

Preparing Patients for Radioiodine Treatment: Increasing Thyroid Cell Uptake and Accelerating the Excretion of Unbound Radioiodine

Milovan Matović

*University of Kragujevac, Medical Faculty; Clinical Centre Kragujevac,
Department of Nuclear Medicine
Serbia*

1. Introduction

The therapeutic application of radioiodine ^{131}I in postoperative ablation of the remaining thyroid tissue, as well as in the treatment of recidivism and/or local and remote metastases of differentiated thyroid carcinoma has been a part of the clinical practice for over 50 years. It is a regular segment of the standard therapeutic procedure in differentiated thyroid carcinoma treatment and it comes recommended by a number of authorities in the field (American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi [AAACE/AME], 2006; Cooper et al., 2006; Pacini et al., 2006; Society of Nuclear Medicine [SNM], 2006, British Thyroid Association [BTA], 2007; Dietlein et al., 2007; Luster et al., 2008; National Comprehensive Cancer Network [NCCN], 2010;). Certain differences in opinion on the subject are concerned only with the dose that is applied, as well as with whether radioactive iodine therapy should be utilized in lower risk patients (Иваницкая&Шантырь, 1981; Haq et al., 2004; Ringel&Ladenson, 2004; Cooper et al., 2006; Pacini et al., 2006; Gheriani, 2006). Several decades of experience have shown indisputable beneficial effects of the administration of ^{131}I as postoperative adjuvant therapy. However, there can be certain adverse effects, beside the beneficial ones, which are a consequence of radiation damage to other tissues and organs. The organs most exposed to the harmful radiation effect of ^{131}I in differentiated thyroid carcinoma treatment are salivary glands, nasolacrimal ducts, stomach epithelium, kidneys, bladder wall, colon, gonads, bone marrow, etc. But, most long-term follow-up studies report a very low risk of secondary malignancies in long-term survivors (Rubino et al., 2003; Brown et al., 2008). However, meta-analysis of two large multicenter studies showed that the risk of second malignancies was significantly increased relative to thyroid cancer survivors not treated with RAI (Sawka et al., 2009). The risk of secondary malignancies is dose related (Rubino et al., 2003), Cumulative ^{131}I activities above 500–600 mCi are associated with a significant increase in risk. There appears to be an increased risk of breast cancer in women with thyroid cancer (Brown et al., 2003; Sandeep et al., 2006; Chen et al., 2001). It is unclear whether this is due to RAI therapy, screening bias or other factors.

The question that arises regarding radioactive iodine administration is: how do we optimize the beneficial therapeutic effects of radioiodine on one hand and minimize the adverse effects on other tissues and organs on the other. The compromise can be achieved in two ways. The first is to increase radioiodine uptake in thyroid tissue/tumour tissue and increasing the therapeutic efficiency of ^{131}I . In other words, the aim is to achieve the best therapeutic effect in the target tissue with as low a dose of ^{131}I as possible. The second is to reduce the adverse effects, i.e. reduce the amount of radiation energy ^{131}I tissues by accelerating the elimination of radioiodine which hasn't been bound by thyroid/tumour tissue.

There is yet another reason why the accelerated elimination of radioiodine from the body of the patient should be striven for. The reason is legal and concerns regulations which exist in every country and which determine the amount of radioactive iodine that patients are allowed to have in their body without being required to receive their treatment in a 'restricted area'. With the doses of radioiodine normally applied in differentiated thyroid carcinoma treatment, hospitalisation of some duration is required in many countries. For this reason, it is in the best interest of the health system to shorten the hospitalisation, i.e. the isolation of the patient being treated with radioactive iodine, without reducing the therapeutic effect of ^{131}I .

There are significant variations in the regulations regarding ^{131}I administration from one country to another. These variations mostly have to do with the upper limit of the radionuclide that can be administered without the patient requiring isolation.

