Histamine receptor 1 and 2 antagonists alter biodistribution of radioiodine

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Running title:
Histamine blockers alter $^{131}$I distribution
ABSTRACT

Nuclear medicine technology assumes responsibility for exam-specific patient preparation procedures. This requires a clear understanding of the possible effects of medications on the outcome of exams. There is evidence that common over-the-counter drugs, histamine 1 (H1) and 2 (H2) receptor blockers and proton pump inhibitors (PPI's), may directly or indirectly affect thyroid function. The objective was to determine whether short-term use of these drugs alters biodistribution of radioiodine in a rat model.

Methods: Rats received no drug (controls) or daily subcutaneous injections of H-1 blocker (promethazine), H-2 blocker (famotidine), or PPI (esomeprazole) commencing 1 day prior to a single intraperitoneal injection of 1 μCi (0.037 MBq) $^{131}$I (NaI) and continuing daily until euthanasia at either 1d or 8d post $^{131}$I. Organ uptake of $^{131}$I by control (C) and drug-treated (D) rats was compared by gamma well counting.

Results: Promethazine significantly increased uptake of $^{131}$I by the thyroid (D:C ratios) both at 1d (1.32) and 8d (1.52) post $^{131}$I. Both famotidine and promethazine (respectively) significantly increased salivary gland uptake of $^{131}$I (D:C ratios) at 1d (1.37, 1.40) and 8d (4.52, 5.57) post $^{131}$I. Promethazine significantly increased gastric $^{131}$I uptake (D:C ratios) at 1d (1.47), and at 8d (1.46) post $^{131}$I. Famotidine and
promethazine (respectively) significantly decreased uptake of $^{131}$I by the liver (D:C ratios) at 1d (0.60, 0.71) post $^{131}$I but resulted in a marked increase over control levels (11.21, 9.28) at 8d. Blood levels of $^{131}$I were not altered by drug treatment. Esomeprazole did not affect radioiodine distribution.

**Conclusion:** H1 and H2 blockers alter the biodistribution of radioiodine in the rat. While the findings remain to be confirmed in humans, these drugs could increase radiation exposure to non-target tissues, particularly the stomach and salivary tissue, during $^{131}$I therapy. Although these studies remain to be confirmed in humans, consideration should be given to avoidance of the elective use of these drugs during radioiodine therapy.

Key words: rat, radioiodine, iodine-131, $^{131}$I, biodistribution, drugs, sialadenitis, xerostomia, gastritis
**Introduction**

The use of radioiodine for the treatment of hyperthyroidism and thyroid cancer remains efficacious since its initial inception in the early 1940’s. Since that time, the number of prescription and over-the-counter medications has rapidly increased. A wide variety of drugs have been proposed to alter the biodistribution of radioiodine, and are still being defined (1). Pharmaceutical-induced alterations in the biodistribution of radioiodine could not only affect the uptake of diagnostic or therapeutic radioiodine by the target thyroid tissue but could also contribute to increased radiation exposure of non-target organs and tissues. A clear understanding of the nature and effect of medications on the biodistribution of radioiodine is critical to the responsible practice of nuclear medicine technology and the provision of appropriate patient preparation instructions.

