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RESEARCH PAPER

The Effect of Formulation on Radioiodide Thyroid Uptake in the Hyperthyroid Cat

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ABSTRACT

This investigation was designed to compare in vitro dissolution profiles from sodium iodide capsules with radioiodide thyroid uptake in hyperthyroid cats using sodium iodide capsules prepared with a formulation exhibiting a complete release of radioiodide (I-123) in vitro and a formulation with an incomplete release of radioiodide. In vitro dissolution profiles for I-123 sodium iodide capsules with two different formulations were determined using the USP XXIII dissolution test. The two formulations studied in vitro were sodium phosphate dibasic powder with 1% magnesium stearate and calcium phosphate dibasic powder with 3% magnesium stearate. By 20 min after initiation of the dissolution test, over 95% of the I-123 was released from capsules of sodium phosphate dibasic powder. The capsules of calcium phosphate dibasic powder reached 75% at 65 min, with no further release occurring thereafter. There was a statistically significant difference in the dissolution profiles of the two formulations. The thyroid uptake of I-123 from capsules exhibiting complete release and incomplete release of radioiodide was determined in hyperthyroid cats. At 4 hr, the mean percentage thyroid uptake value for sodium phosphate dibasic powder with 1% magnesium stearate (complete release formulation) was 12.0% compared to 9.4% for calcium phosphate dibasic powder with 3% magnesium stearate (incomplete release formulation); at 24 hr, the values were 34.4% compared

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to 23.7%. The data suggest that the incomplete dissolution profile observed in vitro may correlate with a reduction in the bioavailability of the radioiodide in vivo. However, using the Wilcoxon signed rank test, statistically significant differences did not occur between the complete release formulation and incomplete release formulation at either 4 hr or 24 hr ($p > .05$*). The results of the in vivo study with five hyperthyroid cats were not conclusive due to the variability in response between individual cats.*

INTRODUCTION

Radioactive sodium iodide is utilized in the diagnosis and treatment of patients with thyroid cancer and hyperthyroidism. Assurance of the bioavailability of the radioiodide (I-123) for uptake by the thyroid is essential to obtain the desired outcome for both imaging techniques and therapy. Variability in the bioavailability of radioiodide among dosage forms could affect the outcome of either a diagnostic study or therapeutic application of the radiopharmaceutical. Also, the presence of an interfering agent in the patient or variations in dietary iodine intake may adversely affect diagnostic or therapeutic outcomes. Therefore, a clear understanding of pharmaceutical factors that may affect the uptake of radioactive sodium iodide is most important.

In a previous study (1), it was shown that the USP XXIII dissolution test can detect differences in I-131 in vitro release profiles for capsules prepared with formulations expected to produce complete versus incomplete release patterns. The present study was conducted to determine if the in vitro release characteristics of I-123 from capsules actually influenced the bioavailability of the radioiodide in vivo, leading to differences in thyroid uptake values that could adversely affect clinical decisions concerning patients. Also, the current investigation was conducted to determine if the USP dissolution test could be applied to sodium radioiodide capsules as a quality assurance procedure.

MATERIALS AND METHODS

Animals

Radioiodine thyroid uptake measurements were made in five hyperthyroid cats, two female and three male, aged between 10 and 15 years. The marked increase in the iodine-accumulating function of the thyroid that is exhibited in hyperthyroid cats provided a greater potential to show significant changes that may not be observed with euthyroid cats. The diagnosis of feline hyperthyroidism was based on the history, physical examination findings, and a plasma thyroxine (T_4) concentration exceeding the upper reference range (30 ng/ml).

Preparation of Granulation and I-123 Sodium Iodide Capsules

Preparation of granulations and labeling procedures were similar to the method of Lee, Shaw, and Peck (1). Granulations were prepared with either sodium phosphate dibasic powder or calcium phosphate dibasic powder. Approximately 0.2 ml of I-123 (Golden Pharmaceuticals, Inc., Golden, CO) labeling solution was added to 1.0 g of the granulation to be labeled for each diluent. After injection of the labeling solution, the wet granulation was mixed for 2 min in a glass bottle. Another 1.0 g of the granulation was added followed by 5 min of shaking. The cap was removed, and the bottle containing the labeled granulation was placed in a hood for overnight drying.

Lubricant was added to the labeled granulation after drying. This was accomplished by adding the desired weight of lubricant to the material still contained in the glass container followed by a 15-min interval of shaking. To prepare the formulation exhibiting a complete release of radioiodide in vitro, 1% of magnesium stearate was added as a lubricant to the granulation of sodium phosphate dibasic powder after overnight drying. To prepare the formulation exhibiting an incomplete release of radioiodide in vitro, 3% of magnesium stearate was added as a lubricant to the granulation of calcium phosphate dibasic powder.

