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The influence of thiamazole, lithium carbonate, or prednisone administration on the efficacy of radioiodine treatment (^{131}I) in hyperthyroid patients

Wpływ podawania tiamazolu, węglanu litu lub prednizonu na skuteczność leczenia jodem radioaktywnym (^{131}I) pacjentów z nadczynnością tarczycy

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Abstract

Introduction: The effects of selected drugs (see below) on the efficacy of (^{131}I) radioiodine therapy were examined.
Material and methods: The study involved 200 hyperthyroid patients, treated with radioactive iodine. They were divided into five groups (40 persons in each). In Group I — patients were administered ^{131}I and thiamazole; in Group II they were given — ^{131}I and lithium carbonate; in Group III they were given — ^{131}I only (the assumed absorbed dose — 150–200 Gy, the same as in Groups I and II, for which Group III was a control group); in Group IV they were given — ^{131}I and prednisone; and in Group V they were given — ^{131}I only (250–350 Gy, the same as in Group IV, for which Group V was a control group). Therapeutic results were analyzed after six months based on clinical and hormonal status. The evaluation also included effects of the initial hormonal status on the outcome of ^{131}I therapy in Groups II and IV (*v.* respective controls, *i.e.* Groups III and V); such analysis was not performed in Group I because all the patients in that group were initially hyperthyroid.
Results: In 145 patients (72.5%) the therapy with ^{131}I was effective. In 55 patients (27.5%) the therapy was ineffective. The application of thiamazole during the peritherapeutic period in patients treated with ^{131}I reduced the effectiveness of radioiodine, while lithium carbonate had no effect on the therapy outcome. Prednisone increased the effectiveness of the therapy with ^{131}I. Normalisation of the initial concentration of TSH was advantageous for the ^{131}I therapeutic outcome only when the assumed absorbed doses of 150–200 Gy were applied, while being of no avail for doses above 250 Gy.
Conclusions: The present results indicate the necessity of careful analysis of administered drugs in hyperthyroid patients while qualifying them to ^{131}I therapy. The initial concentration of TSH has no effect on the efficacy of radioiodine therapy in cases where absorbed doses are regarded to be ablative. **(Pol J Endocrinol 2010; 61 (1): 56–61)**

Key words: *hyperthyroidism, radioactive iodine, antithyroid drugs, lithium carbonate, corticosteroids*

Streszczenie

Wstęp: W pracy zbadano wpływ tiamazolu, węglanu litu i prednizonu na skuteczność leczenia jodem radioaktywnym pacjentów z nadczynnością tarczycy.
Materiał i metody: Do badań zakwalifikowano 200 chorych z nadczynnością tarczycy, leczonych jodem radioaktywnym. Pacjentów podzielono na 5 grup (40 osób w każdej). W grupie I — poza ^{131}I — chorzy dodatkowo otrzymywali tiamazol (preparat Thyrozol), w grupie II — oprócz ^{131}I — węglan litu. Do grupy III zaliczono chorych, którzy otrzymali wyłącznie leczenie ^{131}I przy założonej dawce pochłoniętej 150–200 Gy, czyli takiej samej, jak w grupie I i II; grupa III stanowiła grupę kontrolną dla tych dwóch grup. W grupie IV chorzy otrzymywali leczenie ^{131}I oraz — w okresie okołoterapeutycznym — prednizon w dawce 1 mg/kg mc. W grupie V — chorzy otrzymali wyłącznie leczenie ^{131}I (założona dawka pochłonięta 250–300 Gy), tak samo jak w grupie IV; grupa V stanowiła kontrolę dla grupy IV. Wyniki leczenia zanalizowano po sześciu miesiącach na podstawie badania klinicznego i hormonalnego. Do oceny włączono także wpływ początkowego stanu hormonalnego na skuteczność terapii ^{131}I w grupach II i IV (względem odpowiednich grup kontrolnych, tj. grupy III i V). Takiej analizy nie przeprowadzono w grupie I, ponieważ wszyscy pacjenci w tej grupie mieli początkowo nadczynność tarczycy.
Wyniki: U 145 pacjentów (72,5%) terapia ^{131}I była skuteczna. U 55 pacjentów (27,5%) terapia okazała się nieskuteczna. Zastosowanie tiamazolu w okresie okołoterapeutycznym u pacjentów leczonych ^{131}I zmniejszyło skuteczność radiojodu, podczas gdy leczenie węglanem litu nie miało wpływu na wyniki terapii. Prednizon zwiększył skuteczność leczenia ^{131}I. Normalizacja początkowego stężenia hormonu tyreotropowego (TSH, *thyroid stimulating hormone*) wpływała korzystnie na wynik leczenia ^{131}I tylko wtedy, gdy założona dawka pochłonięta wynosiła 150–200 Gy, podczas gdy dla dawek powyżej 250 Gy korzystnego wpływu nie stwierdzono.