Commonly-used over-the-counter medications that may affect thyroid function in complex ways include histamine-1 (H1) and histamine-2 (H2) receptor antagonists (blockers) as well as proton pump inhibitors (PPI’s). Histamine-2 antagonists and PPI’s are often recommended for control of dyspepsia in patients being treated with radioiodine (2). Histamine-1 antagonists may occasionally be used to treat pruritus (itching) and urticaria (hives) that may occur in patients with
autoimmune hyperthyroidism. There is some evidence in the literature that histamine may affect the neuroendocrine-thyroid axis by complex mechanisms. Histamine has been shown to act both on the hypothalamus and pituitary to inhibit thyroid releasing hormone and thyroid stimulating hormone (3,4). Histamine receptor levels in the brain may be sensitive to thyroid function in both the developing and adult brain (5). Histamine-2 receptors may mediate thyroid releasing hormone-induced increases in thyroxine excretion and may regulate hepatic metabolism of thyroid hormone (6). Conversely, H2 blockers can decrease secretion of thyroid stimulating hormone possibly through a pituitary effect (7). H1-dependent secretion of thyroxine and triiodothyronine has also been described (8). Proton pump inhibitors have also been reported to affect thyroid stimulating hormone levels (9). H2 blockers and PPI’s increase gastric retention of Tc-99m O4-, which shares a similar biodistribution with that of radioiodine. However, there is controversy in the literature regarding the effect of H2 blockers or PPI’s on gastric uptake of radioiodine (10,11). Considering the frequency by which these drugs are utilized in the general population, the potential impact of these medications on the biodistribution of radioiodine by the thyroid and the consequences of non-target irradiation, a controlled
study in rats was designed to determine if short-term use of H1 and H2 antagonists as well as PPI’s alters the biodistribution of radioiodine.

**Materials and Methods**

**Study Design and Rationale**

To determine whether H1 or H2 blockers or PPI’s alter the uptake of radioiodine by thyroid and a number of normal tissues/organs, male Sprague Dawley rats received no drug (controls) or daily subcutaneous injections of a prototypic H-1 blocker (promethazine), H-2 blocker (famotidine) or PPI (esomeprazole) commencing 1 day prior to the intraperitoneal injection of $^{131}$I and continuing to day of euthanasia (1d or 8d post $^{131}$I injection). Uptake of $^{131}$I by the thyroid, salivary gland tissue, stomach, liver and whole blood was assayed by gamma well counting and compared between the control and drug-treated rats.

**Experimental animals and regulatory assurance**

Adult male 2-month-old Sprague Dawley rats weighing 225-250g (Harlan Laboratories, Indianapolis, IN) were utilized for the study. All procedures were performed according to a protocol approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Utah (protocol #13-08011).

**Drug administration**
The rats were divided into cohorts of 8 rats each. Each rat received a single intraperitoneal administration of 1 μCi (0.037 MBq) $^{131}$I (NaI) (in 100 μl isotonic saline). Rat cohorts either received no additional drug (controls), or daily subcutaneous injections of specific drug (famotidine, promethazine, or esomeprazole) commencing 1 day prior to $^{131}$I (NaI) administration, and continuing daily, thereafter, until day of euthanasia (1 or 8 days post radioiodine administration). Drug treatment protocol was as follows:

- **H2 blocker**: famotidine (3 mg/kg twice daily)
- **H1 blocker**: promethazine (1 mg/kg once daily)
- **Proton pump inhibitor (PPI)**: esomeprazole (5 mg/kg once daily)

**Tissue determination of radioiodine levels**

Following euthanasia, *en bloc* resection of the thyroid with adjacent adherent tissues was performed. Samples of (empty) stomach, submandibular salivary glands, liver, and whole blood were obtained and weighed. Tissue uptake of $^{131}$I was then determined by gamma well counting. Tissue content of radioiodine was expressed as % of injected dose per gram of tissue (% ID/g) for all tissues except thyroid. Thyroid uptake was expressed as % ID for the entire thyroid gland. Radioiodine uptake was adjusted for nuclear decay.

**Statistical Analysis**
Biodistribution data was compiled as the mean +/- standard error (SE). Differences in organ uptake of $^{131}$I by control and drug-treated rats were compared by 1-way ANOVA with Dunnett error protection (statistical significance defined as p < .05).

**Results**

**Thyroid**

Normal (control) uptake of $^{131}$I by the thyroid is lower for rats than for humans. The mean percent uptake of radioiodine for the thyroid at 1d following I$^{131}$ administration is 3.19%, compared to typical values in the range of 8-35% for normal humans. Compared to control levels, radioiodine uptake by the thyroid is slightly but significantly increased in rats treated with the H1 blocker promethazine at 1d (1.32-fold increase, p=0.006) and 8d (1.52-fold increase, p=0.008) following the administration of $^{131}$I (Figure 1). Compared to control rats, those treated with either famotidine (H2 blocker) or esomeprazole (PPI) show no significant difference in radioiodine uptake by the thyroid at either 1 or 8d post $^{131}$I administration.