Legal regulations state that anything above that limit requires the therapy to be carried out on hospital premises, or more precisely, in special rooms designated as controlled radiation zones ('restricted areas'). This limit varies in different countries. For example, in Serbia, the upper limit is relatively low and special precautions have to be taken if the radioactivity of ^{131}I exceeds 400 MBq (10.81mCi). In other words, the patient can be released from hospital only when the radioactivity in his body decreases below the level of 400 MBq (the Republic of Serbia, Ministry of environmental protection, 2003). The limit is significantly higher in the EU and USA, where hospitalisation is obligatory only if the radioactivity of ^{131}I exceeds 1110 MBq (30mCi) (1110 MBq). In this case the patient is hospitalised and kept in isolation until their radioactivity level decreases to 30 mCi (1110 MBq) (Tuttle et al., 2000; Society of Nuclear Medicine [SNM], 2006).

In cases of differentiated thyroid carcinoma treatment the doses of ^{131}I vary from 30mCi for the remaining thyroid tissue ablation, to 200 mCi for the treatment of metastases, even though there are several records of the doses reaching as much as 333 mCi (9GBq) (Haq et al., 2004). With the application of these larger doses, the permitted radioactivity limit in the body is reached a few days following the application of the ablation/therapeutic dose of ^{131}I (Venencia et al., 2002). The time necessary to reach the limit depends primarily on the dose applied and the condition of kidney function, as well as on the size of the thyroid/tumour tissue being treated.

2. Methods for increasing radioiodine uptake

2.1 Thyrotropin stimulation (endogenous and exogenous TSH stimulation)

In order to optimize radioiodine uptake in the thyroid remnant or in thyroid tumour tissue, it is necessary either for the patient to have substantially elevated endogenous thyroid-

stimulating hormone levels (serum TSH concentration above 30 mIU/mL), or to perform exogenous TSH stimulation by applying recombinant human TSH (rhTSH).

In the first case, sufficient levels of TSH are most commonly achieved if the patient is left without thyroid hormone replacement therapy for 4 to 6 weeks. The primary problem that frequently arises from thyroid hormone withdrawal as a way of increasing TSH levels is clinically evident hypothyroidism, which some patients find quite disagreeable. The condition is notable for hypometabolism, constipation, increased cholesterol levels in blood, the risk of cardiovascular disorders, and the most severe one – myxedema.

In the second case, exogenous TSH stimulation of the uptake is achieved by the application of rhTSH, available on the market as Thyrogen® (Genzyme). This medication is given to the patient intramuscularly for 2 days, in 0.9 mg doses.

Exogenous stimulation of thyroid minimises the chances of hypothyroidism, and at the same time enables better planning of radioiodine therapy. However, the application of rTSH increases the cost of the treatment significantly, as this medication is relatively expensive.

The results of a number of studies have shown that the final effects of uptake stimulation, both with endogenous TSH, and exogenous rhTSH are equally satisfactory and thus both come equally recommended (Haugen et al., 1999; Pacini et al., 2006).

2.2 Low iodine diet

In order to achieve a better uptake in thyroid/tumour tissue, a low iodine diet is recommended, i.e. the daily intake of not more than 25-75 µg of iodine. Patients should be put on the diet for 10 to 30 days prior to the diagnostic or therapeutic application of ¹³¹I (Maxon et al., 1983; SNM, 2006; Thyroid Cancer Survivors' Association, 2007).

The consequence of the low intake of iodine is iodine depletion in the body, which should result in its increased uptake in thyroid remnants/tumour tissue. Since most countries have legal regulations by which producers are obliged to iodise table salt, this low iodine diet practically presupposes the limitation of table salt intake, which usually proves to be difficult for the patients to put into practice. One teaspoon of iodised table salt contains about 400 micrograms of iodine. Sea salt is also not recommended due to the fact that it contains a significant amount of iodine. The alternative is uniodised salt, which is often difficult to find. Apart from the limitation on table salt, it is essential that the patients avoid foods with high concentration of iodine (above 20 micrograms per meal), and these are the following:

