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Preparation for radioiodine therapy: how to increase therapeutic efficacy and accelerate unbound radioiodine excretion

Priprema za radiojodnu terapiju: kako povećati terapijsku efikasnost i ubrzati ekskreciju nevezanog radiojoda

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Introduction

Therapeutic application of radioiodine ^{131}I in postoperative ablation of the remaining thyroid tissue, as well as in treatment of recidives and/or local and remote metastases of differentiated thyroid carcinoma has been a part of clinical practice for over 50 years. It is a regular segment of the standard therapeutic procedure in differentiated thyroid carcinoma treatment and it is recommended by a number of authorities in the field [1–9]. Certain differences in opinion on the subject are concerned only with the dose which is applied, as well as with whether the therapy should be applied in lower risk patients [4, 6, 9–13]. Several decades of experience have shown the indisputable beneficial effects of ^{131}I application 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 the salivary glands, nasolacrimal ducts, stomach mucus, kidneys, bladder wall, colon, gonads, bone marrow, etc.

The question that arises from the aforesaid is how to achieve a good compromise between the beneficial therapeutic effects of radioiodine on one hand, and adverse effects on other tissues and organs on the other. The compromise could be achieved in two ways. The first one is to increase radioiodine uptake in thyroid tissue/tumor tissue by increasing the therapeutic efficiency of ^{131}I. In other words, the aim is to achieve the best therapeutic effect on the target tissue with as low dose of ^{131}I as possible. The second way is to reduce the adverse effects, *ie* the radiation amount of ^{131}I absorbed by other organs and tissues, by accelerating elimination of radioiodine not bound by thyroid/tumor tissue.

There is yet another reason for accelerated elimination of radioiodine from the body of a patient. The reason is legal and concerns regulations set by every country which determine the amount of radioactive iodine that patients are allowed to have in their bodies without being required to receive their treatment in the restricted area. With the doses of radioiodine normally applied in differentiated thyroid carcinoma treatment, most cases require hospitalization of various duration.

For this reason, it is in the best interest of any health system to shorten hospitalization, *ie* isolation of a patient being treated with radioactive iodine, without reducing the therapeutic effect of ^{131}I. In other words, the cost of hospitalization/isolation of such patients should be reduced.

Concerning legal regulations of ^{131}I doses, there are significant variations from country to contry. These variations mostly apply to the upper limit of radionuclide not requiring a patient isolation.

Legal regulations state that anything above that limit requires the therapy to be carried out in hospital premises, or more precisely, in special rooms designed as controlled radiation zones. This limit varies in different countries. For example, the upper limit in Serbia is relatively low and special precautions have to be taken only if the radioactivity of ^{131}I exceeds 400 MBq. In other words, a patient can be released from hospital only when radioactivity in his body is not more than 400 MBq [14]. The limit is significantly higher in the EU and

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USA, where hospitalization is obligatory only if the radioactivity of ^{131}I is more than 30 mCi (1,110 MBq). In this case a patient is hospitalized and kept in isolation until his/her radioactivity level decreases to 30 mci (1,110 MBq) [4, 15].

In cases of differentiated thyroid carcinoma the treatment doses of ^{131}I vary from 30 mCi for the remaining thyroid tissue ablation, to 200 mCi for treatment of metastases, even though there are several records of the doses reaching as much as 333 mCi (9GBq) [10]. With application of these doses, even the largest ones, the permitted radioactivity limit in the body is reached a few days following application of the ablation/therapeutic dose of ^{131}I [16].

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/tumor tissue being treated.

Methods for increasing radioiodine uptake

Thyrotropin stimulation (endogenous and exogenous thyroid-stimulating hormone stimulation)

In order to achieve a sufficient radioiodine uptake in thyroid remnants/tumor tissue, it is necessary either that a patient has good endogenous thyroid-stimulating hormone-TSH (blood 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 a patient is left without thyroid hormone replacement therapy for 4 to 6 weeks. The primary complication which may arise from this way of increasing TSH levels is hypothyreoidism, which some patients find quite disagreeable. The condition is followed by 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 applying rhTSH, available on the market as Thyrogen® (Genzyme). This medication is given to a patient intramuscularly for 2 days, in 0.9 mg doses.