**Salivary gland**

As shown in Figure 2, there is a slight but significant increase in uptake of radioiodine by salivary gland tissue 1d following $^{131}$I
administration for both famotidine (1.37-fold increase, p=0.006) and promethazine (1.40-fold increase, p=0.004) compared to control levels. However, there is a marked increase in salivary gland uptake of $^{131}$I at 8d in rats treated with famotidine (4.52-fold increase, p<0.0001) and promethazine (5.57-fold increase, p<0.0001). Treatment with esomeprazole does not alter uptake of radioiodine by the salivary tissue at either 1 or 8d following $^{131}$I administration.

Stomach

Compared to control levels, radioiodine uptake by the stomach is significantly increased by the daily administration of promethazine both at 1d (1.47-fold increase, p=0.035) and 8d (2.46-fold increase, p<0.0001) following the administration of $^{131}$I (Figure 3). Compared to control rats, those treated with either famotidine or esomeprazole show no significant difference in radioiodine uptake by the stomach at either 1 or 8d post $^{131}$I administration.

Liver

As shown in Figure 4, when compared to control levels, there is a slight but significant decrease in liver uptake of $^{131}$I at 1d in both famotidine (1.67-fold decrease, p=0.005) and promethazine (1.41-fold decrease, p=0.016) treated rats. However, compared to control levels, there is a marked increase in uptake of $^{131}$I uptake by the liver 8d after
\[^{131}\text{I} \text{administration in rats treated with daily famotidine (11.21-fold increase, } p=0.019) \text{ and promethazine (9.28-fold increase, } p<0.0001). \]

There is no significant difference in uptake of radioiodine by the liver between control rats and those treated with esomeprazole at either 1 or 8d post \[^{131}\text{I} \text{administration.} \]

**Whole blood**

Whole blood levels of \[^{131}\text{I} \text{decreased markedly from 1 to 8d following radioiodine administration. There were no significant differences in content of radioiodine in the blood in control rats at either 1 or 8d post }^{131}\text{I} \text{administration, compared with those treated with famotidine, promethazine or esomeprazole (Figure 5).} \]

**Discussion**

The organs and tissues selected for analysis in this project were chosen for specific reasons. These include the thyroid itself and organs that typically receive a relatively high-absorbed dose of radiation during \[^{131}\text{I} \text{treatment for hyperthyroidism or thyroid cancer, including the salivary tissue and stomach. Whole blood, which is an indicator of whole body burden of radioiodine and an indirect indicator of bone marrow exposure, was also assayed. Radioiodine uptake by the liver was also measured because of data that supports that hepatic metabolism of thyroid} \]
hormone may be regulated by H2 receptors (6). Although the bladder
wall also receives a relatively high dose of exposure (from urinary
excretion), urine activity was not assayed because of the volatile nature
of $^{131}$I in the urine, and difficulty with an accurate collection in small
rodents. Whether the drugs tested could effect urinary excretion of $^{131}$I
was not tested but is thought to be unlikely given the lack of variability in
blood levels of radioiodine between the control rats and the drug treated
cohorts.

Compared to controls, treatment with the H1 receptor blocker,
promethazine, resulted in an increase in radioiodine uptake by the
thyroid, both at 1d post $^{131}$I administration (1.3-fold increase) and at 8d
(1.5-fold increase). This suggests that the use of H1 blockers could
confound the results of diagnostic tests of radioiodine uptake, as well as
uptake determinations that are made for the purpose of calculating an
appropriate dose for treatment of hyperthyroidism. If the radioactive
iodine uptake and therapeutic administration of $^{131}$I are done under
different conditions of exposure to H1 blockers, then dosimetric
decisions based on the radioactive iodine uptake determinations could
be inaccurate. It should be noted that there is no information provided by
this study to indicate that any of the drugs tested result in alterations in
uptake of $^{131}$I by well differentiated thyroid cancer. Famotidine (H2
blocker) and esomeprazole (PPI) do not affect radioiodine uptake by the thyroid at either 1 or 8d post $^{131}$I administration.

