis was 63%. From these 2 studies, it may be seen that the large amount of exogenous iodide used in the 1940 study reduced significantly the percentage uptake of radioiodide for healthy subjects and patients with thyrotoxicosis as compared with a tracer dose of iodide.

In 1950, Childs et al. (*13*) reported the results of a study in which the amount of stable iodide in a dose of radioiodide administered orally to patients was varied. In 7 hyperthyroid patients who received 0.001 mg of stable iodide, the thyroid uptake was 70%. In 7 other subjects who received either 1.0 or 10 mg of stable iodide in the dose of radioiodide, the

TABLE 4
Results of Student–Newman–Keuls Test of Repeated Measurement Studies for Diatrizoate Meglumine and Iohexol

Group	Day 1*†	Day 8*†	Day 15*†	Day 22*†
A	Control	Control	Control Diatrizoate meglumine, 282 mg I/kg Diatrizoate meglumine, 564 mg I/kg Iohexol, 300 mg I/kg	Control Diatrizoate meglumine, 282 mg I/kg Diatrizoate meglumine, 564 mg I/kg Iohexol, 300 mg I/kg Iohexol, 600 mg I/kg
B	Diatrizoate meglumine, 282 mg I/kg	Diatrizoate meglumine, 282 mg I/kg Diatrizoate meglumine, 564 mg I/kg Iohexol, 300 mg I/kg Iohexol, 600 mg I/kg	Iohexol, 600 mg I/kg	
C	Diatrizoate meglumine, 564 mg I/kg			
D	Iohexol, 300 mg I/kg Iohexol, 600 mg I/kg			

*Radioiodide administered 24 h before determination of thyroid uptake.
†Time after termination of administration of interfering agent.
Student–Newman–Keuls test controls type I experiment-wise error rate (α = 0.05) under complete null hypothesis but not under partial null hypotheses.

TABLE 5
Comparison of Relationship Between Dose of Iodide and Percentage Radioiodide Uptake in Thyroid

Reference	Dose of iodide	Radioiodide uptake at 24 h* (%)
Hamilton and Soley (*11*)	14 mg	Normal, 3.0 ($n = 5$) Hyperthyroid, 6.0 ($n = 10$) Hypothyroid, 2.5 ($n = 1$)
Hamilton (*12*)	0.1 μg	Normal, 18.5 ($n = 3$) Hyperthyroid, 63 ($n = 3$) Hypothyroid, 1.5 ($n = 4$)
Childs et al. (*13*)	0.001 mg	Hyperthyroid, 70 ($n = 7$)
	1 mg	Hyperthyroid, 34.3 ($n = 7$)
	10 mg	Hyperthyroid, 7.6 ($n = 7$)
	100 mg	Hyperthyroid, 5.5 ($n = 1$)
	380 mg	Hyperthyroid, 4.0 ($n = 1$)
Sternthal et al. (*14*)	10 mg	Euthyroid, 19.4 After iodide, 12.5 ($n = 5$)
	30 mg	Euthyroid, 21.8 After iodide, 1.5 ($n = 5$)
	50 mg	Euthyroid, 19.7 After iodide, 1.5 ($n = 5$)
	100 mg	Euthyroid, 17.2 After iodide, 0.7 ($n = 5$)
This study	0.76 mg I/kg†	Control, 9.9 ($n = 5$) Treated group, 4.0
	1.52 mg I/kg‡	Control, 9.9 ($n = 5$) Treated group, 2.8
	3.04 mg I/kg§	Control, 10.1 ($n = 5$) Treated group, 2.7

*Percentage administered dose of radioiodide.
†Value of 1 mg/kg of KI.
‡Value of 2 mg/kg of KI.
§Yu (*15*).

uptake values were 34.3% and 7.6%, respectively. The 1.0-mg dose of stable iodide administered to hyperthyroid patients produced about a 50% reduction in the percentage ^{131}I thyroid uptake as compared with that of patients who received the 0.001-mg dose. The authors stated that a dose of ≤0.1 mg of stable iodide may be used in the normal biosynthesis of thyroid hormones. However, they indicated that biosynthesis appeared to be suppressed by stable iodide in excess of 0.1 mg in hyperthyroid patients. As may be seen in Table 5, 100 and 380 mg of stable iodide contained in radioiodide given to patients by Childs et al. did not significantly lower the percentage value compared with 10 mg. An apparent saturation effect from excessive stable iodide appeared to be occurring.