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

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 are equally recommended [6, 17].

Low iodine diet

In order to achieve better uptake in thyroid/tumor tissue, a low iodine diet is recommended, *ie* 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 ^{131}I [18, 19].

The consequence of low iodine intake is iodine depletion, which could result in its increased uptake in thyroid remnants/tumor tissue. Since most countries have legal regulations by which producers are obliged to iodize 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 iodized table salt contains about 400 μg of iodine. Sea salt is also not recommended due to the fact that it contains a significant amount of iodine. The alternative is uniodized 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 μg per meal), and these are as 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 μg of iodine, or an average of 115 μg); 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 μg per meal) is recommended as follows: fresh meat (meat contains 25–130 μg of iodine per pound), up to 5 ounces a day of fresh meat such as chicken, beef, pork, lamb, and veal are fine on the low-iodine diet; 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; 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/tumor 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 [20–23].

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 radioio-

dine retention in the thyroid/tumor tissue [24–27]. Researchers agree that administration of 0.8–1.2 mmol/L of lithium carbonate results in an increased uptake and prolonged retention of radioiodine in thyroid/tumor tissue, which doubles the dose absorbed, without a 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 [28].

Retinoids and increased expression of NaI symporter system

Better penetration of ^{131}I into the remnant thyroid/tumor tissue can be achieved through an increased expression of genes which code the synthesis of NaI symporter by means of retinoids or their metabolites, which bind with retinoic A and X receptors (RAR and RXR), resulting in an increased expression of these genes and an increased synthesis of NaI symporters. At the end of this chain is the achievement of the increased iodine uptake in thyroid/tumor tissue. However, there are contradictory data concerning the efficiency of this sort of adjuvant therapy in thyroid iodine uptake. While some researchers [29–31] 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 tumor tissue, especially in follicular carcinomas, others [32] do not find a significant efficiency in the increase of thyroid iodine uptake, based on researches on large groups of subjects.

However, the latest research on NaI symporter system expression, as well as identification of genes which code its synthesis [33–37] will probably allow for a new approach in radioiodine therapy of thyroid carcinomas, which focuses on the optimisation of the dose administered to patients, *ie* on increasing the efficiency of this therapy.

Methods for increasing unbound iodine excretion from thyroid/tumor tissue

Hydration

The relevant literature suggests that accelerated urinary excretion of ^{131}I can be achieved by extensive hydration. However, there are also data which do not support this. For example, Giebisch et al. [37] 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 urine and a decrease in radioactive urine retention in the urinary tract, which contributes to the decrease in the dose absorbed by the urinary bladder wall and surrounding organs.

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 [38]. For these reasons, it is considered that administration of laxatives is not necessary in patients who have at least one stool a day.

Diuretics

For the purpose of reducing the absorbed dosage 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 from thyroid/tumor tissue – 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 [39] 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. The majority of researches points to the fact that faster elimination of radioiodine can be achieved by the application of additional diuretic therapy [40–46], but the results of some other researches show that the administration of diuretics leads to increased radioiodine uptake in the thyroid tissue [20–22, 47]. The data concerning the studies of the urinary excretion of iodine and the effects of diuretics on its urinary excretion published so far are in part contradictory. They do not present a clear picture of what kind of benefits, if any, we have from applying this additional therapy to patients suffering from differentiated thyroid carcinoma, treated with radionuclides.

The published data were obtained either from studies performed on animals [41–43], or from studies on patients who did not suffer from differentiated thyroid carcinoma and had not been operated on previously, but who received radioiodine doses far smaller than those given to patients suffering from differentiated thyroid carcinoma [22, 40, 44, 46].

There has been a small number of researches on the effects diuretics have on radioiodine clearance in patients who were treated with therapeutic doses of ^{131}I, but the conditions under which these researches were conducted were to a certain degree different from the ones typical for clinical practice and the way this therapy is normally carried out [45, 47, 48].