Sialadenitis and a dry mouth (xerostomia) caused by radiation damage to salivary tissue is one of the more common and bothersome side effects of $^{131}$I therapy. There is also some data that supports an increase in secondary primary salivary gland malignancies in thyroid cancer patients treated both with low (ablative) and high doses of $^{131}$I (12, 13). Measures to mitigate radiation damage to the salivary tissue are typically aggressively employed with $^{131}$I treatment, including the use of salivation-inducing maneuvers, such as sucking on sour candy, chewing gum and good oral hydration. Despite these maneuvers, there is significant variability in the magnitude of uptake of radioiodine observed in the salivary tissue on clinical radioiodine scans, either with $^{123}$I, or on post therapy $^{131}$I scans following treatment of thyroid cancer. The causes of variability in magnitude of uptake of radioiodine by salivary tissue are not well understood. However, concomitant use of either H1 or H2 blockers, which are commonly taken as over the counter drugs, could contribute to higher levels of uptake of $^{131}$I in some patients. With H1 and H2 blocker treatment, there is a 1.37 and 1.40-fold increase, respectively over control levels in radioiodine uptake by salivary gland 1d following administration of $^{131}$I. Treatment with H1 and
H2 blockers result in more substantial elevations in uptake of radioiodine by salivary tissue 8d post $^{131}$I administration (4.5 and 5.57-fold increase over control levels), suggesting that both increased uptake and delayed clearance of radioiodine by salivary tissue may result from nonspecific histamine receptor blockade. That H1 and H2 blockers could contribute to the complication of sialadenitis, dry mouth and salivary gland malignancies with radioactive iodine treatment is a theoretical risk, but one that is relatively easy prevented, by avoidance of these drugs in patients who will receive $^{131}$I for therapeutic purposes.

Compared to control levels, radioiodine uptake by the stomach is significantly increased by promethazine treatment both at 1d (1.47-fold increase) and 8d (2.46-fold increase) following the administration of $^{131}$I. The gastric wall receives a relatively high dose of absorbed dose of radiation with $^{131}$I treatment, which has raised theoretical concerns for radiation-induced gastritis and late atrophic gastritis as a complication of radioiodine treatment. A recent report cites an increased risk of second primary tumors, including those of the stomach, in thyroid cancer survivors, although it is not clear whether this is due to radioiodine treatment (14). A possible trend in induction of gastric cancers from radioactive iodine associated with treatment of benign thyroid diseases has also been reported, although this remains to be conclusively
confirmed (15). There is therefore possible that irradiation of the gastric wall from 131I may increase the risk of gastric cancer. Treatment of rats with famotidine or esomeprazole did not result in any change in gastric uptake of radioiodine.

The liver may be an important organ in the microsomal deiodination of T4 to T3, and in the modulation of systemic effects of thyroid hormone (16, review). There is also evidence that histamine may play a role in the regulation of hepatic metabolism of thyroid hormone (6). There is a slight but significant decrease in radioiodine uptake by the liver at 1d post 131I administration in both famotidine (1.67-fold decrease) and promethazine (1.41-fold decrease) treated rats. However, compared to control levels, there is a marked increase in uptake of 131I uptake by the liver 8d after 131I administration in rats treated with daily famotidine (11.21-fold increase) and promethazine (9.28-fold increase). The basis for these observations are unclear but support an active role in the processing of thyroid hormone by the liver which can be significantly altered by both H1 and H2 blockers. There is no significant difference in uptake of radioiodine by the liver between control rats and those treated with esomeprazole at either 1 or 8d post 131I administration.