In 1980, Sternthal et al. (*14*) reported the results of a study in which baseline determinations of thyroid uptake of a tracer dose of ^{123}I were performed in euthyroid subjects. One week later, a repeated tracer dose of ^{123}I was given, followed 1–5 min later by oral administration of 10, 30, 50, or 100 mg of stable iodide as NaI. The 24-h percentage ^{123}I thyroid uptake in euthyroid subjects after 10 mg of stable iodide was 12.5% compared with 19.4% before administration of stable iodide (Table 5). The 10-mg dose of stable iodide produced about a 35% reduction in the percentage ^{123}I thyroid uptake as compared with the baseline values in the same subjects. A 30-mg dose of stable iodide administered to 5 euthyroid subjects produced about a 90% reduction in the percentage ^{123}I thyroid uptake (21.8% vs. 1.5%). Sternthal et al. stated that the thyroid uptake of ^{123}I can be markedly suppressed by the administration of a single dose of 30 mg of stable iodide to euthyroid subjects. They found that the percentage radioiodide uptake values in euthyroid subjects receiving a 50- and a 100-mg dose of iodide were 1.5% and 0.7%, respectively. The percentage radioiodide uptake did not change significantly even though the dose of stable iodide was doubled. As may be observed in Table 5, in our preliminary investigation (*15*) using the same design as in the current investigation, a 3.04-mg I/kg dose of stable iodide did not significantly change the percentage uptake in the thyroid as compared with a 1.52-mg I/kg dose of stable iodide. The apparent saturation of the thyroid by the stable iodide that was observed in the work of Childs et al. (*13*) and Sternthal et al. appeared to occur in the current research.

From Table 5, it may be noted that Childs et al. (*13*) found that a single dose of 1.0 mg of stable iodide as compared with 0.001 mg reduced the radioiodide percentage uptake value by 50% in the hyperthyroid patients. Sternthal et al. (*14*) found that it required a single dose of 10–30 mg of stable iodide as compared with a tracer dose of radioiodide to reduce the radioiodide percentage uptake value by 50% in euthyroid subjects. This provides evidence that the influence of stable iodide on a radioiodide thyroid uptake value may depend on the condition of patients and may be one reason why considerable variability exists in the literature regarding the potential interference caused by the same agent containing stable iodide. Also, the studies by Hamilton and Soley (*11*) and Hamilton (*12*), Childs et al., and Sternthal et al. demonstrated the importance of the amount of stable iodide on the degree of interference. This effect was also observed in our investigation with rats.

In our study, rats receiving KI appeared to exhibit a rebound effect on day 15. This may be similar to the effect noted by Langer (*16*) for antithyroid drugs such as potassium thiocyanate, potassium perchlorate, and PTU. Langer stated that thyroid hormone synthesis was depressed by the antithyroid drugs, resulting in a reduction in radioiodide thyroid uptake. He indicated that the depression was followed by a recovery and ultimately an increase in radioiodide uptake compared with that of controls due to the effect of thyroid-stimulating hormone. Langer concluded that the rebound phenomenon did not depend on the chemical nature of the antithyroid drug used. Greer (*17*) reported that a rebound phenomenon seems concomitant with the return of the depressed thyroid to normal. Grayson (*18*) also reported that there is a rebound phenomenon after withdrawal of

antithyroid drugs. It is known that iodides inhibit thyroid hormone synthesis and release. Thus, it is possible that the excessive KI used in our investigation exhibited the same effect as that of antithyroid drugs.

Levy and Marshall (*19*) studied a group of 8 normal human subjects who were treated with 300 mg of PTU daily for 7 d. The radioiodide 24-h percentage thyroid uptake value for the group was 8.8% as compared with a value of 20.5% for normal subjects receiving a 300-mg placebo dose daily for 7 d. The 300-mg dose of PTU produced about a 57% reduction in the percentage ^{131}I thyroid uptake value as compared with that of the subjects receiving the placebo. Langer (*16*) reported the results of a study of normal rats (weighing about 200 g) that were treated with one 4-mg (20 mg/kg) dose of PTU. The drug was given orally at the same time as ^{131}I was injected intraperitoneally. Animals were killed later at various times and radioiodide uptake was determined in the isolated thyroid. The 8-h percentage radioiodide uptake in control animals was 14%, whereas only 1% was present in PTU-treated rats. In our investigation, ^{131}I 24-h percentage uptake values in rats receiving a PTU dose of either 3.5 mg/kg or 7 mg/kg were 2.9% and 2.8%, respectively, in comparison with 9.9% for control animals. The control and treated values between the 2 rat studies may differ because of the difference in the time of determining the radioiodide uptake. The results of Levy and Marshall with normal humans are closer in agreement with the findings of our study with rats.