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

Furosemide

Furosemide is effective, cheap and widely used. Abbott and Kovacic [49] have analysed the data concerning the effects of furosemide from both medical and veterinary literature. Based on a considerable number of analyzed 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 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 alcalosis, which are the most common adverse effects of this diuretic. For the purpose of hypokalemic and hypochloremic alcalosis 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 [23] 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.

Our results were somewhat similar to the ones obtained by Maruca et al. [48], who concluded that diuretics 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 thyreodectomy 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 tumor tissue. According to their findings, the total iodine uptake and retention in tumor tissue was mostly the consequence of total body retention, and not some specific mechanism at the cell level of thyroid/tumor tissue.

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 researches by Seabold et al. [45] and Norfray and Quin [20] provide possible further evidence for this.

Namely, Seabold et al. [45] 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 in the hospital premises.

Based on experiments on animals, Norfray and Quinn [20] 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. 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/tumor tissue can be achieved by 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, *ie* total body retention, instead of just an increase in the avidity of thyroid tissue for iodine cannot be excluded either.

Other researchers [20–22] also found that furosemide does not increase iodine excretion, but on the contrary, that it decreases it. According to the data provided by Kapucu et al. [46], 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 [40] 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 iodide depletion (with previous low iodine diet and the administration of manitol) on ^{131}I biokinetics and thyroid function, on a group of 8 patients. According to their results, iodide 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 ^{131}I uptake if NaI is applied together with manitol.

It should be stressed that in our research on mice [50] 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/tumor tissue uptake under the influence of Furosemide therapy, but our results indirectly support the data provided by Maruca et al. [48] that in cases of increase the most likely reason is, up to a certain point, an increase in ^{131}I levels in blood, *ie* an increase in total body retention of this 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. [19]. 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/tumor tissue remain high 96 hours following the diuretic preparation.

Other diuretics

Based on the results obtained from a controlled study, Tepmonkogol [21] concluded that the binding of radioiodine in the thyroid gland is as many as 7.18 times higher when hydrochlorothiazides are applied 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 hyperthyreosis who had been treated with radioiodine. Similar results were obtained by Ding et al. [47], who showed that application of hydrochlorothiazides prior to application 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 [44] analysed the fluctuations in urinary excretion of Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^- and I^-. Based on the results of this study, as well as on the previous studies done on animals [41–43], 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 [51] 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 (*ie* low chloride/low sodium diet) was prescribed, the increase in chlorine reabsorption 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 same goes for its blood levels, which directly influences the prolongation of patient hospitalization in the restricted area after the application of radioiodine therapy, due to the maintenance of high exposition dose. 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.

Recommendations and conclusion

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

Both exogenous and endogenous methods of TSH stimulation are equally valid from the point of view of achieving the uptake, but keeping a 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 which comes with the use of rhTSH comes at a higher cost. It is up to a 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/tumor tissue. However, it should be considered that there can be a possible interference of this diet with the potential use of diuretics in patients treated with radioiodine.

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 of its levels in blood, which in turn indirectly prolongs the hospitalisation period. All this also results in a higher dose being absorbed by the patient's critical organs. For this reason, administration of diuretics to accelerate urinary excretion of radioiodine cannot be recommended, at least not in patients who had previously been on a low iodine diet.

When it comes to methods for accelerating excretion of radioiodine which has not been bound to the thyroid/tumor tissue, extensive hydration of patients is recommended, as it reduces the absorption in the critical organs by diluting urine and increasing the number of mictions, even though it does not result in the increased iodine excretion.

Laxative administration in patients who have regular emptying of the bowel can cause certain discomfort to patients, so this is not clinically justified as necessary.

Administration of lithium is an efficient method of increasing the uptake of radioiodine in thyroid/tumor tissue, but it is not recommended in routine clinical practice, since its administration can have serious complications in case of overdose. An increase in NaI symporter system expression in thyroid/tumor tissue, achieved by the application of retinoids, results in the desired 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. Further research on the identification of the gene responsible for coding NaI symporter system synthesis can provide a new approach to radioiodine treatment of thyroid carcinoma in the prospects of increasing the efficiency of the therapy.

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