- seafood (fish, shellfish, seaweed, seaweed tablets, kelp). These are all very high in iodine and should be avoided. Food containing sea-based additives, such as carrageenan, agar-agar, algin, alginate and nori should also be avoided.
- milk and dairy products such as cheese, cream, yogurt, butter, ice cream, milk chocolate, powdered dairy creamers, whey, casein and others which contain significant amounts of iodine (250 ml of milk- 1 cup or 16 tablespoons, contain from 88 to 168 micrograms of iodine, or an average of 115 micrograms).
- egg yolks or whole eggs
- bread and pastry
- salty processed foods such as potato chips and cured and corned foods such as hot dogs, ham, corned beef, sauerkraut, bacon, sausage, and salami.

- soybeans and most soy products (soy sauce, soy milk, tofu)
- red, orange, or brown processed food, pills and capsules, because the artificial colour (erythrosine) used for these foods contains significant amounts of iodine
- iodine-containing vitamins and food supplements

A limited daily intake of food which contains moderate amounts of iodine (5-20 micrograms per meal) is recommended. This includes the following:

- fresh meats (meat contains 56-290 micrograms of iodine per kilogram). Up to 140 grams a day of fresh meats such as chicken, beef, pork, lamb, and veal are fine on the low-iodine diet.
- grains, cereals. Up to 4 servings per day of grains, cereals, pasta, and breads without iodine-containing ingredients are fine for this diet. Homemade baked goods and cereals are best for this diet.
- rices. Similar to grains, rices vary in the amount of iodine depending on the region where they are grown, so rice should be eaten only in limited amounts. Some low-iodine diets recommend avoiding rice.

These instructions can often pose a problem because some guidelines only say that certain items or certain food categories should be avoided, and do not give details within categories, or else they just give lists of foods and ingredients that are allowed, without limits on quantities consumed.

Even though most recommendations and guides list iodine diet as an essential part of the preparation for radioiodine therapy application due to the fact that it increases the binding of iodine in thyroid/tumour tissue, there are also other, contrasting data. Some researches have shown that the effects of low iodine diet can include an increased iodine retention, instead of iodine depletion, especially if it is combined with the application of diuretics (Hamburger, 1969; Norfray & Quinn, 1974; Tepmongkol, 2002, Matovic et al. 2009a).

2.3 Lithium

The inhibiting effects of lithium carbonate on the release of iodine from the thyroid tissue are also useful in radioiodine treatment of differentiated thyroid carcinoma, for the purpose of achieving prolonged and increased radioiodine retention in the thyroid/tumour tissue (Briere et al., 1974; Gershengorn et al., 1976; Rasmusson et al., 1983; Pons et al., 1987). Researchers agree that the administration of 0.8-1.2 mmol/L of lithium carbonate results in an increased uptake and prolonged retention of radioiodine in thyroid/tumour tissue, which doubles the dose absorbed, without significant adverse whole-body irradiation. However, the majority of authors urge caution in using this medicine and suggest careful monitoring of its levels in plasma for the purpose of avoiding adverse effects, primarily intoxication, which affects the central nervous system and kidneys, and can potentially be fatal (Simard et al., 1989).

2.4 Retinoids and an increasing expression of NaI symporter system

Better accumulation of ^{131}I into the remnant thyroid/tumour tissue can be achieved through an increased expression of genes that enhance the synthesis of the NaI symporter. Retinoids or their metabolites, which bind with retinoic A and X receptors (RAR and RXR), are known

to result in an increased expression of genes which lead to an increased synthesis of NaI symporters. This will theoretically lead to increased iodine uptake in thyroid/tumour tissue. However, there are contradictory data concerning the efficiency of this sort of adjuvant therapy in thyroid iodine uptake. While some researchers (Van Herle et al., 1990; Grunwald et al., 1998; Koerber et al., 1999) point out that the administration of 13-cis retinoic acid (in Accutan, Roche Laboratories, Nutley, NJ, USA) prior to radioiodine application increases its uptake in the tumour tissue, especially in follicular carcinomas, others (Gruning et al., 2003) do not find a significant efficiency in the increase of thyroid iodine uptake, based on studies of large groups of subjects.