In 1959, Ogden and Sheline (*20*) determined the radioiodide thyroid uptake at 24 h in 19 euthyroid human subjects after intravenous administration of 30 mL of diatrizoate meglumine. Values were depressed in comparison with a normal population of euthyroid subjects. In a repeated study in the euthyroid subjects, the ^{131}I thyroid uptake 24-h values had returned to the normal range by 4 d. In our study, a return to control value was observed 15 d after treatment in rats receiving about twice the dose of diatrizoate meglumine, based on a milligram-per-kilogram basis. The difference may be due to the total dose of iodide in the contrast agent or the species studied.

Although a search of the published literature provided only the publication of Ogden and Sheline (*20*) specific to the effect of diatrizoate meglumine on radioiodine uptake in the thyroid and none on iohexol, several articles on the effect of other radiopaque contrast agents were found (Table 6). As may be observed in Table 6, the time of interference for different contrast agents varies and is influenced by the condition of the patient—for example, euthyroid or hyperthyroid. This is noteworthy because many tables of contrast agents and their length of interference in an RAIU study do not list original articles. Also, several contrast agents may be included under a general classification. Listing the specific agents, clarification of the potential length of interference, and the condition of the patient would be beneficial to nuclear pharmacists and nuclear medicine personnel with regard to the potential problem from a contrast agent in an RAIU study.

The importance of knowing clearly the interference of agents on radioiodide uptake by the thyroid is illustrated in a study published by Turton et al. (*26*). The authors conducted a retrospective chart review of patients in an outpatient nuclear medicine setting who were given Na^{131}I therapy for Graves' disease. They compared the outcome of the therapy in patients receiving PTU as compared with that of non–PTU-treated patients. In their discussion they noted that the effect of PTU on iodine uptake in the thyroid lasts 12–24-h and, thus, it has been thought that PTU therapy should be discontinued 3–6 d before radioiodide therapy. However, the authors found that treatment failure rates increased markedly in patients receiving the last dose of PTU 7–14 d before radioiodide therapy. The authors recommended that PTU therapy be discontinued for at least 2

TABLE 6
Comparison of Several Studies of Contrast Agents and Interference in Radioiodide Thyroid Uptake

Reference	Contrast media	Means of administration	Time to return to normal
Rogers and Robbins (*21*)	Iodipamide	Intravenous	Average 90 d in 4 euthyroid persons
Slingerland (*22*)	Iopanoic acid	Oral	7 d in 1 hyperthyroid person
Newman and Cupp (*23*)	Iodalphionic acid	Oral	30 d in 10 euthyroid persons
Clark and Shipley (*24*)	Iopanoic acid	Oral	60 d in 74 euthyroid persons
Ogden and Sheline (*20*)	Diatrizoate meglumine	Intravenous	4 d in 19 euthyroid persons
	Iopanoic acid	Oral	58 d in 6 euthyroid persons
Jaffiol et al. (*25*)	Ioxaglate meglumine	Intravenous	30 d in 10 euthyroid persons
This study	Diatrizoate meglumine (282 mg I/kg)	Intravenous	15 d*
	Diatrizoate meglumine (564 mg I/kg)	Intravenous	15 d*
	Iohexol (300 mg I/kg)	Intravenous	15 d*
	Iohexol (600 mg I/kg)	Intravenous	21 d*

*In 5 euthyroid rats.

wk to optimize the outcome of the initial therapy and to reduce the need for a second treatment that would increase overall cost and increase the time that the patient remains thyrotoxic.

CONCLUSION

Utilization of the euthyroid rat as a model to determine the influence of an interfering agent on the uptake of radioiodide in the thyroid allowed the detection of the influence of one specific agent compared with that of another as well as the dose administered. The time for recovery after administration of an interfering agent could be determined at various time intervals in the same rat acting as it's own control. It appears that carefully controlled investigations with the rat would be beneficial in reducing confusion generated by reports of clinical cases and human studies that are subject to variables such as the functional state of the thyroid. It is recommended that further investigations be conducted with rats and, in particular, with hyperthyroid rats that will more closely model the state of the thyroid in patients subjected to a radioiodide thyroid uptake study. Data generated would provide added information for nuclear pharmacists and nuclear medicine personnel to prevent or explain unexpected results in an RAIU study.

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