The labeled formulation was placed in a 5-cc plastic syringe connected to a plastic tube with a diameter of 0.3 cm. Filling of the gelatin capsule (no. 4 capsule) by gravity was accomplished by tapping the syringe lightly. Capsule weight was determined before and after filling using an analytical balance to obtain the weight of the formulation within the capsule. The mean weights of granulations

of sodium phosphate dibasic powder and calcium phosphate dibasic powder were 0.17 ± 0.012 g and 0.18 ± 0.015 g, respectively. For each formulation for each cat, 10 capsules were prepared; 2 capsules were used for the in vivo radioiodide uptake study (one for the cat and one as a standard), and 6 capsules were used for the in vitro dissolution study. The remaining two capsules were employed to determine the 100% activity value used in calculations of dissolution profiles.

Dissolution Test

For the dissolution studies, 6 capsules of two formulations to be tested in cats were employed. Dissolution profiles were determined for each in vivo study. The dissolution studies were conducted according to the USP XXIII dissolution test (2). Briefly, each unit consisted of a 1000-ml glass beaker and a motor-driven metallic shaft connected to a paddle blade. The stirring element was placed at the prescribed distance of 25 ± 2 mm from the bottom of the 1000-ml glass beaker and rotated at 50 rpm. The beaker containing 900 ml distilled water was maintained at 37°C + 0.5°C. Sampling (1 ml) was conducted at 5, 10, 15, 20, 30, 40, 50, 65, 80, 95, 110, 125, and 140 min after the placement of the capsules in the beaker. Each capsule was placed in a wire cage to prevent floating. A volume of distilled water equal to the sample was added to each beaker immediately after each sampling. Using the methodology of Yu, Peck, and Shaw (3,4), the samples were counted in an autogamma counter (Minaxi® 5000, Packard, Inc., Meriden, CT). Net sample counts were corrected for background, radioactive decay, and volume factor. Data were expressed as a percentage of initial activity determined from counting data obtained from the 100% activity capsules.

Radioiodine Uptake Measurements

Thyroidal uptake of both formulations of radioiodine was measured in each of the five cats. Following the study of one formulation, 1 week was allowed for decay of any residual I-123 before the second thyroid uptake study was conducted. Iodine-123 was employed in the study instead of I-131 because of the desirability of a shorter half-life radionuclide to allow a repeat study with the same cat. For the radioiodide thyroid uptake studies, cats were restrained using isoflurane anesthesia. The length of the anesthesia was brief (30–60 min). Food was withheld 12 hr prior to the first scan. Food was reintroduced after recovery from anesthesia and removed 12 hr prior to the 24-hr scan. Each hyperthyroid cat was administered a 100-μCi I-123 capsule orally, and thyroidal and abdominal uptake were measured at 4 and 24 hr with a gamma camera with a medium energy collimator (Omega 500, Ohio-Nuclear, Inc., Solon, OH).

Each cat was imaged in an anterior position with the collimator positioned 5 cm below the ventral surface of the neck. The detector was positioned to include a region from the top of the head to the middle of the heart. Acquisition of the thyroid image was accomplished by the accumulation of 50,000 counts. After imaging the thyroid region, an image of the abdomen was obtained with the same scintillation camera and collimator using the same acquisition time employed to obtain the thyroid image. The cat was removed from the imaging table, and a 100-μCi I-123 capsule was imaged using the same acquisition time employed to obtain the thyroid image, that is, to accumulate 50,000 counts. Four regions of interest (ROI) (thyroid, background, abdomen, and radioactive capsule) were delineated with a light pen on the display of the camera. Counts were obtained for each region. Percentage uptake values were obtained using the counts obtained from the radioactive capsule as 100%.

Experimental Design and Statistical Analysis

The Wilcoxon signed rank test can be used when a paired measurement study is conducted (5). For in vivo thyroidal and abdominal data, the statistical comparisons at 4 hr and 24 hr between formulations were made with the aid of the Wilcoxon signed rank test for nonparametric variables. In addition, a repeated-measures test was used to detect the variability in thyroid and abdominal data between cats (6). Data obtained from in vitro dissolution studies were examined statistically using the multiple *t* test.