However, the latest findings on NaI symporter system expression, as well as the identification of genes which encode its synthesis (Mandell et al., 1999; Spitzweg et al., 2001; Castro et al., 2001; Chung et al., 2002; Kogai et al., 2006) will probably allow for new approaches in radioiodine therapy of differentiated thyroid carcinomas, that focus on the optimisation of the dose administered to patients, by increasing the efficiency of this therapy.

3. Methods for increasing unbound iodine excretion

3.1 Hydration

The relevant literature suggests that the accelerated urinary excretion of ^{131}I can be achieved by extensive hydration. However, there are also data that do not support this. For example, Giebisch et al. (Giebisch et al., 1956) concluded in their research on dogs that water diuresis does not induce iodine diuresis, as 95% of the filtered iodine gets reabsorbed by the tubules in proximity to water absorption spots. Even so, extensive hydration is recommended in patients receiving radioiodine therapy, since it can lead to the dilution of radioiodine in the urine and a decrease in radioactive iodine retention in the urinary tract, which contributes to the decrease in the dose absorbed by the urinary bladder wall and surrounding organs.

3.2 Laxatives

In order to accelerate elimination of ^{131}I through stool, some experts prescribe laxatives to expedite bowel evacuation, especially in patients with constipation. Others, however, hold the opinion that only a small, insignificant amount of the applied radioiodine is eliminated in this way, and that therefore laxatives are not of great importance (Hays, 1993). For these reasons, it is considered that the administration of laxatives is not necessary in patients who have at least one stool a day.

3.3 rhTSH (Thyrogen®)

There are data that renal radioiodine excretion is ~50% faster during euthyroidism versus hypothyroidism due to reduced renal function in hypothyroidism. Administration of rhTSH minimises the chances of hypothyroidism and could be indirectly useful in accelerating of unbound radioiodine elimination. However, based on their meta analysis study, Freudenberg and co-workers (Freudenberg et al., 2010) suggests (but without statistically significant evidence), that rhTSH administration may results in a lower radiation dose to DTC metastases than does thyroid hormone withdrawal (THW). Further studies should resolve this issue.

3.4 Diuretics

For the purpose of reducing the absorbed dose in critical organs and tissues of patients treated with radioiodine, a simple and efficient method is often recommended for the excretion of unbound ^{131}I - extensive hydration in combination with additional diuretic therapy.

In a study conducted on 49 adult subjects with and without thyroid and kidney function impairment, Bricker and Hlad (Bricker&Hlad, 1955) concluded that ^{131}I gets excreted from the body by means of passive filtration in glomeruli and gets partially reabsorbed by the tubuli by means of passive back-diffusion, without any active tubular transport mechanisms.

There are various, often contradictory data in the literature concerning the effects of diuretics on the biokinetics of radioiodine elimination. The majority of studies point to the fact that faster elimination of radioiodine can be achieved by the addition of diuretic therapy (Russell&Ingbar, 1965; Fregly&Gennaro, 1965; Fregly, 1966; McCarthy et al., 1967; Fregly&McCarthy, 1973; Seabold et al., 1993; Kapucu et al., 2003), but the results of other studies show that the administration of diuretics leads to increased radioiodine uptake in the thyroid tissue (Hamburger, 1969; Norfray&Quinn, 1974; Ding et al., 2004; Tepmongkol, 2002). The data concerning the studies of the urinary excretion of iodine and the effects of diuretics on its urinary excretion published so far are contradictory. They do not present a clear picture of what kind of benefits, if any, can be gained by adding diuretic therapy to radioactive iodine treatment protocols. This is probably at least in part due to the fact that the published data were obtained either from studies performed on animals (Fregly&Gennaro, 1965; Fregly, 1966; McCarthy et al., 1967), or from studies on patients who did not suffer from differentiated thyroid carcinoma and had not been operated on previously, and who received radioiodine doses far smaller than those given to patients suffering from differentiated thyroid carcinoma (Russell&Ingbar 1965; Fregly&McCarthy, 1973; Tepmongkol, 2002; Kapucu 2003).

