The sodium-iodine symporter and the proton-pump inhibitors in –related to the side effects of– the treatment of thyroid cancer with iodine-131

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Abstract

Iodine-131 (^{131}I) administered to patients for imaging or treatment, concentrates in the gastrointestinal tract, including the salivary glands, stomach and bowel. In Nuclear Medicine practice this biological property of iodine causes side effects when the therapeutic dose of ^{131}I is large. This occurs during the treatment of patients with differentiated thyroid carcinoma (DTC). During this clinical application, the dose of ^{131}I is higher than 3.7 GBq. Side effects of this treatment with respect to the stomach, include gastritis as an inflammatory reaction to radiation, anorexia due to gastric atrophy and rarely megaloblastic anemia due to lack of the endogenous factor. Side effects can also include xerostomia. We have recently tried to prevent gastric side effects by prescribing proton pump inhibitors (PPI) for patients with DTC prior to treatment with ^{131}I. PPI block the excretion of hydrochloric acid from the gastric mucosa and are utilized for the prevention and treatment of gastritis, gastric ulcers and gastroesophageal reflux. Whole body scans before or after the administration of PPI, showed that PPI do not interfere with the biologic distribution of ^{131}I. These findings were not surprising. Recent studies in animals and humans have shown that the accumulation and concentration of iodine by the thyroid gland is the result of the selective action of sodium iodine symporter (Na+I+symporter, NIS). Furthermore, it was shown that the accumulation and concentration of ^{131}I in the parietal cells of the gastric mucosa, the ductal cells of the salivary glands and the alveolar epithelial cells of the mammary glands, is analogous to the biologic action of NIS in the thyroid cells. The gastric mucosa accumulates iodine from the capillaries via the extracellular/extravascular space and finally excretes it into the lumen of the stomach, from where it is passively transferred into the bowel, where it is partially reabsorbed to once again enter its metabolic cycle. On the contrary, as it is now known, the PPI have an entirely different metabolic action, which is unrelated to that of the NIS, although both mechanisms coexist in the parietal cells of the gastric mucosa. Thus, during the application of ^{131}I for imaging or for the treatment of DTC patients, except for the short period of time immediately after the oral administration, when the radionuclide passes through the stomach, the concentration of ^{131}I in the gastrointestinal tract is due to its active accumulation and excretion by the gastric mucosa. PPI act only on the hydrochloric acid secretion not affecting the biologic properties of iodine.

Keywords: Sodium-iodine symporter – Proton-pump inhibitors – Thyroid cancer treatment – ^{131}I biologic properties

When iodine-131 (^{131}I) is administered to patients for imaging or treatment, the radioisotope concentrates in the gastrointestinal tract, including the salivary glands, stomach and bowel. In Nuclear Medicine practice this biological property of iodine constitutes a problem because it causes side effects when the therapeutic dose of ^{131}I is large. This occurs during the treatment of patients with differentiated thyroid carcinoma, either when, following thyroidectomy, the remnants of the thyroid gland are ablated, or when the tumor itself is treated as in case of metastases or recurrence of the disease. During this clinical application, the dose of ^{131}I is higher than 3.7 GBq. Side effects of this treatment with respect to the stomach, include gastritis as an inflammatory reaction to radiation, anorexia due to gastric atrophy and rarely megaloblastic anemia due to lack of the endogenous factor. Side effects with respect to the salivary glands can include xerostomia because of destruction of the glands and rarely partial impairment of taste due to destruction of the taste sensors [1-5]. We recently witnessed the effort of an endocrinologist colleague to prevent gastric side effects by prescribing proton pump inhibitors (PPI) for patients with differentiated thyroid carcinoma prior to treatment with ^{131}I. PPI block the excretion of hydrochloric acid from the gastric mucosa and are utilized for the prevention and the treatment of gastritis and ulcers as well as to treat side effects of gastroesophageal reflux. The scintigraphic observations during this trial provided the opportunity to study and review this issue.