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Wnioski: Wyniki pracy — będąc potwierdzeniem korzystnego wpływu steroidów i niekorzystnego wpływu leków przeciwtarczycowych na skuteczność ^{131}I u pacjentów z nadczynnością tarczycy — wskazują na konieczność dokładnej analizy leków przyjmowanych przez pacjentów podczas kwalifikacji do terapii radiojodem. Początkowe stężenie TSH nie ma wpływu na skuteczność leczenia radiojodem, w przypadku kiedy dawki pochłonięte są zbliżone do dawek ablacyjnych. **(Endokrynol Pol 2010; 61 (1): 56–61)**

Słowa kluczowe: *nadczynność tarczycy, jod radioaktywny, leki przeciwtarczycowe, węglan litu, kortykosteroidy*

Introduction

The treatment of hyperthyroidism in the course of Graves' disease (GD) and toxic nodular goitre (TNG) by means of radioactive iodine (^{131}I) is a commonly recognized and widely used therapeutic procedure in patients with preserved iodine uptake capacity of the thyroid gland [1–3].

It is known, both from clinical practice and from numerous scientific reports, that it is not always possible to apply radioiodine in hyperthyroidism treatment as monotherapy [4–6].

Hyperthyroid patients manifesting enhanced symptoms of toxicosis undergo, as a rule, special preparation before ^{131}I administration, including the administration of antithyroid drugs, *e.g.* thiamazole, in order to reduce hormonal resources in the thyroid gland [7, 8].

Radioiodine (^{131}I) treatment of patients with GD and coexisting Graves' orbitopathy (GO) introduces the risk of increased symptoms of the latter disease. Therefore, corticosteroids are administered as a prophylactic protection [9, 10].

Effective half-life (EHL) is a dosimetric parameter affecting the outcome of ^{131}I therapy in treatment of hyperthyroid disease. In other words, the term EHL denotes the period during which the activity of the isotope applied to a patient for therapeutic purpose is halved. EHL for ^{131}I is, on average, six days. In 10-15% of patients, a short EHL is observed, which is then corrected by lithium carbonate administration in order to extend the period of radioiodine EHL and to increase, in this way, the absorbed dose of radioiodine [4, 11, 12].

Taking into consideration the above-mentioned facts and observations, the goal of the study was to evaluate the outcome of^{131}I treatment in hyperthyroid patients, when combined with parallel administration of thiamazole or lithium carbonate or prednisone.

The effect of the initial hormonal status on the final therapeutic effect also became a subject of the study evaluation in ^{131}I-treated patients, in whom combined, parallel administration of lithium carbonate or prednisone was applied.

Material and methods

The reported retrospective study involved 200 patients with hyperthyroidism, treated with radioactive iodine (^{131}I). In the evaluated population of 200 patients, the following five (5) groups were identified:

— Group I — patients with TNG or GD, receiving thiamazole in a dose of 15–20 mg daily. Thiamazole was not administered to those patients on the day of radioiodine administration;
— Group II — patients with TNG or GD and demonstrating short EHL, administered lithium carbonate in a daily dose of 750 mg for 3 days before the therapy with ^{131}I, to be further continued for the subsequent 7 days after radioiodine therapy completion;
— Group III — patients with TNG or GD, treated exclusively with radioiodine (a control group for the patients in Group I and Group II);
— Group IV — patients with GD and coexisting GO, receiving prednisone in a dose of 1 mg per kg of body weight during the peritherapeutic period (first — continued in full dose for 4 weeks, starting the administration a day before ^{131}I application, to be gradually withdrawn with 5 mg/week reduction rate);
— Group V — patients with GD without GO, treated exclusively with radioiodine (a control group for the patients in Group IV).

In the studied population of patients, the hormonal status was analyzed based on serum concentrations of free triiodothyronine (fT_3), free thyroxine (fT_4), fT_4) and thyrotropin (TSH) before the application of ^{131}I.

The following two subgroups of patients were distinguished:

— patients in hormonal and clinical euthyroidism, following pretreatment with thiamazole,
— patients with TSH suppression (< 0.3 mIU/ml) and with increased levels of fT_3 and/or fT_4, as well as with slight symptoms of hyperthyroidism.