There have been a small number of studies on the effects of diuretics on radioiodine clearance in patients who were treated with therapeutic doses of ^{131}I , but the conditions under which these studies were conducted were to a certain degree different to the ones typical for clinical practice and the way this therapy is normally carried out (Maruca et al., 1984; Seabold et al., 1993; Ding et al., 2004).

The effects of furosemide, hydrochlorotiazide, manitol, ethacrynic acid and acetazolamide on radioiodine urinary excretion have been studied so far. Out of all the diuretics, furosemide has been studied most.

3.4.1 Furosemide

Furosemide is effective, cheap and widely used. Abbott and associates (Abbott et al., 2008) have analysed the data concerning the effects of furosemide from both the medical and veterinary literature. Based on a considerable number of analysed papers, they concluded that one of the chief effects of furosemide includes iodine depletion in the body, which is achieved through a decrease in its reabsorption in the thick ascending limb of Henle's loop. Furosemide acts as the inhibitor of Na-K-Cl cotransporter 2 (NKCC 2), which is the

mechanism present in the majority of other diuretics, excluding spironolactone. The inhibition of co-transporter NKCC 2 is dose-dependent with respect to the concentration of furosemide in the lumen, rather than in plasma. The administration of furosemide brings about an increase in sodium, chloride and water in distal collecting ducts, resulting in increased renal excretion of potassium and hydrogen. This can result in some patients developing hypokalemic and hypochloremic alkalosis, which is the most common adverse effects of this diuretic. For the purpose of hypokalemic and hypochloremic alkalosis prevention, it is advised that patients receive potassium chloride together with furosemide in cases of long term therapy.

When it comes to the influence of furosemide on radioiodine excretion, numerous and often contradictory data have been published. Some of them point to the fact that this diuretic influences the acceleration of iodine urinary excretion leading to iodine depletion. However, in one of our previous studies (Matovic et al., 2009a) it has been unmistakably shown that this diuretic, in combination with low iodine diet, slows down the elimination of radioiodine in patients treated with this radionuclide (figure 1. and figure 2.).

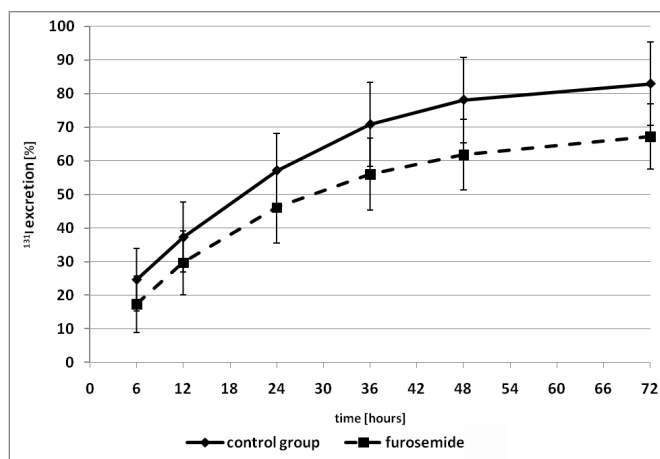


Fig. 1. Urinary excretion of radioiodine in patients treated with furosemide (■), and in the control group patients(●).

Our results were somewhat similar to the ones obtained by Maruca et al. (Maruca et al., 1984), who concluded that diuretic-mediated iodide depletion is not universally successful and that it is far less effective than it was considered before, therefore casting some doubt on its clinical benefits. Their aim was to achieve iodine depletion with low iodine diet and diuretics (Hydrochlorotiazide and Furosemide) in patients who had previously undergone thyroidectomy due to differentiated thyroid carcinoma. The results they obtained point to the fact that this low iodine diet and diuretics increase the uptake of iodine in the tumour tissue. According to their findings, the total iodine uptake and retention in the tumour tissue was mostly the consequence of total body retention, and not some specific mechanism at the cell level of thyroid/tumour tissue.

