

Effects of drugs on the efficacy of radioiodine (^{131}I) therapy in hyperthyroid patients

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Abstract

The treatment of hyperthyroidism is targeted at reducing the production of thyroid hormones by inhibiting their synthesis or suppressing their release, as well as by controlling their influence on peripheral tissue (conservative therapy, medical treatment). Radical treatment includes surgical intervention to reduce the volume of thyroid tissue or damage of the mechanisms of thyroid hormone synthesis by radioiodine (^{131}I) administration. Radioiodine (^{131}I) is a reactor radionuclide, produced as a result of uranium decomposition and emission of β and γ radiation. The therapeutic effects of the isotope are obtained by the emission of β radiation. In the paper, the effects of administered drugs (antithyroid, glucocorticosteroids, lithium carbonate, inorganic iodine, β -blockers) on the final outcome of radioiodine therapy in patients with hyperthyroidism are discussed.

Key words: hyperthyroidism, medical treatment, (^{131}I) radioiodine therapy.

Hyperthyroidism is a syndrome of clinical and biochemical symptoms, resulting from the exposure of tissues to an excess of thyroid hormones: thyroxine (T_4) and triiodothyronine (T_3). The thyroid gland is usually the source of excessive production of thyroid hormones, other tissues being less responsible for this production. Diffuse goitre (in Graves' disease) is most frequently at the base of hyperthyroidism, multinodular goitre holding the second position in the ranking of hyperthyroidism causes, while the third place is occupied by the autonomous single thyroid nodule.

Although the causes of hyperthyroidism may vary, the symptoms resulting from the excess of free thyroid hormones – FT_4 (free thyroxine) and FT_3 (free triiodothyronine) – in the circulation, as well as their actions on cell receptors in target tissue and organs, are similar in all the identified forms of hyperthyroidism.

They result from increased activity of the sympathetic part of the autonomous nervous system and from enhanced catabolism. The usually observed symptoms include: body weight decrease, increased appetite, warmth intolerance, hyperhidrosis, and symptoms associated with stimulation of the nervous system: irritability, anxiety, tremor of hands, weakened muscular power, and excessive fatigability. Usually, additional symptoms from the circulation are also observed, such as tachycardia,

increased systolic pressure, and frequent rhythm disorders – mainly atrial fibrillation. In elderly patients, circulatory disturbances may be the only symptoms of hyperthyroidism. Additionally, hair loss, brittleness of the nails, more frequent rhythm of bowel emptying and a tendency towards rare menstruation in women may also be observed.

In the case of hyperthyroidism in the course of Graves' disease, symptoms of orbitopathy may also appear.

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Radioiodine (¹³¹I) is a reactor radionuclide, produced as a result of uranium decomposition and emitting β and γ radiation. The therapeutic effects of the isotope are obtained by the emission of β radiation. The radiation dose absorbed by the thyroid stimulates the formation of free radicals, which damage DNA structure, causing either cellular death or loss of its growth and division abilities.

Radioiodine therapy is a method of choice applied in the case of a single autonomous toxic nodule. Radioiodine should be a first-stage treatment in Graves' disease in the hyperthyroid state or after relative euthyroidism is attained by means of short-term therapy with antithyroid drugs. In the toxic nodular goitre (also in Graves' disease), radioiodine is used when administered antithyroid drugs either fail or are not tolerated or their use is contraindicated, as well as in cases of hyperthyroidism recurrence after operation or as prophylactic treatment in the thyrocardiac syndrome and in cases of contraindications to surgery or patient's refusal of operation. Radioiodine treatment may sporadically be administered in patients with subclinical hyperthyroidism, if autonomous foci have been identified in scintigraphic imaging.

Absolute contraindications to radioiodine therapy include: gestation, breast feeding and suspected thyroid malignancy. On the other hand, relative contraindications may be such as: low iodine uptake by the thyroid, hyperthyroidism with high hormonal values, leading to risk of thyroid crisis, the presence of "cold" nodules in scintigraphic evaluation, together with the result of fine-needle aspiration biopsy (FNAB), indicating a benign lesion and, eventually, infiltrative orbitopathy in Graves' disease in its active phase.

