Whole-body radioiodine retention 72 hours after ^{131}I therapy is paradoxically higher in patients treated with furosemide and potassium chloride than in a control group

Matovic MD, Jankovic SM, Jeremic M, Tasic Z, Vlajkovic M. Unexpected effect of furosemide on radioiodine urinary excretion in patients with differentiated thyroid carcinomas treated with iodine 131. Thyroid 2009;19:843-8.

SUMMARY

BACKGROUND Diuretics are frequently administered to patients receiving therapeutic radioactive iodine (^{131}I) with the intent of accelerating renal elimination of unbound ^{131}I. This is done to reduce the adverse effects of ^{131}I and shorten the hospital stay. The aims of this prospective study were to investigate the influence of furosemide on the urinary excretion of ^{131}I in patients with differentiated thyroid cancer and to investigate whether diuretics are useful in reducing the whole-body retention of ^{131}I and whole-body radiation in patients with thyroid cancer treated with ^{131}I.

METHODS A total of 43 patients with differentiated thyroid cancer (DTC) treated with ^{131}I in the Department of Nuclear Medicine at the Clinical Center in Kragujevac, Serbia, were recruited for study from September 2007 through September 2008. All patients had total thyroidectomy and ^{131}I therapy. Patients with a history of kidney or urologic diseases were excluded from the study. Prior to ^{131}I therapy, all patients had an ultrasound examination that confirmed the presence of both kidneys without evidence of urinary stasis. One day prior to ^{131}I therapy, serum urea and creatinine were measured and found to be within the references ranges of 3.0 to 8.0 nmol/L and 50 to 105 µmol/L, respectively.

Prior to ^{131}I therapy, levothyroxine was discontinued for 4 to 6 weeks to achieve a serum thyrotropin (TSH) concentration of at least 35 µIU/ml. Two weeks prior to ^{131}I, a diagnostic whole-body ^{131}I scan was performed with 3 mCi (111 MBq) of ^{131}I. The mean (±SD) thyroid ^{131}I uptake was only 3.55±3.45% prior to therapeutic ^{131}I that was administered on a fixed-dose approach. Twenty patients were treated with 150 mCi (5.55 GBq) for presumed residual tumor and 23 were treated with 100 mCi (3.7 GBq) for postoperative remnant ablation. Three hours after the administration of ^{131}I, 23 patients were given 20 mg of furosemide and 250 mg of potassium chloride every 8 hours for the next 3 days. Twenty control patients received neither furosemide nor potassium chloride. The patients were divided into two groups, a control group (DTC-CG) and a furosemide group (DTC-FG). After the administration of ^{131}I, the patients collected all their urine and recorded micturition times and urine volumes. A 5-ml urine sample was taken from each patient to measure retention of therapeutic ^{131}I. Average micturition sample fractions (%) were calculated for all patients in both groups for the following time periods: 6, 12, 24, 36, 48, and 72 hours after therapeutic ^{131}I was administered. Individual whole-body radiation measurements were made immediately after ^{131}I administration and 72 hours thereafter, using the same probe on each patient at a distance of 2 meters. The 72-hour whole-body radiation measurements were corrected for ^{131}I decay and were expressed as a fraction (%) of the initial value. After 72 hours, venous blood samples were taken from each patient to measure blood radioactivity by a gamma counter.

RESULTS A total of 43 patients were enrolled in the study, of which 35 were women (81%) and 8 were men (19%), ranging in age from 14 to 17 years (mean [±SD], 45.2±14.41). Of

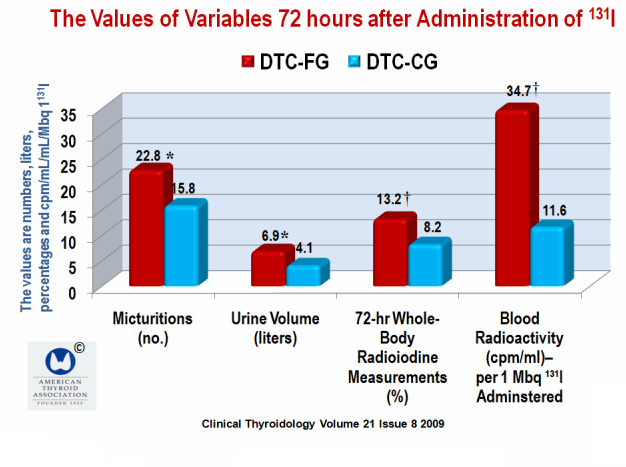

Figure 1. This figure shows that the group treated with furosemide (DTC-FG) micturated significantly more often and passed larger volumes of urine as compared with the control group (DTC-CG). However, the whole-body ^{131}I measurements and blood radioactivity retention were nonetheless higher in the DTC-FG group than in controls. *P <0.001. †P = 0.01