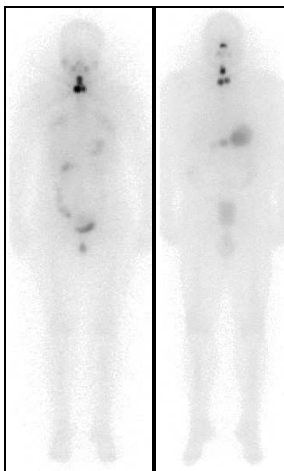


Fig. 2. Scintigrams obtained 72h post therapy with 3.70 GBq of ^{131}I in patients with (left) and without (right) furosemide additional therapy. Increased amount of radioiodine in thyroid rest in case of previous furosemide therapy. Both patients had similar thyroid rest (uptake of radioiodine was about 2% in both patients).

The presumption that low iodine diet plays an important role in how furosemide affects iodine biokinetics can be supported by the data obtained from a number of researchers, who found that furosemide and other diuretics cause an increase in iodine excretion in those patients who were not put on a prior low iodine diet. A comparison between a research by Seabold et al. (Seabold et al., 1993) and Norfray and Quin (Norfray&Quinn, 1974) provide possible further evidence for this. Specifically, Seabold et al. found that in patients who had not been on a low iodine diet and who had received radioiodine ablation therapy, furosemide as an adjuvant therapy accelerated the excretion of radioactive iodine, which enabled those patients to spend far less time on the hospital premises.

Based on experiments in animals, Norfray and Quinn found that intraperitoneal application of furosemide leads to an increased iodide excretion, which in turn results in a decrease in iodide pool in their bodies. The same authors found that supplemental iodide diet does not reduce this effect of furosemide, even though the thyroid radioiodine uptake increases in comparison to the control group under the influence of diuretic therapy, which reduces the iodide pool. This indirectly points to the fact that an uptake increase in thyroid/tumour tissue can be achieved by the administration of diuretics as well. However, they did not measure blood radioactivity, so the possibility that an increase in uptake under the influence of furosemide is at least in part a consequence of increased blood radioactivity, i.e. total body retention, instead of just an increase in the avidity of thyroid tissue for iodine cannot be excluded either.

Other researchers (Hamburger, 1969; Norfray&Quinn, 1974; Tepmongkol, 2002) also found that furosemide does not increase iodine excretion, but on the contrary, that it decreases it. According to the data provided by Kapucu and associates (Kapucu et al., 2003), the administration of Furosemide results in the loss of iodine from subjects' bodies (iodine depletion).

They noticed that after a 5-day furosemide therapy a better penetration of iodine into the thyroid gland was noted in patients who had not previously been on a low iodine diet, than in those who had been on the diet for 14 days, without receiving furosemide. The authors think the explanation for this lies in the loss of sodium from extracellular fluid which is greater when furosemide is administered than when preceded by a low iodine diet alone.

However, Russell and Ingbar (Russell&Ingbar, 1965) state that there is an intrathyroid, pituitary-independent mechanism of increasing thyroid function as an answer to the reduction in iodine concentration in plasma. As far back as 1965 they studied the effect of iodine depletion (with previous low iodine diet and the administration of manitol) on ¹³¹I biokinetics and thyroid function, on a group of 8 patients.

According to their results, iodine depletion resulted in decreased iodine levels in blood, an increase in thyroid iodine transfer and the speed of thyroid clearance, as well as an increase in thyroid iodine uptake followed by a decrease in absolute iodine accumulation. These authors concluded within the same study that there is no increase in thyroid iodine clearance and ¹³¹I uptake if NaI is applied together with manitol.

It should be stressed that in our research on mice (Matovic et al., 2009b) we did not note an increased radioiodine retention in thyroid tissue when we applied furosemide, even though they had undergone a low iodine diet. This can point to the fact that iodine biokinetics has certain species specific characteristics, either at the level of kidneys, or at the level of thyroid gland.