The patient's preparation for radioiodine treatment includes the following steps:

- withdrawal of preparations containing iodine and iodides (expectorant agents or Lugol's solution 3 weeks before the onset of therapy, radiological contrasting agents 4 weeks before the therapy, amiodarone 4-6 months before the planned onset of radioiodine administration); the recommended period of withdrawal of applied thyrostatic agents varies among different centres, being a subject of debate for many authors;
- exclusion of pregnancy;
- medical history of the patient and physical examination, evaluation of the hormonal status (measurement of thyrotropin [TSH], FT₄ and FT₃ concentrations, as well as of antiTSHR antibodies [less frequently, also antiTPO] in the case of Graves' disease), dosimetric studies, sonographic imaging of the thyroid gland, and fine-needle aspiration biopsy (FNAB) in the case of focal changes.

Radioiodine treatment is administered at nuclear medicine centres authorised to use ¹³¹I. The treatment protocol requires in-patient conditions when the activity of ¹³¹I exceeds 800 MBq.

In the treatment of benign thyroid diseases, several ways of radioiodine administration have been practised:

- administration of constant activity, empirically determined on the basis of the degree of severity of hyperthyroidism symptoms [1];
- administered activities are determined with regards to thyroid mass [2];
- administered activities are calculated on the basis of goitre mass, the assumed activity per 1 g of thyroid tissue and iodine uptake by the thyroid after 24 h [3];
- calculation of administered activity, based on thyroid mass, the assumed absorbed dose, the maximal iodine uptake and the effective half-life (EHL) of iodine in the thyroid [4].

In the last two models of radioiodine therapy, several dosimetric parameters have been identified, on the basis of which the isotope activity is calculated, namely:

- 1) iodine uptake – the degree of radioiodine (¹³¹I) accumulation, expressed as the percent of provided diagnostic activity;
- 2) thyroid mass – estimated in approximation on the basis of data obtained from ultrasound imaging of the thyroid gland;
- 3) absorbed dose – a dosimetric parameter, having the greatest influence on the effect of radioiodine (¹³¹I) therapy; so far, there has been no method of absorbed dose determination which would provide total therapeutic success of treating thyroid diseases with radioiodine; the values of absorbed dose, as proposed by various authors, have been determined empirically, and so: for nodular goitre – 120-150 Gy [3], for Graves'

disease – 60-80 Gy [2, 3]; recently, elevated absorbed doses are more and more often used: for Graves' disease – 200-300 Gy [5, 6], for nodular goitre – 150-300 Gy [7];

4) EHL of radioiodine – a combination of the physical half-life and the biological half-life.

The EHL is the period of time during which the activity of the isotope applied to the patient is halved. The EHL is determined by measurements of isotope activity above the studied organ and performed under constant conditions. The EHL for ^{131}I , administered in the form of sodium iodide (NaI), is approximately 6 days, 8 days at the maximum. In about 10-15% of patients, a very short EHL period is observed, which indicates a quick turnover of iodine in the thyroid. One of the ways to extend EHL and, in consequence, the presence of iodine in the thyroid, is an increase of the biological half-life, since the physical half-life is a constant value. This can be achieved by using lithium carbonate.

Lithium carbonate inhibits hormone release from the thyroid gland, and suppresses the formation of colloid drops and thyroglobulin (Tg) proteolysis, stimulated by TSH and cyclic adenosine monophosphate (cAMP). The aforesaid element can be accumulated in the thyroid and, after its concentration reaches a certain level, it may block the synthesis of T_4 and T_3 at several stages of its course. Those observations have brought about lithium carbonate applications in combination with radioiodine, leading to the observation that lithium carbonate, when administered in combination with ^{131}I , may reduce the recovery period from hyperthyroidism [8].

The ability of lithium carbonate to suppress iodine release from the thyroid is used in patients with a short EHL of radioiodine [9, 10]. The application of lithium carbonate in the therapy should precede radioiodine administration by approximately 3-4 days, to be then continued for 7 days after radioiodine therapy is completed. The most common dose is 500-700 mg (10 mg/kg b.w.) to obtain the concentration of 0.4-0.8 nmol/l in blood. The administration of lithium carbonate, continued for a few days as complementation of radioiodine therapy, does not really provide any risk of occurrence of any side effects.

Patients with enhanced hyperthyroidism are prepared for radioiodine therapy by receiving antithyroid drugs in order to decrease the resources of thyroid hormones in the thyroid gland. This approach reduces the risk of exacerbation of hyperthyroidism symptoms after radioiodine therapy and decreases the incidence of radiation-induced thyroiditis.