RESULTS AND DISCUSSION

Dissolution Profiles

In vitro dissolution profiles for capsules of the two formulations employed in studies of radioiodide thyroid uptake were conducted for each cat. Very little variability in dissolution profiles was observed between capsules prepared for each study of an individual cat. As may be observed in Fig. 1, which is a typical profile of the dissolution studies, formulation influenced the I-123 release profile in vitro. By 20 min, 95% or more of the activity

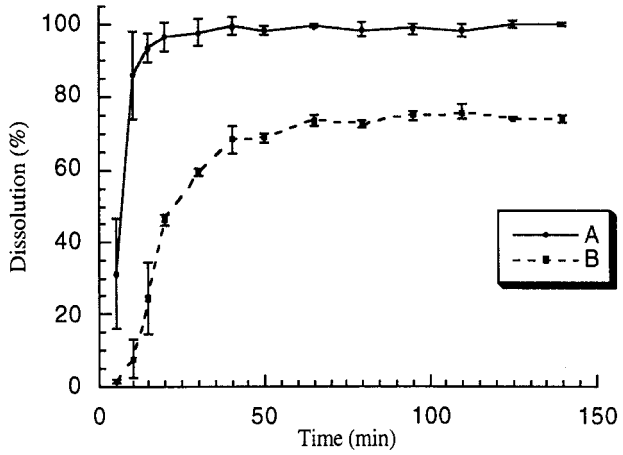

Figure 1. Dissolution profiles for (A) iodine-123 sodium phosphate dibasic granulation with 1% magnesium stearate and (B) calcium phosphate dibasic granulation with 3% magnesium stearate formulations.

was released from capsules prepared with the sodium phosphate dibasic granulation with 1% magnesium stearate (A). The contents from formulation A released almost immediately after initiation of the dissolution studies. The capsule appeared to disintegrate and dissolve very quickly. Capsules of calcium phosphate dibasic granulation with 3% magnesium stearate (B) released on average 46% of the I-123 at 20 min. On average, about 75% of the activity was released at 65 min and remained about the same until the end of the study (140 min). The capsule appeared to dissolve slowly in relation to formulation A because of the amount of magnesium stearate present. Based on subjective visual observation, a small part of the contents from the capsules dispersed in the bottom of the beaker and had not completely dissolved at the termination of the study.

Statistical differences in the dissolution profile between the two formulations existed at all time intervals ($p < .05$). As may be noted in Fig. 1, the standard deviations for the percentage release values for formulation A are larger at early sampling intervals and much smaller later. This is due to the inhomogeneity of I-123 within the 900 ml of water at the time of rapid release of I-123 from the capsules. The small paddle blade does not circulate the I-123 within the large volume as quickly as desired. However, this is a normal finding and typical of the outcome using the USP apparatus for dissolution. It is interesting to note that the standard deviations for values for formulation B are smaller at the early sampling intervals and after. This would be expected of a formulation that releases the radioactivity more slowly.

Table 1

Thyroxine (T_4) Level in Individual Cats

	Case				
	1	2	3	4	5
Sex	Male	Female	Male	Male	Female
Age	10	12	15	11	15
T_4 (ng/ml)	64	39	88	76	59

Hyperthyroid Cats

Thyroid Uptake

The plasma T_4 values for the hyperthyroid cats ranged from 39 to 88 ng/ml. Individual values are presented in Table 1. Table 2 shows the mean percentage radioiodine activity values for radioiodide thyroidal uptake at 4 and 24 hr after I-123 administration to the cats. At 4 hr, the mean percentage thyroid uptake value for formulation A (complete release formulation) was 12.0%, compared to 9.4% for formulation B (incomplete release formulation). As may be seen in Table 3, three of five cats exhibited a decreased thyroid uptake at 4 hr when using the incomplete release formulation in comparison to the complete release formulation. In four of five cats, at 24 hr the thyroid uptake values for the incomplete release formulation were lower than those observed for the compete release. The mean percentage thyroid uptake value for the complete release was 34.4%, compared to 23.7% for the incomplete release at 24 hr (Table 2). It appears that the incomplete dissolution profile observed in vitro may cor-

Table 2

Mean Radioiodide Uptake Percentage in the Thyroid

	Formulation Percentage Uptake[a] (Mean ± SD)	
Time (hr)	A[b]	B[c]
4	12.0 ± 8.3	9.4 ± 9.2[d]
24	34.3 ± 19.4	23.7 ± 18.4[d]

[a]Percentage uptake for five hyperthyroid cats.
[b]Sodium phosphate dibasic granulation with 1% magnesium stearate.
[c]Calcium phosphate dibasic granulation with 3% magnesium stearate.
[d]No statistical difference (Wilcoxon test).