In our research, which included patients treated with radioiodine, we did not determine whether there is an increase in thyroid/tumour tissue uptake under the influence of furosemide therapy, but our results indirectly support the data provided by Maruca et al. that in cases of increase the most likely reason is, up to a certain point, an increase in ¹³¹I levels in blood, i.e. an increase in total body retention of the radionuclide under the influence of additional furosemide therapy.

An important role in this mechanism is played by the preceding low iodine diet, which can be concluded based on the data provided by Hamburger et al. (Hamburger et al., 1969). They determined the uptake in thyroid/tumour tissue in a group of 25 patients with a confirmed diagnosis of inoperable thyroid carcinoma, who had previously been treated with diuretics and a low iodine diet. What was achieved by a combination of a low iodine diet and diuretics (manitol and ethacrynic acid) was doubled, or even tripled uptake in 16 patients, mild increase in 3, and no increase in 6 patients. According to their data, radioiodine levels in thyroid/tumour tissue remain high 96 hours following the diuretic preparation.

3.4.2 Other diuretics

Based on the results obtained from a controlled study, Tepmongkol (Tepmongkol, 2002) concluded that the binding of radioiodine in the thyroid gland is as many as 7.18 times higher when hydrochlorothiazides were administered together with a low iodine diet. The control group comprised patients who were on a low iodine diet, but who received neither hydrochlorothiazide, nor other diuretics. The control group showed an increase in the

uptake as well, even though a significantly smaller one, amounting to 1.33 times the original binding. The study was performed on patients suffering from hyperthyroidism who had been treated with radioiodine. Similar results were obtained by Ding and his associates (Ding et al., 2004), who showed that the administration of hydrochlorothiazide prior to the dosing of radioiodine can significantly increase the dose absorbed by the thyroid tissue. The study included patients suffering from differentiated thyroid carcinoma who had previously undergone thyroidectomy.

In a study performed on 18 young male subjects following an acute administration of hydrochlorothiazide and acetazolamide, Fregly and McCarthy (Fregly&McCarthy, 1973) analysed the fluctuations in urinary excretion of Na, K, Ca, Mg, Cl and I. Based on the results of this study, as well as on the previous studies done on animals (McCarthy et al., 1967, Fregly, 1966, Fregly&Gennaro, 1965), the authors concluded that hydrochlorothiazide has a significant effect on an increase in iodine excretion, which is closely tied to an increase in chloride excretion, while there was no increase in either iodine, or chloride excretion in those treated with acetazolamide.

Judging by all the aforementioned data, the most probable cause of the decrease in ^{131}I excretion under the influence of diuretics is the state of iodine depletion caused by the prior low iodine diet. For some reason this state is characterised by an absence of iodine reabsorption blockage in the tubuli under the influence of diuretic therapy, and paradoxically, results in increased iodine reabsorption.

Walser and Rahill (Walser&Rahill, 1965) concluded that the reabsorption of iodine and chlorine is done in the same part of the nephron by means of passive diffusion with a constant ratio of tubular permeability. Since the low iodine diet was at the same time low chloride, as well as a low sodium diet (due to the reduced table salt intake), it is possible that the explanation for this unexpected and paradoxical effect of diuretics on radioiodine excretion lies in that very fact.

Namely, it is possible that in cases where low iodine diet (i.e. low chloride/low sodium diet) was prescribed, the increase in the reabsorption of chlorine gets followed by an increase in iodine reabsorption at the level of the ascending segment of Henle's loop and the proximal tubules. As a consequence, iodine excretion decreases, instead of increasing, and the same goes for its blood levels, which directly influence the prolongation of patient hospitalisation in the restricted area after the application of radioiodine therapy, due to the maintenance of high circulating levels. For this reason it is not advisable to use additional diuretic therapy for the purpose of speeding up the urinary excretion of radioiodine, at least not in patients who had previously been on a low iodine diet.