The age of the 200 patients in the study varied within the range 19 to 81 years, while the mean age for the entire population was 52.1 ± 13.1 years (mean age ± ± standard deviation), including 171 women – their mean age being 51.7 ± 12.8 years and 29 men — their — the mean age being — 54.8 ± 15.1 years.

All the patients were ultrasonographically examined in order to evaluate thyroid volume. Scintigraphic examination of the thyroid gland was performed in all the patients, together with radioiodine uptake (RAIU) capacity after 24, 48, and 72 hours from administration of a diagnostic capsule with ^{131}I, using a set with a scintillating probe.

With subsequent measurements of thyroid RAIU, EHL of radioiodine was determined and expressed in days.

Radioactive iodine (^{131}I) was administered in a hospital environment in rooms specially adapted and intended for the procedure. The patients were administered ^{131}I in fasting state, orally, as Na ^{131}I (natrium iodide). Each patient obtained written information on the principles of the treatment and regulations of radiological protection, and provided written informed consent for the treatment protocol. The irradiation activities applied to patients were within the limits of the doses used in hyperthyroidism therapy. The patients in Groups I, II, and III received therapeutic activity of ^{131}I, calculated on the basis of assumed absorbed dose in the range 150 to 200 Gy, while the patients in Groups IV and V received ^{131}I therapeutic activity calculated on the basis of assumed absorbed dose in the range 250 to 350 Gy.

The applied therapeutic activities of ^{131}I in the examined group of patients were calculated based on the formula proposed by Marinelli et al. [13].

The effects of radioiodine therapy were evaluated after six months by observation of the clinical status of the patients and by laboratory measurements of TSH and thyroid hormone concentrations.

The results of ^{131}I treatment were assigned to two subgroups in each of the study groups, according to the following criteria:

— effective therapy — obtaining the status of euthyroidism or hypothyroidism,
— ineffective therapy — persistent hyperthyroidism.

Methods of selection of homogenous groups of patients with regard to absorbed dose and statistical analysis

It appears from the analyses performed by a number of authors that the parameter demonstrating the highest influence on the efficacy of ^{131}I therapy is the absorbed dose [14, 15], indicating that the higher the absorbed dose, the better the outcome of the therapy with ^{131}I [5, 14]. Therefore, among the patients with hyperthyroidism, treated with radioactive iodine and submitted to retrospective analysis, an attempt was made to select groups of patients that would be homogenous with regard to the absorbed dose (150–200 Gy — Groups I, II, and III and 250–350 Gy — Groups IV and V).

Since it was not possible to group patients with exactly the same values of absorbed dose, Pearson's point-biserial statistics was applied to particular groups in order to answer the question as to what extent the differences in applied absorbed doses affected the overall outcome of radioiodine therapy. Within each study group (I-V), the absorbed doses were compared between patients in whom the therapy was effective (euthyroidism or hypothyroidism) and ineffective (persistent hyperthyroidism). No statistically significant differences were found in those comparisons: Group I — $p = 0.66$, Group II — $p = 0.21$, Group III — $p = 0.45$, Group IV — $p = 0.30$, and Group V — $p = 0.37$. Such results suggest homogeneity of the examined groups as to the absorbed doses received during ^{131}I treatment. The above approach enabled an attempt to be made to evaluate the effects of administered drugs on the outcome of ^{131}I therapy.

We applied χ^2 test for the evaluation of the relationship between the employed protocol of treatment and the effectiveness of ^{131}I therapy. Two-tailed Fisher's exact test was used for the assessment of influence of initial hormonal status on the outcome of ^{131}I therapy, i.e. detection of possible significant differences between therapy success and failure. For the comparison of medians of absorbed doses in control groups, U Mann-Whitney's test was applied. The Statistica 6.0 software package was employed for calculations. A level of significance $p \leq 0.05$ was regarded as statistically significant.

Results

The number and percentage of patients with effective radioiodine therapy in particular groups are given in Table I.

Table I. *Effectiveness of radioiodine therapy in particular examined groups of patients*

Tabela I. *Skuteczność terapii radiojodem w poszczególnych badanych grupach pacjentów*

Examined groups	Effective therapy			Ineffective therapy
	Euthyroidism (Eu)	Hypothyroidism (HypT)	Eu + HypT	
Group I	14 subjects 35%	8 subjects 20%	22 subjects 55%	18 subjects 45%
Group II	11 subjects 27.5%	18 subjects 45%	29 subjects 72.5%	11 subjects 27.5%
Group III	24 subjects 60%	7 subjects 17.5%	31 subjects 77.5%	9 subjects 22.5%
Group IV	12 subjects 30%	23 subjects 57.5%	35 subjects 87.5%	5 subjects 12.5%
Group V	11 subjects 27.5%	17 subjects 42.5%	28 subjects 70%	12 subjects 30%