Antithyroid drugs are thionamide derivatives and are divided into two groups:

- derivatives of thiouracil – propylthiouracil (Thyrosan [Sun-Farm]);
- derivatives of imidazole – thiamazole (Metizol [ICN Polfa-Rzeszów], Thyrozol [Merck]).

Typically, the treatment begins with the dose of 30-60 mg of thiamazole or 400-600 mg of propylthiouracil per day, while after 4-8 weeks, the doses are reduced to maintenance doses: 5-20 mg of thiamazole or 50-200 mg of propylthiouracil per day.

These drugs inhibit the initial stages of thyroid hormone synthesis, exerting suppressive effects on iodine oxidation and organification, regulated by thyroid peroxidase activity. They also inhibit the binding of monoiodotyrosine (MIT) and diiodotyrosine (DIT) particles into 3,5,3'-triiodo-L-thyronine and the binding of two DIT particles into 3,5,3',5'-tetraiodo-L-thyronine. Moreover they directly affect Tg structure modification. Thionamides may also indirectly modify the production of T_3 and T_4 , thus affecting the growth of follicular thyroid cells by suppression of the proliferogenic effect of insulin-like growth factor I on thyrocytes. Additionally, thiouracil derivatives inhibit the transformation of T_4 into T_3 in peripheral tissues. Because the discussed preparations do not inhibit iodine transportation to the thyroid or block the release of hormones stored in the thyroid, control of the thyroid gland is not regained immediately – requiring, in the majority of cases, a few weeks to be established. When the status of euthyroidism or close to euthyroidism is obtained, a few days before radioiodine administration, antithyroid drugs should be withdrawn, as many authors indicate their unfavourable effects on the final outcome of radioiodine therapy [11]. They explain this assumption by reference to the fact that antithyroid drugs decrease, in general, iodine uptake by the thyroid and, reducing the intrathyroid iodine resources, they contribute to quick iodine turnover in the thyroid. In consequence, the effective half-life of radioiodine in the thyroid is shorter, thus also reducing the efficacy of ^{131}I treatment. There are also other authors [12, 13] who claim that Metizol, in contrast to Propyl (Thyrosan), does not affect the final outcome of ^{131}I therapy. The discussions concern the issue of how many days before radioiodine administration antithyroid drugs should be withdrawn to regain satisfactory iodine uptake by the thyroid. Some authors think that the withdrawal of antithyroid drugs 2 days before radioiodine application increases its effectiveness even by 50% by longer EHL and increased iodine uptake [11, 14].

Also Kobe *et al.* [15], in a group of 571 patients with Graves' disease, withdrew antithyroid agents, regardless of the preparation used (carbimazole, methimazole, propylthiouracil), 2 days before scheduled radioiodine therapy onset.

Kubota *et al.* [16] compared the efficacy of ¹³¹I therapy after withdrawal of thyrostatic agents 2 days before radioiodine application vs. 7 days before the therapy onset, with FT₄ concentration measurement after 24 h from the isotope administration. They demonstrated a significant increase of FT₄ in the group of patients with withdrawal of thyrostatics 7 days before radioiodine therapy, with no statistical difference in the efficacy of therapy between the groups. The authors concluded that the 2-day break in administration of thyrostatics is sufficient and advantageous, especially in elderly patients and in those with cardiovascular history – no aggravation of hyperthyroidism after ¹³¹I administration.

Other authors propose thyrostatic drugs to be withdrawn 3-7 days before radioiodine treatment [17-20].

In turn, a group of Danish authors [21] assume that the application of propylthiouracil before ¹³¹I therapy worsens its efficacy, despite withdrawal of the thyrostatic agent 4 days before radioiodine administration vs. the group of patients prepared for ¹³¹I therapy with β-adrenergic blocking drugs only. The same authors [22] unequivocally proved worse efficacy of radioiodine in those patients who had been administered thiamazole during the peritherapeutic period vs. the group of patients in whom the drug had been withdrawn 8 days before isotope application.

The studies of some of the above-mentioned authors have been summarised in a collective work by Walter *et al.* [23]. A lack of consensus appears from the review, regarding the time point of thyrostatics' withdrawal before radioiodine therapy, while all the authors underline a negative influence of the thyrostatics used on the final outcome of ¹³¹I therapy.