4. Methods for salivary glands and nasolacrimal ducts protection

Some authors recommend measures to prevent damage of the salivary glands and nasolacrimal ducts. Damage of those organs results with transient loss of taste and excessive tearing (epiphora), as clinical complications. Methods for prevention of those complications have included usage of amifostine, hydration, sour candies, and cholinergic agents (Mandal&Mandal, 2003). However, in relevant literature there are not enough evidence to recommend for or against these methods. There are even authors (Nakada et al, 2005) who suggested sour candy may actually increase salivary gland damage.

5. Conclusion

With the aim of achieving a satisfactory compromise between high therapeutic efficiency of radioiodine therapy on thyroid/tumour tissue and the need to decrease its adverse effects on other tissues and organs, it is necessary for the patient to be carefully selected and adequately prepared.

The most basic part of the preparation is the achievement of high TSH stimulation in order to increase radioiodine uptake in the thyroid/tumour tissue. Both exogenous and endogenous methods of TSH stimulation are equally valid from the point of view of achieving the uptake, but keeping the patient without substitution for several weeks can be highly disagreeable, and in some patients even dangerous, due to the possible complications. On the other hand, the convenience that comes with the use of rhTSH comes at a higher cost. It is up to the patient and the physician to estimate which method of TSH stimulation to use by evaluating the cost/benefit of exogenous and endogenous TSH stimulation in each individual case.

The low iodine diet comes right after TSH stimulation as the second most important step in the preparation of patients for radioiodine therapy, its purpose being to increase the radioiodine uptake in thyroid/tumour tissue. However, it should be borne in mind that there can be a possible interference of this diet with the potential use of diuretics in patients treated with radioiodine. In any case, it is indisputable that a low iodine diet helps achieve a higher radioiodine uptake in the thyroid/tumour tissue, and it should therefore be prescribed to patients who are to receive the radioiodine therapy.

The administration of lithium is an efficient method of increasing the uptake of radioiodine in thyroid/tumour tissue, but it is not recommended in routine clinical practice, since its administration can have serious complications in case of an overdose. An increase in NaI symporter expression in thyroid/tumour tissue, achieved by the application of retinoids, results in a favorable increase in radioiodine uptake. Even though it does not belong to the clinical routine, this method can be useful in patients who have lost the ability to accumulate radioiodine in the tumour tissue. These patients are characterised by the secretion of thyroglobulin, a positive PET scan and a negative radioiodine scan. Further research on the identification of the gene responsible for the coding of NaI symporter system synthesis can provide a new approach to radioiodine treatment of thyroid carcinoma in the sense of dose optimisation, i.e. the prospects of increasing the efficiency of the therapy.

When it comes to methods aimed at accelerating the excretion of radioiodine that has not been bound to the thyroid/tumour tissue, extensive hydration of the patients is recommended, as it reduces the absorption in the critical organs by diluting the urine and increasing urinary volume, even though it does not result in increased iodine excretion.

Laxative administration in patients who have regular emptying of the bowel can cause certain discomfort to the patients, so this is not clinically justified nor necessary, having in mind the small quantity of radioiodine that gets eliminated in this way.

In patients who had been on a low iodine diet there is a decrease in excretion of ^{131}I under the influence of diuretics, which results in an increase in its levels in blood, which in turn indirectly prolongs the hospitalisation period. The patient has to be detained in the restricted area following the radioiodine therapy due to the high circulating levels that are

maintained in their bodies. All this also results in a higher dose being absorbed by the patient's critical organs. For this reason, the administration of diuretics for the purpose of accelerating urinary excretion of radioiodine cannot be recommended, at least not in patients who had previously been on a low iodine diet.

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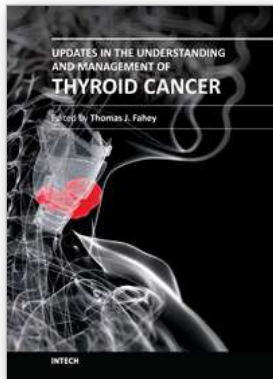
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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