Table II. *Comparison of ^{131}I therapy effectiveness in Groups I and III ($\chi^2 = 4.53$, $p = 0.03$)*

Tabela II. *Porównanie skuteczności terapii radiojodem w grupach I i III ($\chi^2 = 4,53$, $p = 0,03$)*

Therapy effectiveness	The number of patients in particular groups		
	Group I	Group III	Total
Effective therapy	22 (27.50%)	31 (38.75%)	53 (66.25%)
Ineffective therapy	18 (22.50%)	9 (11.25%)	27 (33.75%)
Total	40 (50.00%)	40 (50.00%)	80 (100.00%)

Table III. *Comparison of ^{131}I therapy effectiveness in Groups II and III ($\chi^2 = 0.27$, $p = 0.61$)*

Tabela III. *Porównanie skuteczności terapii radiojodem w grupach II i III ($\chi^2 = 0,27$, $p = 0,61$)*

Therapy effectiveness	The number of patients in particular groups		
	Group II	Group III	Total
Effective therapy	29 (36.25%)	31 (38.75%)	60 (75.00%)
Ineffective therapy	11 (13.75%)	9 (11.25%)	20 (25.00%)
Total	40 (50.00%)	40 (50.00%)	80 (100.00%)

Table IV. *Comparison of ^{131}I therapy effectiveness in Groups IV and V ($\chi^2 = 3.66$, $p = 0.05$)*

Tabela IV. *Porównanie skuteczności terapii radiojodem w grupach IV i V ($\chi^2 = 3,66$, $p = 0,05$)*

Therapy effectiveness	The number of patients in particular groups		
	Group IV	Group V	Total
Effective therapy	35 (43.75%)	28 (35.00%)	63 (78.75%)
Ineffective therapy	5 (6.25%)	12 (15.00%)	17 (21.25%)
Total	40 (50.00%)	40 (50.00%)	80 (100.00%)

Comparison of the efficacies of radioiodine therapy in particular groups are given in Tables II, III, and IV.

The obtained values of χ^2 statistics indicate that thiamazole administration had unfavourable effects on the outcome of ^{131}I therapy (Table II).

Administration of lithium carbonate had no effect on the outcome of ^{131}I therapy (Table III). However, prednisone administration had advantageous effects on the outcome of ^{131}I therapy (Table IV).

Evaluation of the influence of initial hormonal and clinical status on the outcome of ^{131}I therapy was conducted only in the groups of patients receiving lithium carbonate or prednisone. The analysis was not performed in the patients receiving thiamazole (Group I), since all the patients in that group were initially hyperthyroid. For the analysis in question, at the beginning of study the following two subgroups were identified in the prednisone group and lithium carbonate group: 1) patients with suppressed TSH concentrations and elevated concentrations of thyroid hormones, and 2) patients with normal TSH concentrations. Next, the patients were assigned to one of the following two subgroups according to the final effect of therapy: 1) effective therapy (euthyroidism or hypothyroidism) or 2) ineffective therapy (hyperthyroidism).

The obtained results of the above-mentioned analysis demonstrated that in Group II, in patients with initially normal TSH concentrations, the effectiveness of therapy was 100.0% (11/11 patients), while in patients with suppressed TSH, the therapy was effective in 62.0% (18/29 patients). Similarly, in Group III, in patients with normal TSH concentrations at the beginning of the study, the efficacy of therapy was 91.0% (21/23 patients) whereas in patients with suppressed TSH, the therapy effectiveness amounted to 59.0% (10/17 patients). It can be assumed that the normal TSH values, obtained prior to the basic treatment (^{131}I), exerted a beneficial effect on the efficacy of radioiodine therapy ($p = 0.02$, in both Groups II and III, two-tailed Fisher's exact test).

A similar analysis of the relationship between the initial level of TSH and the therapy effectiveness was performed for Groups IV and V, with the following results: in Group IV, in patients with normal TSH concentrations, the therapy was effective in 86.0% (12/14 patients), while in patients with suppressed TSH concentrations the therapy was effective in 88.5% (23/26 patients). In Group V, in patients with normal values of TSH concentrations at the beginning of study, the therapy was effective in 85.0% (11/13 patients), while in patients with suppressed TSH concentrations, the therapy was effective in 63.0% (17/27 patients).