For the trial, PPI, namely esomeprazole 40 mg daily and pantoprazole 40 mg daily, were prescribed to 18 patients, who were treated with large doses of ^{131}I to either ablate remnants of the thyroid gland in 11 patients with 3.7-7.5 GBq, or to treat recurrent or metastatic differentiated thyroid carcinoma in 7 patients with 7.5-21.8 GBq. The administration of PPI began the day of the treatment and continued for one week, until the total body scan was acquired. Effects of this trial were observed on total body scans obtained at 48 h on a selective evaluation and at 8-10 days post treatment on a routine evaluation. The post treatment total body scans of these patients and of the patients without preparation with PPI, were reviewed by two nuclear medicine physicians regarding the accumulation of ^{131}I in the gastrointestinal tract, the salivary glands, and the remnants of the thyroid gland, as well as in areas of tumor recurrence and tumor metastases.

First, the 10 days post treatment scans were reviewed and, in both groups of patients i.e. in those prepared with PPI as well as those without preparation with PPI, the stomach was nearly empty (Fig. 1). More precisely, in patients who were treated with PPI the scans, which were acquired 8-10 days fol-

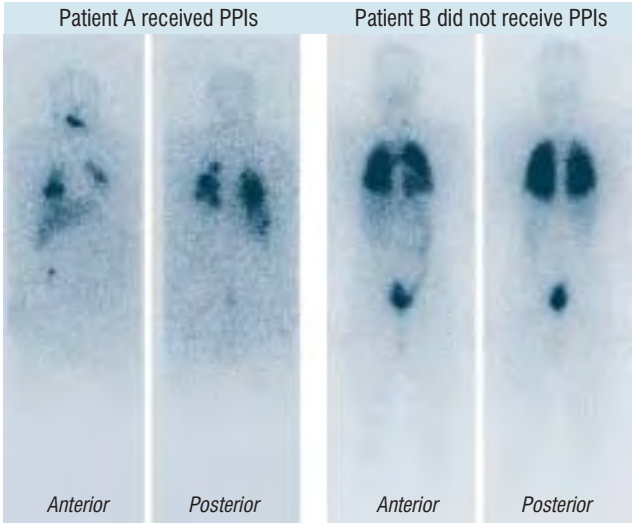


Figure 1. Total body scans of patients 10 days after treatment with ^{131}I

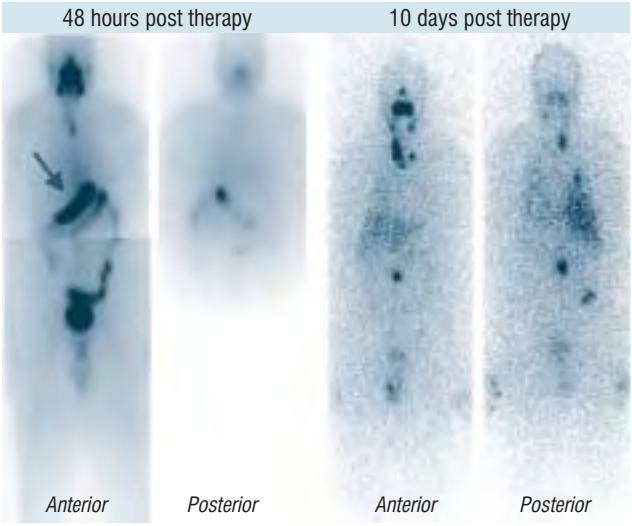


Figure 2. Scans of a patient who received PPI at 48 h and 10 days

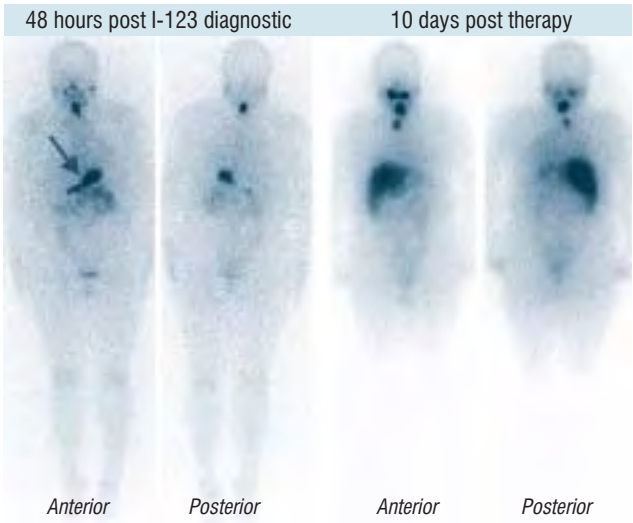
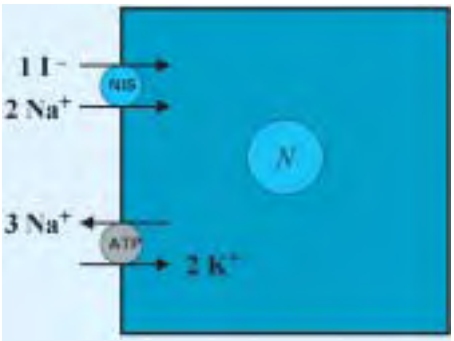


Figure 3. Scans of a patient who did not receive PPI at 48 h and 10 days



ATP=Na$^+$/K$^+$A T Phosphatase; NIS=Na/I Symporter
NIS co-transports 2 sodium ions and 1 iodide ion. Sodium gradient provides energy to this transfer, as generated by Na/K ATPase.

From: Dohanet al: The Sodium/Iodide Symporter (NIS): *Endocrine Reviews 24(1):48-77, 2003.*