There are some limitations with regard to this study. To insure that all rats received an equivalent amount of radioiodine systemically,


$^{131}$I was administered by intraperitoneal injection. This route of administration should reproduce the vascular drainage pathway resulting from oral administration of radioiodine (mesenteric veins to portal vein). The intraperitoneal route of administration has been utilized in a number of rodent studies studying the biodistribution and therapeutic effects of radioiodine (17-19). Although there is no theoretical mechanistic basis to suggest that H1 or H2 blockers or PPI’s could alter enteric absorption of $^{131}$I, this was not specifically assessed and the future confirmation of the effects of these medications with an oral route of radioiodine administration may be appropriate. In addition, further studies to confirm that similar effects are observed in humans, as we have demonstrated in this preclinical rodent model, may also be warranted.

Despite these limitations, there is sufficient preclinical experimental evidence provided herein to support that elective use of H1 blockers be discontinued prior to diagnostic measurements of radioiodine uptake by the thyroid. Both H1 and H2 blockers should be withheld prior to, and at least 1 week following $^{131}$I administration for therapeutic purposes. In this study, esomeprazole did not alter the biodistribution of radioiodine. However, the reader should be aware that there is a single brief report describing increased uptake of radioiodine by the stomach in patients taking omeprazole, another PPI, compared to
patients not taking the drug (10). The interval necessary for discontinuation of the drugs prior to $^{131}$I administration would vary as a function of the specific pharmacokinetic profile of the formulation, which can generally be obtained from the available drug package insert. In general, it is necessary to wait 4 to 5 elimination half-lives following cessation of a drug before pharmacologic activity is no longer present. However, it is important to realize that elimination half-lives can be altered by liver and kidney disease, and are generally longer when a drug is taken chronically, rather than sporadically.

**Conclusion**

This preclinical study in a rat model supports that two categories of commonly used drugs, H1 and H2 receptor antagonists, alter the biodistribution of $^{131}$I (NaI). Although comparison studies in humans have not been performed, the preclinical evidence herein supports that it may be appropriate to avoid the use of these drugs in patients in whom diagnostic or therapeutic administration of radioiodine is required.
REFERENCES


FIGURE 1. Effect of drug treatment on $^{131}$I uptake by the thyroid.

Shown are the effects of treatment with H-1 receptor antagonist (promethazine), H-2 receptor antagonist (famotidine), and proton pump inhibitor (esomeprazole) on uptake of $^{131}$I (NaI) by the entire thyroid (resected en bloc) in the rat at 1 day (white bars) and at 8d (black bars) following the intraperitoneal administration of radioiodine. Rat cohorts either received either no additional drug (controls), or subcutaneous injections of a specific drug (famotidine, promethazine, or esomeprazole) commencing 1 day prior to $^{131}$I (NaI) administration, and daily thereafter until day of euthanasia (1 or 8 days post radioiodine administration). White and black bars denote the mean uptake value (% ID per entire thyroid) of radioiodine per cohort (N=8 for each cohort). Error bars
represent the standard error of the mean. Compared to untreated control rats, statistically significant increases in radioiodine uptake by the thyroid occurred both at 1 and 8 days post $^{131}$I administration only in promethazine treated rats. Treatment with esomeprazole and famotidine did not alter radioiodine uptake by salivary tissue. An asterisk (*) denotes statistically significant differences between drug-treated and control rats.
FIGURE 2. Effect of drug treatment on $^{131}$I uptake by salivary tissue.

Shown are the effects of H-1 receptor antagonist (promethazine), H-2 receptor antagonist (famotidine), and proton pump inhibitor (esomeprazole) on uptake of $^{131}$I (NaI) by salivary gland tissue in the rat at 1 day (white bars) and at 8d (black bars) following the intraperitoneal administration of radioiodine. Rat cohorts either received either no additional drug (controls), or subcutaneous injections of a specific drug (famotidine, promethazine, or esomeprazole) commencing 1 day prior to $^{131}$I (NaI) administration, and daily thereafter until day of euthanasia (1 or 8 days post radioiodine administration). White and black bars denote the mean uptake value (% ID/gm) of radioiodine per cohort (N=8 for each cohort). Error bars represent the standard error of the mean. Compared
to untreated control rats, statistically significant increases in radioiodine uptake by the salivary gland tissue occurred both at 1 and 8 days post $^{131}$I administration in both famotidine and promethazine treated rats. Esomeprazole did not affect salivary gland uptake of radioiodine. An asterisk (*) denotes statistically significant differences between drug-treated and control rats.
FIGURE 3. Effect of drug treatment on 131I uptake by stomach.