Radioactive iodine should not be used in patients with high concentrations of free thyroid hormones (FT₃ and FT₄) because of the risk of hyperthyroidism exacerbation, caused by release of the hormones into the circulation in the course of temporary thyroiditis. The highest risk associated with these patients is the exacerbation of cardiological problems. Sometimes, however, it is difficult to obtain normal thyrometabolic status before radioiodine therapy; there are patients in whom even a short withdrawal of thyrostatics' application increases the severity of hyperthyroidism symptoms. Therefore, in those patients, antithyroid drugs are administered during the peritherapeutic period of ¹³¹I administration.

In sporadic cases, the enhancement of hyperthyroidism is manifested as a thyroid crisis. Therefore, in some of these patients, a few days before radioiodine treatment, antithyroid drugs are applied again in order to shorten the phase of

hyperthyroidism. It may, on one hand, weaken the therapeutic effects of radioiodine [6, 18], while providing, on the other hand, safety of the entire therapy application, enabling the status of euthyroidism to be obtained earlier.

Mijanhout *et al.* [24] monitored the applied management after radioiodine therapy in 16 Dutch hospitals. They found that only in one hospital were no thyrostatic agents administered after ¹³¹I therapy, in two hospitals thyrostatic agents were administered only when indicated, while in the other ones, thyrostatics were applied after radioiodine therapy, their administration being continued for several weeks. At our department, thyrostatic agents are applied after radioiodine treatment only in case of enhanced hyperthyroid symptoms, in elderly patients with cardiological disorders.

Antithyroid drugs, especially thionamides, reveal local immunosuppressive activity in the thyroid, which is closely associated with their antioxidative function. Their effects include, among others, reducing lymphocytic infiltrations in the thyroid and decreasing the concentrations of antithyroid autoantibodies. This, among other things, explains the higher efficacy of thionamides vs. other antithyroid drugs in the treatment of auto-immunological diseases of the thyroid gland [25]. Antithyroid drugs may reduce the symptoms and signs of Graves' orbitopathy. On the other hand, the use of these drugs may induce adverse effects. Serious adverse symptoms are rarely observed (< 1%). The most dangerous is agranulocytosis, which may rapidly develop and is usually revealed during the first 3-4 months from therapy initiation. Agranulocytosis is manifested by fever and infection symptoms. The necessary therapy assumes the withdrawal of antithyroid drugs, application of antibiotics of broad spectrum of action and growth factors, necessary to stimulate bone marrow regeneration. Usually, after 2-3 weeks of therapy, the patients fully recover [26]. Hepatitis, vasculitis and the lupus-like syndrome are rare but recognized complications, demanding withdrawal of the drugs. Side effects, milder in character, are more commonly observed (1-5% of patients), including pruritus, rash, transient granulocytopenia, fever, arthralgia and gastric symptoms. All these symptoms may disappear spontaneously despite the continuation of antithyroid treatment; however, they usually require one thyrostatic drug to be replaced by another. Also, cases of cross-hypersensitivity are sometimes observed.

Many authors have focussed attention on the possibility of occurrence or exacerbation of orbitopathy in patients with Graves' disease treated with radioiodine [27, 28]. In order to prevent any enhancement of the inflammatory process in the

orbital cavity, attempts are undertaken at prophylactic application of glucocorticosteroids [6, 18, 29, 30].

The anti-inflammatory and immunosuppressive effects of glucocorticosteroids are the features used in the treatment of orbitopathy; glucocorticosteroids also inhibit the synthesis of glycoaminoglycans by fibroblasts [29]. It has been demonstrated that properly treated and controlled hyperthyroidism protects against the development of unfavourable changes in the eye. Orbitopathy progression has been observed in those patients whose status of hyperthyroidism required administration of several doses of radioiodine, in comparison with those groups of patients in whom hypothyroidism was induced already after the first administered dose.