Figure 4. Schematic illustration of NIS function in cells

lowing therapy, showed that in 7 of the 18 patients there was no gastrointestinal tract accumulation of the ^{131}I, in 9 the gastrointestinal tract accumulation was substantially decreased, compared to diagnostic scans, and only in 2 persons appeared the same with the activity in the diagnostic pre-treatment scans of the 2 days post the small 185 MBq dose of the ^{131}I. In patients who were not treated with PPIs the 8-10 days following therapy scans showed that, in 10 of the 20 patients there was no gastrointestinal tract accumulation of ^{131}I, in 8 the gastrointestinal tract accumulation was substantially decreased, compared to diagnostic scans, and only in 2 persons appeared the same with the activity in the diagnostic pre-treatment scans of the 2 days post the small 185 MBq dose of the ^{131}I. On the contrary, the salivary glands, the tumor remnants and the tumors, showed accumulation of ^{131}I in all these scans. Then, the 48 h post therapy scans were reviewed, where the stomach demonstrated ^{131}I accumulation in all patients in both groups (Fig. 2 and 3) in addition to the other sites mentioned above. Therefore the gastrointestinal tract including the stomach, the salivary glands and the bowel did not show any difference as for the accumulation of ^{131}I between the two groups and similarly the remnants and the tumor. Following this observation, there was no reason to continue the trial. The conclusion was that the PPI have no effect on the accumulation of ^{131}I by the wall of the stomach, or by the salivary glands; therefore it is not expected for the PPI to have any effect on the development of side effects after therapeutic administration of ^{131}I. Fortunately, the PPI did not influence the accumulation of ^{131}I by the remnants of the thyroid gland or by the tumor itself and for this reason the fundamental scope of the treatment was not negatively affected (Fig. 1-3).