Table 3

Individual Cat Radioiodide Uptake Percentage in the Thyroid

	Percentage Uptake (4 hr) Formulation		Percentage Uptake (24 hr) Formulation	
Cat	A[a]	B[b]	A[a]	B[b]
1	23.3	13.9	57	55
2	9.3	1.2	29.4	9.9
3	17.6	23.4	51.1	24.7
4	6.8	3.0	24	17
5	3.0	5.6	10.2	12.0

[a]Sodium phosphate dibasic granulation with 1% magnesium stearate.
[b]Calcium phosphate dibasic granulation with 3% magnesium stearate.

relate with a reduction in the bioavailability of the radioiodide in vivo. However, using the Wilcoxon signed rank test, there was no significant difference between formulation A and formulation B at 4 hr and 24 hr thyroid uptake ($p > .05$).

Comparison of percentage thyroid uptake of radioactivity with analysis of variance (ANOVA) indicated that the subject factor was significant since the F value was 9.05 ($p < .05$). However, the formulation factor was insignificant since the F value was 3.96 ($p > .05$). These results indicate that the reduced percentage radioiodide thyroid uptake at 24 hr obtained with the incomplete release formulation (23.7%), in comparison to the complete release (34.4%) formulation, was due to the effect of individual cats. The statistical results for thyroid radioiodide uptake at 4 hr showed that the subject factor was insignificant ($p > .05$), and the formulation factor was insignificant ($p > .05$) as well. Thus, the percentage values of 12.0% compared to 9.4% radioiodide uptake did not differ and were not influenced by either animal or the formulation.

Abdominal Activity

Table 4 lists the mean percentage radioiodine activity values in the abdomen for the complete and incomplete release formulations at 4 and 24 hr after I-123 administration. At 4 hr, the mean percentage abdominal activity value for formulation A (complete release formulation) was 16.4%, compared to 20.8% for formulation B (incomplete release formulation). It may be noted in Table 5 that, at 4 hr, four of five cats had higher abdominal radioactivity when using the incomplete release formulation. Although it appears that the abdominal area in four cats had slightly higher activity at 4 hr and at 24 hr two cats had higher activity from the A versus the B formulation, there was no significant difference (Wilcoxon rank test, $p > .05$).

Table 4

Mean Radioiodide Activity Percentage in the Abdomen

	Formulation Percentage Present[a] (Mean ± SD)	
Time (hr)	A[b]	B[c]
4	16.4 ± 6.9	20.8 ± 14.4[d]
24	10.7 ± 5.5	9.4 ± 5.7[d]

[a]Percentage present for five hyperthyroid cats.
[b]Sodium phosphate dibasic granulation with 1% magnesium stearate.
[c]Calcium phosphate dibasic granulation with 3% magnesium stearate.
[d]No statistical difference (Wilcoxon test).

CONCLUSIONS

The in vitro dissolution profiles were consistent between capsules prepared for individual cats. The time to attain 95% release of the radioiodide for capsules prepared with the sodium phosphate dibasic granulation with 1% magnesium stearate ranged from 15 to 20 min. For the calcium phosphate dibasic granulation with 3% magnesium stearate, 75% release was attained in 65 to 95 min. The dissolution profiles for the formulation resulting in incomplete release of the radioiodide from capsules were consistent as well. These results suggest that the

Table 5

Abdominal Radioactivity in Individual Cats

	Percentage Present (4 hr) Formulation		Percentage Present (24 hr) Formulation	
Cat	A[a]	B[b]	A[a]	B[b]
1	10.6	10.9	5.5	11.4
2	27.8	30.7	18.8	18.1
3	17.2	8.7	13.8	6.1
4	11.3	12.6	8.6	3.5
5	15.2	41.3	6.7	7.9

[a]Sodium phosphate dibasic granulation with 1% magnesium stearate.
[b]Calcium phosphate dibasic granulation with 3% magnesium stearate.

USP XXIII dissolution test could serve as an indicator of the influence of formulation and/or preparation on the release of radioiodide from capsules used in radioiodide thyroid uptake studies or for treatment of diseases of the thyroid.

The results of the in vivo study with five hyperthyroid cats were not conclusive. At 24 hr after administration of the radioiodide capsules, ANOVA and expected mean squares testing indicated that the animal was the factor resulting in any differences in radioiodide thyroid uptake. The formulation factor was not significant. Also, the Wilcoxon signed rank test showed that there were no statistical differences for mean radioiodide thyroid uptake values between the two formulations at 4 hr or 24 hr after administration of the capsules.

In the present investigation, potential differences in the bioavailability of radioiodide between the two formulations were observed in some of the cats. To establish conclusively that there can be formulation-induced differences in radioiodide thyroid uptake, additional studies must be conducted. Larger numbers of animals would increase the statistical power of the data. Formulations with greater differences in dissolution profiles could be employed. While the results of this investigation are not conclusive, they indicate that the USP XXIII dissolution test has potential for determining dissolution profiles for radioiodide capsules, and that further investigation of formulation and the resultant effects on radioiodide thyroid uptake should be considered.

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