At present, two treatment protocols are used: a few months' therapy with oral glucocorticosteroids, administered in gradually decreased doses, or treatment with pulses of methylprednisolone. The former protocol involves prednisone (Encorton, Polfa-Pabianice) administrations in a dose of 1-2 mg/kg b.w./day for 6-8 weeks, followed by dose decrease until total withdrawal. It is effective, especially with regards to the changes associated with connective tissue inflammation, as among other effects it brings about quick pain relief; it is also used in optic nerve neuropathy. Unfortunately, the troubles related to eye muscles and exophthalmos regress at a slower pace, and often recur after dose reduction or drug withdrawal. In order to limit the commonly known complications and adverse effects of glucocorticosteroids, a treatment with methylprednisolone pulses has been proposed at a dose of 0.5-1.0 g, to be administered by intravenous infusion for 3 consecutive days of the week for 3-7 weeks.

Corticosteroids are not commonly used as complementary treatment prior to radioiodine therapy. However, there are some authors [31] who obtained compensation of the thyrometabolic state by means of antithyroid drugs only after prednisone addition, which allowed performance of effective radioiodine therapy. Other authors [32] believe that the use of corticosteroids during radioiodine treatment is, from the prognostic point of view, rather negative for the general outcome of radioiodine therapy. In turn, other authors [33] found that the use of corticosteroids had no effect on the final therapeutic effect in hyperthyroid patients with Graves' disease.

Corticosteroids are applied in the treatment of thyroid crisis, being administered by intravenous infusion. Their suppressive effect on hormone release from the thyroid gland and on the conversion from T_4 to T_3 in peripheral tissues are the two factors utilised in thyroid crisis therapy.

Thyroid crisis may also be treated with inorganic iodides, administered as Lugol's solution or saturated solution of potassium iodide (SSKI), due to its property of instant blocking of thyroid hormone release from the gland. There are also other authors [34, 35] who claim that the administration of inorganic iodine during the peritherapeutic period of treatment with ^{131}I improves the efficacy of radioiodine therapy in patients with hyperthyroidism. They also say that the administration of inorganic iodine in the peritherapeutic period of ^{131}I treatment extends EHL and, in consequence, increases the provided dose of radioiodine.

In specific cases of iodine-induced thyrotoxicosis, e.g., in hyperthyroidism caused by amiodarone administration, potassium perchlorate may be applied. It is a substance which strongly suppresses the accumulation of iodides in the thyroid by competitive inhibition of the iodine pump. This agent, which should be administered in a dose of 1000 mg/day, is now very rarely applied for hyperthyroidism treatment, as its long-term administration may lead to irritation of the gastric mucosa and toxic reactions. In clinical situations in which – for cardiological reasons – it is not possible to withdraw amiodarone, when thyroid functions return to normal balance, an option of radical treatment should be considered, e.g., by radioactive iodine. It is possible in hyperthyroidism of type I. In type II, resulting from thyroid destruction, iodine uptake is usually very low, which precludes radioiodine administration. One may, however, find authors [36] who succeeded in radioiodine treatment in type II hyperthyroidism, induced by amiodarone, obtaining in the eventual outcome either euthyroidism or hypothyroidism. The authors of the study applied, however, very high activities of radioiodine (up to 80 mCi ^{131}I), which are not routinely used in the treatment of hyperthyroidism. This raises even more doubts, as this type of hyperthyroidism reveals a self-limiting character for itself and may thus spontaneously lead to hypothyroidism.

Taking into account the adrenergic component of thyrotoxicosis, various drugs from the group of adrenergic antagonists are applied as complementary treatment of hyperthyroidism. β -Adrenergic receptor blocking drugs (propranolol, metoprolol, atenolol, nadolol) inhibit the increased sympathomimetic activity. Propranolol also reveals membranous activity, decreases the activity of type I 5'-deiodinase and, in consequence, increases the transformation of T_4 into inactive reverse T_3 (rT_3), thereby causing T_3 concentration reduction in the blood. This drug does not have internal sympathomimetic activity and exerts favourable effects on the, so-called, peripheral symptoms of hyperthyrosis: tachycardia,

hidrosis, and nervous irritability. It also reduces the symptoms of fine tremor and eyelid retraction. If there are no contraindications, propranolol is useful in controlling hyperthyroidism symptoms, both before and after radioiodine therapy, while waiting for therapeutic results of administered radioiodine. Propranolol is most often recommended in doses of 30-120 mg per day.

Radiotherapy leads to regression of hyperthyroidism symptoms and to reduction of goitre size, but is associated with a possibility of hypothyroidism, the frequency of which increases in time. In case of a lack of normalisation of thyroid functions after 6 months from radioiodine therapy, it is usually decided to give a subsequent dose of radioiodine.

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