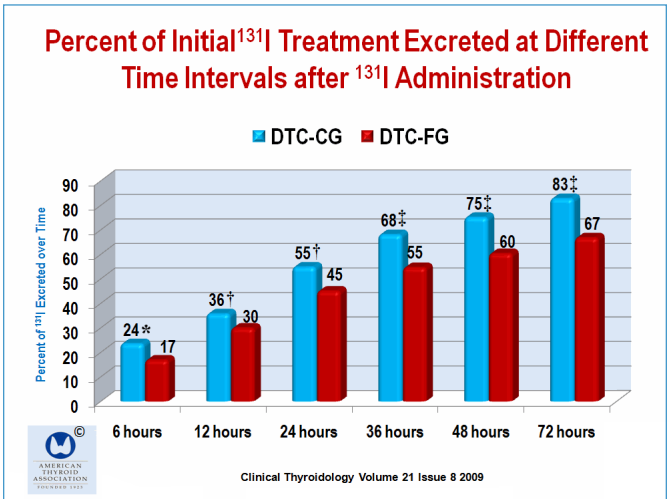

Figure 2. This figure shows the rates of radioiodine excretion from 6 to 72 hours after the administration of ^{131}I. The group treated with furosemide (DTC-FG) excreted significantly less radioiodine over 72 hours as compared with the control group (DTC-CG),*P <0.01, †P < 0.05, ‡P <0.001

this group, 39 had papillary thyroid cancer (91%), 2 had well-differentiated minimally invasive follicular cancer (5%), and 2 had Hürthle-cell carcinoma (5%).The pathological tumor–node–metastases (TNM) classification was T1N0, N1, and Nx in 14, 4, and 3 patients, respectively, and T2N0, N1, and Nx in 2, 1, and 1 patients, respectively; and T4N0, N1, and Nx in 2, 1, and 1 patients, respectively. None had distant metastases.

During the 72-hour period after ^{131}I therapy, patients who were taking furosemide and potassium chloride micturated significantly more frequently than controls. They passed larger volumes of urine and were found to have greater retention of blood radioactivity as compared with controls. Comparing the DTC-FG and DTC-CG groups, the mean number of micturitions 72 hours after the administration of ^{131}I, was 22.81±8.22 vs. 15.83±5.00 ($P<0.001$), the urine volumes were 6865.81±3416.07 vs. 4070.87±2098.68 ml ($P = 0.001$), and the blood radioactivity was 34.66±24.84 vs. 11.64±8.32 counts/min/ml of blood per 0.02 mCi (1 MBq) of ^{131}I ($P = 0.01$) (Figure 1).

Mean ^{131}I excretion in the DTC-CG and DTC-FG groups at 6, 12, 24, 36, 48, and 72 hours after ^{131}I administration was 23.61±8.84 vs. 16.93±8.32% ($P<0.01$) at 6 hours, 35.80±9.92 vs. 28.97±9.39 ($P<0.05$) at 12 hours, 54.89±10.02 vs. 45.05±10.46 at 24 hours ($P<0.05$), 68.10±11.46 vs.54.66±10.55 ($P<0.01$) at 36 hours, 75.14±11.62 vs. 60.39±10.42 ($P<0.001$) at 48 hours, and 82.81±12.42 vs. 66.80±9.61 ($P<0.001$) at 72 hours (Figure 2).

CONCLUSION Whole-body radioiodine retention 72 hours after ^{131}I therapy is paradoxically higher in patients treated with furosemide and potassium chloride, being 1.6-fold greater than that in the control group. The authors do not recommend furosemide as an adjunct therapy for ^{131}I ablation in patients who have been iodine-depleted by a low-iodine diet. The authors concluded that whether iodine depletion is the cause of the paradoxical effect remains uncertain.

COMMENTARY

This study was designed to explore whether furosemide would accelerate the renal excretion of unbound urinary iodine, and whether this would decrease the adverse effects of ^{131}I and shorten the hospital stay of patients. Just the opposite was observed. Urinary ^{131}I excretion was significantly lower in patients who were taking furosemide, and their blood radioactivity levels were almost threefold those in patients not taking the diuretic. The authors concluded that the exact mechanism for this paradoxical effect of furosemide is unclear and should be studied further.