These findings were not surprising [1-9]. Recent studies in animals and humans have proven that the accumulation and concentration of iodine by the thyroid gland is the result of the selective action of sodium iodine symporter (Na+I+symporter, NIS), which is present in the external surface, in relation to the follicles, of the cellular membrane of the epithelial cells of the thyroid gland as shown in Figure 4 [9]. The function of the cells

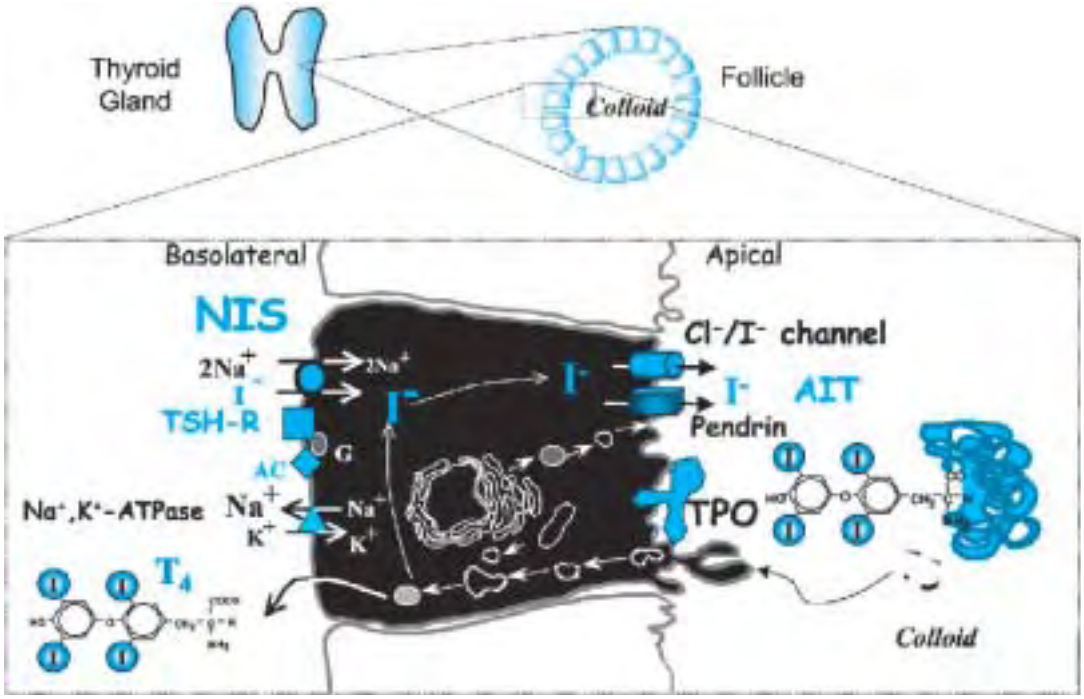


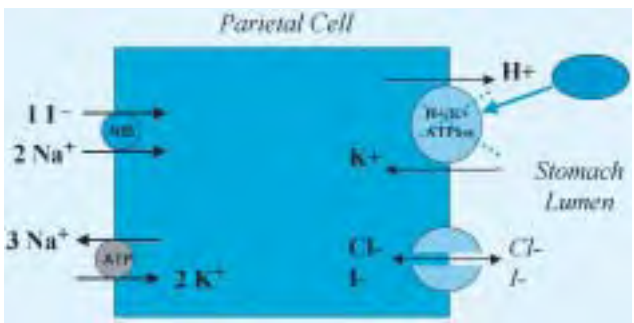
Figure 5. Schematic illustration of NIS function in the thyroid cell

Circle, Active accumulation of I–, mediated by the NIS; *triangle,* Na^+/K^+ATPase; *square,* TSH receptor; diamond, adenylatecyclase; *ellipse,* G protein; *cylinder,* I–efflux toward the colloid; TPO, TPO-catalyzed organification of I–; *arrows pointing from the apical to the basolateral side* indicate endocytosisof iodinated Tg, followed by phagolysosomalhydrolysis of endocytosediodinated Tgand secretion of both thyroid hormones. AIT, Apical I–transporter.

