

# Effect of furosemide on radioiodine-131 retention in mice thyroid gland

## Abstract

Retention of iodine in the thyroid gland is the result of renal excretion and transport of iodine to thyroid cells. Both processes are affected by furosemide. The aim of our study was to test whether furosemide influenced radioiodine-131 ( $^{131}\text{I}$ ) retention in the thyroid gland of living mice. Our methods were as follows: After 15 days of low-iodine diet, 19 Swiss mice received an intra-peritoneal injection of  $0.37\pm0.03\text{MBq}$  of  $^{131}\text{I}$ . Thereafter, 11 mice were treated with intraperitoneal injections of furosemide (0.3mg/kg, every 8h, for 72h), Group A and 8 mice served as controls, Group B. Seventy-two hours after  $^{131}\text{I}$  administration, the mice were anaesthetized, their thyroids were carefully extirpated, and their radioactivity was measured by a gamma counter. Our results showed that the mean value of  $^{131}\text{I}$  retention after 72h was 63.09% in Group A and 82.25% in Group B. The difference between these two groups was significant ( $T=3.0919$ ,  $P=0.0033$ ). In conclusion, furosemide after the administration of  $^{131}\text{I}$ , decreases retention of  $^{131}\text{I}$  in the thyroid gland in mice. The well known increase of iodine renal excretion by furosemide and consequently decrease of iodine blood pool may be the reason for this decreased  $^{131}\text{I}$  retention by the thyroid gland.

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- Thyroid retention of  $^{131}\text{I}$
- Furosemide after  $^{131}\text{I}$
- Renal function
- Iodine blood pool
- Mice

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## Introduction

Furosemide is a diuretic, which inhibits luminal  $\text{Na}^+/\text{K}^+/2\text{Cl}^-$  transporter in the thick ascending limb of Henle's loop, decreasing reabsorption of  $\text{NaCl}$  and increasing urinary output [1]. However, this frequently prescribed drug also influences transport of ions across cell membranes in extra-renal tissues. It decreases movement of  $\text{K}^+$  and  $\text{Cl}^-$  across the apical membrane of choroid plexus cells into cerebrospinal fluid [2], inhibits  $\text{Na}^+-\text{K}^+-\text{Cl}^-$  co-transport in lactating rat mammary tissue [3], and attenuates co-transport of sodium plus potassium ions in red cells [4].

Thyroid follicular cells actively absorb iodides from blood by a basement membrane sodium/iodide symporter and translocate them by apical membrane transporter, to follicular lumen [5]. This absorption is inhibited by perchlorate and thiocyanate ions. Furosemide also inhibits transport of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$  in thyroid cells, and decreases sodium concentration both in cytoplasm and in luminal fluid [6, 7]. In living rats, furosemide influences iodide transport into the follicular cells and increases thyroid iodide uptake [8]. Increase in thyroid  $^{131}\text{I}$  uptake was also achieved in man [9], after giving for 15 days furosemide to patients and producing iodide depletion before  $^{131}\text{I}$  administration. Some other studies have also found that furosemide increased renal excretion of iodide in rats and dogs [10], and enhanced  $^{131}\text{I}$  clearance in patients with thyroid cancer [11]. Since  $^{131}\text{I}$  is used for the treatment of thyroid cancer, effects of furosemide on thyroid uptake of iodine and its renal excretion could have clinical implications.

The aim of our study was to test the effects of parenteral furosemide on thyroid retention of radioiodine, long after the administration of furosemide, in living mice.

## Materials and methods

### The animals

This study was conducted on 19 white, Swiss mice of both sexes, 10 weeks old, 25-34g in weight, taken from the animal farm at Medical-Military Academy, Belgrade, Serbia. The animals were jointly housed in colony rooms with 12/1h light/dark cycle at  $21\pm2^\circ\text{C}$  and had free access to food and water. All animal experiments were carried out with permission obtained from the Ethics Committee of the Medical Faculty, University of Kragujevac.

## The experiment

Furosemide (Lasix®, Jugoremedija d.o.o., Serbia), thiopental sodium (Thiopental®, Link, U.K.) and  $^{131}\text{I}$  (Institute for Nuclear Sciences, Vinca, Serbia) were used.

The mice were divided into Group A, 11 experimental mice, 6 male and 5 female and Group B, 8 controls, 4 male and 4 female. Both groups were on low-iodine diet prepared according to prescription given by the Veterinary Institute, Subotica, Serbia (corn 58%, cattle flour 7%, milk substitute 2%, soy bean 28%, sunflower oil 2%, chalk 1%, calcium phosphate 1% and vitamins 1%) for 15 days before administration of  $^{131}\text{I}$ , and throughout the experiment. Both Groups received an intraperitoneal injection of  $^{131}\text{I}$ , with average activity of  $0.37 \pm 0.03\text{MBq}$ . The radioactivity of administered  $^{131}\text{I}$  was calculated as difference between radioactivity of prepared full syringe before the administration, and radioactivity of empty syringe after the intraperitoneal injection, corrected for the background. Measurements were made in a gamma counter (Wallace Wizard 1470, PerkinElmer Life Sciences, Wallace Oy, U.S.A.). After the administration of  $^{131}\text{I}$  all animals were housed separately in colony rooms with 12/12h light/dark cycle at  $21 \pm 2^\circ\text{C}$  and had free access to low-iodine food and water.