A few studies found that the administration of diuretics can improve ^{131}I clearance, reducing radiation burden and shortening of hospital stay. For example, Seabold et al. found that the mean half-time of ^{131}I renal clearance for the patients treated with furosemide decreased by 12 hours ($P<0.05$) but was not significantly decreased for those who received thiazides (1). However, another study by Tepmongkol et al. (2) found that hydrochlorothiazide significantly improved 24-hour ^{131}I uptake in patients with a normal iodide pool, as compared with patients who were on a low-iodine diet.

In another study, Maruca et al. (3) tested the efficacy of iodine depletion and diuretics as a means of enhancing ^{131}I uptake by DTC metastases. Total-body iodine decreased about 65%, and the amount of ^{131}I taken up and retained by tumor increased almost 150%; however, ^{131}I renal clearance decreased by 56% and total-body radiation from 150 mCi increased almost 70%. As a consequence, the authors concluded that iodine-depletion regimens are less effective than prior studies have suggested. Still, it is difficult to compare studies of the effects of diuretics on ^{131}I retention, because the study protocols were so different.

Of considerable importance, all of the previous studies, including that by Matovic et al., used thyroid hormone withdrawal to prepare patients for ^{131}I therapy, and as a consequence, hypothyroidism that almost certainly diminished renal clearance developed in all of the patients. This is a major issue.

Using recombinant human TSH (rhTSH) provides insight about excretion rates of ^{131}I in patients pretreated with rhTSH as compared with thyroid hormone withdrawal. In 2006, Pacini et al. (4) first found that whole-body radiation was approximately one-third lower with rhTSH preparation for remnant ablation with 100 mCi of ^{131}I as compared with thyroid hormone withdrawal. This observation subsequently sparked further study.

Hanscheid et al. (5) found that the effective half-time of ^{131}I in the thyroid remnant was nearly 1.5-fold greater after rhTSH than after thyroid hormone withdrawal ($P = 0.01$), whereas the mean 48-hr ^{131}I thyroid uptakes were not significantly different between the rhTSH and thyroid hormone withdrawal. The maximum mean absorbed dose of ^{131}I to the blood was almost 2-fold greater with thyroid hormone withdrawal than with rhTSH ($P <0.0001$), indicating that higher activities of radioiodine might be safely administered after exogenous stimulation with rhTSH.

A more recent study by Remy et al. (6) found the mean effective total-body ^{131}I half-life (10.5 hr) was significantly shorter (31%) among patients pretreated with rhTSH as compared with patients who underwent thyroid hormone withdrawal (15.7 hr). This is thus a 31% reduction in total-body radiation in patients pretreated with rhTSH. The ^{131}I residence times in the stomach and in the rest of the body were significantly shorter in patients who received rhTSH as compared with those who underwent thyroid hormone withdrawal, but the residence times were similar in the colon and bladder. The difference in total-body ^{131}I retention was correlated with renal function: patients who had thyroid hormone withdrawal had a longer mean effective ^{131}I half-life that was mainly due to delayed renal excretion of ^{131}I.

There is little doubt that the most important feature of ^{131}I therapy is the extent to which the isotope is concentrated by thyroid tumors and normal tissues throughout the body. Retention of ^{131}I in these tissues is a two-edged sword. With malignant tumors, the goal is to increase retention time of the isotope in tumor cells, thus increasing the ^{131}I effective half-life without exerting this effect in normal tissues. Still, with

normal tissues such as the salivary glands, lacrimal ducts, stomach, and breast tissues—all of which contain sodium iodide symporters—the prolonged half-life of ^{131}I in the body is injurious to normal tissues and potentially produces second malignancies years after the isotope has been administered.

There are other ways to influence the effective half-life of ^{131}I in thyroid tumor cells, such as using low-iodine diets and administering lithium prior to ^{131}I therapy (7). Yet the most widely used method that has been used for decades is to manipulate serum TSH concentrations by withdrawing thyroid hormone, paradoxically decreasing the effective half-life of ^{131}I in tumor tissue and increasing the whole-body retention of ^{131}I in normal tissues. The most sensible approach is to perform remnant ablation with rhTSH preparation and to use the smallest possible amount of ^{131}I to achieve remnant ablation, which is somewhere between 30 (8) and 50 mCi (9).

It seems probable that the findings by Matovic et al. reflect the physiologic changes related to thyroid hormone withdrawal that produces overt hypothyroidism, which significantly reduces renal clearance of ^{131}I. The outcome of this study likely would have been much different had rhTSH been used to decrease the duration of hospitalization and to decrease whole-body retention of ^{131}I.

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