Shown are the effects of treatment with H-1 receptor antagonist (promethazine), H-2 receptor antagonist (famotidine), and proton pump inhibitor (esomeprazole) on uptake of $^{131}$I (NaI) by the (empty) stomach in the rat at 1 day (white bars) and at 8d (black bars) following the intraperitoneal administration of radiiodine. Rat cohorts either received either no additional drug (controls), or subcutaneous injections of a specific drug (famotidine, promethazine, or esomeprazole) commencing 1 day prior to $^{131}$I (NaI) administration, and daily thereafter until day of euthanasia (1 or 8 days post radiiodine administration). White and black bars denote the mean uptake value (% ID/gm) of radiiodine per cohort (N=8 for each cohort). Error bars represent the standard error of
the mean. Compared to untreated control rats, statistically significant
increases in radioiodine uptake by the stomach occurred both at 1 and 8
days post $^{131}$I administration only in promethazine treated rats.

Treatment with esomeprazole and famotidine did not alter gastric
radioiodine uptake. An asterisk (*) denotes statistically significant
differences between drug-treated and control rats.
FIGURE 4. Effect of drug treatment on $^{131}$I uptake by liver.

Shown are the effects of treatment with H-1 receptor antagonist (promethazine), H-2 receptor antagonist (famotidine), and proton pump inhibitor (esomeprazole) on uptake of $^{131}$I (NaI) by the liver in the rat at 1 day (white bars) and at 8d (black bars) following the intraperitoneal administration of radioiodine. Rat cohorts either received either no additional drug (controls), or subcutaneous injections of a specific drug (famotidine, promethazine, or esomeprazole) commencing 1 day prior to $^{131}$I (NaI) administration, and daily thereafter until day of euthanasia (1 or 8 days post radioiodine administration). White and black bars denote the mean uptake value (% ID/gm) of radioiodine per cohort (N=8 for each cohort). Error bars represent the standard error of the mean. Compared
to untreated control rats, statistically significant decreases in radioiodine uptake by the liver occurred at 1 days post $^{131}$I administration both in famotidine and promethazine treated rats. At 8 days post $^{131}$I administration, the opposite pattern occurred, with a significant increase in hepatic uptake of $^{131}$I in famotidine and promethazine treated rats, compared to controls. Esomeprazole did not alter hepatic radioiodine uptake. An asterisk (*) denotes statistically significant differences between drug-treated and control rats.
FIGURE 5. Effect of drug treatment on 131I uptake by whole blood.

Shown are the effects of treatment with H-1 receptor antagonist (promethazine), H-2 receptor antagonist (famotidine), and proton pump inhibitor (esomeprazole) on uptake of $^{131}$I (NaI) by whole blood in the rat at 1 day (white bars) and at 8d (black bars) following the intraperitoneal administration of radioiodine. Rat cohorts either received either no additional drug (controls), or subcutaneous injections of a specific drug (famotidine, promethazine, or esomeprazole) commencing 1 day prior to $^{131}$I (NaI) administration, and daily thereafter until day of euthanasia (1 or 8 days post radioiodine administration). White and black bars denote the mean uptake value (% ID/gm) of radioiodine per cohort (N=8 for each cohort). Error bars represent the standard error of the mean. When
compared to control rats, no significant differences were noted in content of $^{131}$I in whole blood samples for rats treated with any of the 3 drugs either at 1 and 8 days post radioiodine administration.
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