PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 145, 286–288 (1974)

Furosemide Mediated Elevations of Thyroid Iodide Uptake in the Rat (37794)

JOSEPH F. NORFRAY AND JAMES L. QUINN, III
(Introduced by F. del Greco)

Department of Nuclear Medicine, Northwestern Memorial Hospital, Northwestern University Medical School, Chicago, Illinois 60611

Previous authors have shown that the human iodide pool can be depleted if the patient is on an iodide deficient diet, and if a short-term, high dose, regimen of mannitol or ethacrynic acid is used (1–3). Other authors have shown that a depleted iodide pool can cause an iodide deficient goiter (4) and an elevation in the radioactive iodide uptake (5, 6). Because of the increasing use of the new, potent diuretics, it was decided to undertake a study of the long term use of Furosemide (Lasix), a new potent diuretic, on the rat iodide pool while on adequate dietary iodide.

Materials and Methods. Twenty male Sprague–Dawley rats weighing between 210–230 g were used. Ten rats were selected as controls and ten rats were used for the experiment. Both groups received the same diet of Rockland Mouse/Rat (Complete) which had an iodide content of 0.00012%. The furosemide Group was injected intraperitoneally with 20 mg of furosemide/kg daily for 14 days. Both groups received supplemental water solutions of sodium and potassium chloride.

On the fourteenth day, both groups were injected intraperitoneally with 4.5 μCi of ^{131}I. After 24 hr, the animals were sacrificed, total thyroidectomies were performed, and the ^{131}I uptakes were determined by well counting.

Results. The rat thyroid uptake values separated into two distinct groups (Table I). The furosemide animals had higher absolute thyroid ^{131}I uptake.

The Standard Deviation and Student's t Distribution of the rat thyroid uptakes were determined. The Standard Deviation (S) of the uptakes in the furosemide group were twice that of the controls. Using Student's t Distribution the results were found to be "highly significant" ($t = 8.04$ and $p < .005$).

The Rockland Mouse/Rat (Complete) feed contained a large amount of iodide (0.00012% by weight). Each rat ate between 10–15 g/day. The dietary intake of iodide for each rat/day was 20–25 μg or about 100 μg/kg (200 g rats). The normal human dietary consumption of iodide is about 2.85 μg/kg (70 kg man). Therefore, each rat received about 35 times the normal human iodide intake in the United States.

Discussion. Our results suggest that furosemide, a newer more potent diuretic, can cause iodide depletion. This loss of iodide can affect both the thyroid gland and thyroid ^{131}I uptake. Earlier diuretics have not been shown to cause iodide depletion. In 1951, it was reported that patients receiving meralluride injections had a falsely lowered serum

TABLE I. Rat Thyroid 24 hr Percent ^{131}I Uptake

	Furosemide	Control
1.	0.096	0.047
2.	0.103	0.040
3.	0.132	0.075
4.	0.116	0.040
5.	0.121	0.064
6.	0.146	0.032
7.	0.108	0.047
8.	0.114	0.071
9.	0.099	0.090
10.	0.127	0.052
Mean ± 1 S.D.	0.117 ± 0.015	0.056 ± 0.018
	$P < .005$	

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precipitable iodine (7). Thorough investigation showed that the serum iodide wasn't altered in the patient. The low results were produced by an insoluble mercuric iodate compound in the analytic procedure.

The iodide pool comprises the extracellular space in humans. The concentration of iodide in this space is extremely low—0.08–0.60 μg/100 ml (4). The major source of the iodide is from dietary intake, and in the United States, the average normal intake is between 150–200 μg/day (8, 9). Certain tissues in the body have the ability to concentrate iodide, and thereby are in equilibrium with the iodide pool. These tissues include: RBC (1:1.8)*, salivary (1:15), gastric (1:40) (10), breast, thyroid, and choroid plexus (plasma:tissue ratio).* The iodide pool can be decreased during hemorrhage, diarrhea, vomiting, and lactation. Loss of iodide in the stool is insignificant—about 10 μg/day (8).

The iodide pool is continually being decreased by the thyroid (producing thyroid hormones) and the kidney (excreting the inorganic iodide). In the human, the thyroid gland is in direct competition with the kidney. The thyroid clearance of iodide is normally about 17 ml/min (4, 8, 10). Certain diuretics cause an increase in renal clearance of iodide. Acute depletion of the iodide pool can be effected using large doses of mannitol and ethacrynic acid on patients with iodide deficient diets (1–3). Our results suggest that long-term use of furosemide can deplete the rat iodide pool even while on large amounts of iodide.

What is the mechanism of excess iodide excretion from mannitol, ethacrynic acid, and furosemide administration? It seems that iodide excretion is related to chloride excretion. An increased renal clearance of chloride will cause an increased renal clearance of iodide (11). Once the iodide and chloride are in the lumen of the proximal and distal convoluted tubules, the tubules are less permeable to the iodide, so more iodide is excreted (12–14). It should be noted that ethacrynic acid and furosemide work throughout the ascending loop of Henle and the proximal tubule of the nephron and thereby cause a significant loss of chloride (15, 16). The loss of chloride can be so extensive as to cause hypochloremic alkalosis (15, 17).

To evaluate the depletion of the rat iodide pool, the uptakes of ^{131}I were determined. It has been shown that depletion of the iodide pool causes an increase in the uptake of ^{131}I (5, 6, 9, 18).

As was seen in the table, the ^{131}I uptakes in the Lasix and Control Groups were very small when compared to the original dose of ^{131}I. This is probably due to the expanded iodide pool as a result of the large amount of iodide in the Rockland Diet.

Conclusions. 1. Intraperitoneal injection of 20 mg of furosemide/kg/day can cause an increased excretion of iodide in rats, thereby lowering their iodide pool.

2. The effect of furosemide on the iodide pool is seen to occur after long-term use–a 2-wk course of the diuretic was given.

3. Supplemental dietary iodide will not prevent the effect of furosemide, but furosemide will still cause a loss of iodide, and thereby significantly elevate the radioactive iodide uptakes when compared to controls.

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Received Sept. 4, 1973. P.S.E.B.M., 1974, Vol. 145.