From Dohanet al: The Sodium/Iodide Symporter (NIS): *Endocrine Reviews 24(1):48-77, 2003.*

of the thyroid gland has been further revealed, as presented in Figure 5 [4-11]. Furthermore, it has been shown that the accumulation and concentration of ^{131}I in the parietal cells of the gastric mucosa, the ductal cells of the salivary glands and the alveolar epithelial cells of the mammary glands, is based on the NIS biologic mechanism of action, as in the thyroid cells [9, 12]. TSH stimulates only iodine uptake by the thyroid gland, because TSH receptors are present only in the thyroid cell membrane [9]. The gastric mucosa accumulates iodine from the capillaries via the extracellular/extravascular space and finally excretes it into the lumen of the stomach, from where it is passively transferred into the bowel, where it is partially reabsorbed to once again enter its metabolic cycle [1-5, 12].

On the contrary, as it is now known, the PPI have an entirely different metabolic action, which is unrelated to that of the NIS (Fig. 6), although both mechanisms coexist in the parietal cells of the gastric mucosa [7]. The PPI are substitute benzimidazoles and generally are given orally in the form of capsules. They are absorbed in the first part of the small intestine and have a relatively short half-life in the circulation, of 1-2 h. The duration of their action however is prolonged because of the specific mechanism with which they act on the gastric mucosa. The PPI are lipophilic bases, cross from local circulation the membrane of the parietal cells and enter into the acidic tubules of these cells. Inside this acidic environment, the PPI acquire one proton (H^+) and convert to the activated sulfenamide type of the medication, which is covalently connected to the H+/K+ ATPase enzyme. This connection



ATP=Na^+/K^+ A T Phosphatase; NIS=Na/I Symporter.The hydrogen potassium ATPase (H/K ATPase) pumps hydrogen out of the parietal cell to the stomach lumen andit is blocked by Proton Pump Inhibitors (PPIs). PPIs have no effect on NIS

From Wolfe M: Overview and Comparison of the Proton Pump Inhibitors for the Treatment of Acid-Related Disorders. *UpToDate–www.uptodate.com1-14, 2006*

Figure 6. Action of PPI and NIS in gastric mucosa parietal cells

results in the permanent inhibition of the excretion of hydrochloric acid from the proton pump. The parietal cell must either produce new proton pumps or activate non-active ones in order to be able to restore the excretion of hydrochloric acid [7]. As shown in Figure 6, the action of PPI is not exerted on the Cl or I atoms, but on the acid excretion. Based on the above, one should not expect to observe an effect of the PPI on the accumulation of ^{131}I by the wall of the stomach. In theory it could be possible for the PPI to indirectly affect the action of NIS. This, however, would be undesirable, as it would negatively affect the accumulation of ^{131}I by the tumor cells,

which is based on the same biologic mechanism, and the entire treatment would be jeopardized [8, 9]. Fortunately, such an action did not occur in our study. The evaluation was not quantitative, only visual, based on the scans, but it showed adequately that in patients, who received PPI, the accumulation of ^{131}I either by the tumors and the remnants of the thyroid, or by the wall of the stomach and the salivary glands, did not differ from that in patients who had not taken PPI. This experience was in agreement with the related theory.

Therefore, when ^{131}I is administered to patients either for imaging or for treatment, except for the short period of time immediately after the oral administration, when the radionuclide passes through the stomach, the observed concentration of this radioisotope in the gastrointestinal tract is due to its active accumulation and excretion by the gastric mucosa [1, 2]. ^{131}I is actively accumulated from the blood, by the parietal cells of the gastric mucosa and is not absorbed from the contents of the stomach. Specifically ^{131}I is accumulated from the extravascular/extracellular space into the parietal cells by the NIS ie by the same mechanism responsible for the accumulation of iodine by the thyroid gland [3]. Regardless of the route of administration, the ^{131}I is eventually accumulated in considerable quantities by the gastric mucosa. It is then excreted into the lumen of the stomach and subsequently passively transferred into the small bowel, where a substantial percentage is reabsorbed into the circulation to continue its metabolic cycle for a few days. Similarly, iodine is actively accumulated by the salivary glands [3]. Finally, PPI do not affect the biologic properties of iodine. Specifically, with respect to gastric mucosa, they have a totally different biologic mechanism of action than iodine and do not interfere or prevent side effects from ^{131}I ablation.

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