Group A mice received an intra-peritoneal injection of furosemide ( $0.3\text{mg/kg}$ ) 2h after the administration of  $^{131}\text{I}$ , repeated at 8h-intervals for 72h. Group B did not receive furosemide.

After 72h, the mice from both groups were anaesthetized by intraperitoneal injection of thiopentone sodium ( $50\text{mg/kg}$ ), and their thyroid glands were carefully extirpated (Fig. 1). The radioactivity of each extirpated thyroid gland was measured in a gamma counter (Wallace Wizard 1470, PerkinElmer Life Sciences, Wallace Oy, U.S.A.) and corrected for the background radioactivity and for spontaneous disintegrations of  $^{131}\text{I}$  during the 72h (by multiplication with a factor of 1.296). Radioactivity of the thyroid glands was expressed as percentage of the administered radioactivity, i.e. fixation of  $^{131}\text{I}$  in the thyroid (%).

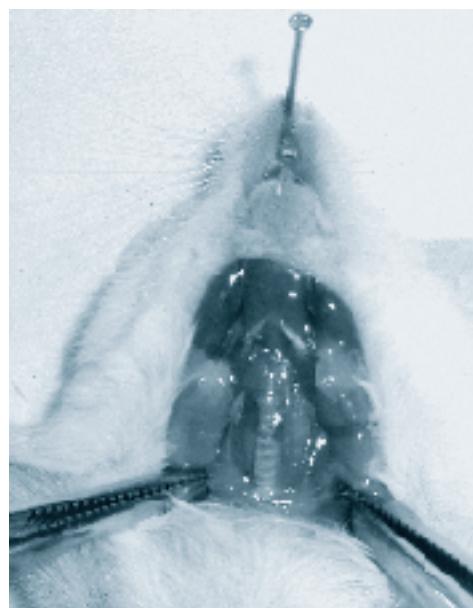
After the extirpation of thyroid glands, the experimental mice were sacrificed by exsanguinations.

## Statistics

Fixation of  $^{131}\text{I}$  in the thyroid glands was expressed by the mean and standard deviation (SD) of the measurements, and then compared by Student's t-test for small independent samples. The difference was considered significant if probability of null hypothesis was less than 0.05.

## Results

The mean value of  $^{131}\text{I}$  retention (fixation) in the thyroid 72h after the intra-peritoneal  $^{131}\text{I}$  injection, expressed as percentage of the administered radioactivity still present in the thyroid gland after 72h, was  $63.09 \pm 15.88\% (\pm \text{SD})$  in Group A, and  $82.25 \pm 11.12\% (\pm \text{SD})$  in Group B.



**Figure 1.**  
Prepared thyroid gland on an anaesthetized mouse prior to its extirpation.

## Discussion

Intensity and duration of  $^{131}\text{I}$  retention in the thyroid gland is important when administering therapeutic or diagnostic doses to the thyroid. Retention of  $^{131}\text{I}$  is due to renal excretion and to transport of  $^{131}\text{I}$  to thyroid cells. Furosemide and other drugs may influence both processes, providing renal function is normal [12].

Previous studies confirmed the prevailing effect of furosemide on renal function and on retention of  $^{131}\text{I}$  in the thyroid gland. By increasing renal excretion of  $^{131}\text{I}$  [10, 11], furosemide decreases available  $^{131}\text{I}$  blood pool used for  $^{131}\text{I}$  uptake by the thyroid gland. Molecular  $^{131}\text{I}$  uptake in thyroid cells may be enhanced by furosemide [8]. This effect cannot overcome decreased  $^{131}\text{I}$  blood pool, thus,  $^{131}\text{I}$  uptake and retention are decreased. Studies have shown that the size of  $^{131}\text{I}$  blood pool and  $^{131}\text{I}$  uptake and retention by thyroid gland are correlated [13].

In our study, the decrease of  $^{131}\text{I}$  retention of the thyroid gland was examined 3 days after furosemide administration, thus, it represents net retention and not early uptake of  $^{131}\text{I}$ . Other studies have shown that decreased retention of  $^{131}\text{I}$  was due to increased renal excretion and to consequent decrease of  $^{131}\text{I}$  blood pool. Thus, furosemide may be used as a diuretic to improve  $^{131}\text{I}$  clearance in patients with thyroid cancer treated with large doses of  $^{131}\text{I}$ , reducing the radiation burden and shortening hospitalization time [11, 14]. It is important that in order to increase  $^{131}\text{I}$  clearance and decrease its retention in the thyroid gland, furosemide must follow the administration of  $^{131}\text{I}$ .

Our results should be cautiously applied to humans, since differences in species may exist, inducing different pharmacokinetics of  $^{131}\text{I}$  [15].

*In conclusion*, furosemide after the administration of  $^{131}\text{I}$ , decreases retention of  $^{131}\text{I}$  in the thyroid gland in mice. The well known increase of iodine renal excretion by furosemide

and consequently decrease of iodine blood pool may be the reason for this decreased  $^{131}\text{I}$  retention by the thyroid gland.

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