Summing up, in Group IV a similar effectiveness of therapy was obtained regardless of the initial TSH concentration, while in Group V a slightly higher efficacy was found in patients with normal values of TSH concentrations at the beginning of treatment. However, in both instances, the results were statistically insignificant (two-tailed Fisher's exact test, Group IV — $p = 0.99$, Group V — $p = 0.2$). Thus, it may be concluded that both in the group of patients, receiving ^{131}I together with prednisone in the peritherapeutic period (Group IV)

and in the controls (Group V), the initial hormonal status had no effect on the final outcome of ^{131}I therapy.

Discussion

The treatment of hyperthyroidism with radioactive iodine is a very effective method; however, remission is not obtained in all patients after a single dose of radioiodine. For many years, therapeutic methods have been searched for to improve their efficacy. There are some premises that simultaneous administration of radioactive iodine and of certain thyroid function affecting drugs could improve the overall outcome of treatment. Studies on the use of antithyroid drugs combined with radioiodine have been conducted for a number of years, although the effects of these drugs on the effect of radioiodine therapy is still a subject of dispute. We have confirmed, in the present study, that thiamazole used in combination with ^{131}I reduces the therapeutic effectiveness of this isotope. Similar conclusions have been drawn by other authors [16–18], who explain the observation by the fact that antithyroid drugs decrease iodine uptake by the thyroid gland. In addition, by deteriorating the intrathyroid iodine resources, they contribute to the so-called quick turnover of iodine in the thyroid gland. In consequence, the EHL of radioiodine is shorter and the overall effectiveness of treatment is lower. Some authors [16, 19] underline the radioprotective effects of antithyroid drugs, which result in a lower biological effect with comparable dose absorbed by the thyroid gland.

However, some other authors did not see any influence of antithyroid drugs on the outcome of radioiodine therapy in their studies [20, 21].

Radioactive iodine should not be used in patients with high concentrations of free thyroid hormone (fT_3 and fT_4) because of the risk of hyperthyroidism enhancement. However, sometimes it is difficult to obtain normal thyrometabolic status before radioiodine therapy; there are also patients in whom even a short-term withdrawal of antithyroid drug administration enhances the symptoms of hyperthyroidism. Therefore, regarding those patients, administration of antithyroid drugs is recommended during the peritherapeutic period of ^{131}I therapy.

In the above-mentioned literature items, only Sabri et al. [14] evaluated the correlation between the effectiveness of therapy with ^{131}I in hyperthyroid patients who were given thyrostatic drugs and the value of the absorbed dose of irradiation. In their study, similarly to our present contribution, Pearson's statistics was applied — point biserial statistics.

Short EHL of iodine in the thyroid gland is an essential problem before radioiodine administration planning because it results in shorter exposition time of the thyroid tissue to irradiation, thus deteriorating the final outcome of ^{131}I therapy. However, it seems that complimentary administration of lithium carbonate may improve the results of ^{131}I in hyperthyroidism.

Bogazzi et al. [12] studied two groups of hyperthyroid patients. The patients of one of these groups were treated with radioiodine only, while the patients in the second group additionally received lithium carbonate in a dose of 900 mg/day for six consecutive days starting on the day of ^{131}I therapy onset. In their study, in the group of patients who were receiving lithium carbonate, higher efficacy of radioiodine therapy was observed; earlier, euthyroidism was obtained in those patients with more pronounce reduction of goitre size. The authors explain their results by the antithyroid drug properties of lithium carbonate and extended retention of the radionuclide in the thyroid [12]. Similar conclusions were obtained by Dunkelmann et al. [4]. Contrary to general expectations, the authors of that study did not demonstrate any significant effect of lithium carbonate on the outcome of radioiodine therapy in the studied group of patients [4]. There are also other reports contradicting the advantageous effects of lithium carbonate on the overall outcome of ^{131}I therapy [22, 23]. In our present study we have failed to demonstrate any beneficial effect of lithium carbonate for ^{131}I therapeutic outcome.

Corticosteroids are not commonly used as complimentary treatment before ^{131}I administration; first of all, they play a key role in treating thyroid orbitopathy. According to many authors [5, 10, 24], corticosteroid administration should be considered in cases of radioiodine treatment of hyperthyroidism with accompanying thyroid orbitopathy. They are believed to prevent the symptoms of orbitopathy from becoming more acute. Therefore, following the recommendations, as found in literature, the studied patients in Group IV — *i.e.* patients with hyperthyroidism in the course of GD with accompanying GO, received corticosteroids in the "peritherapeutic" period of ^{131}I administration in a dose of 1 mg per kg of body weight/day. All the patients with hyperthyroidism in the course of GD (Group IV and Group V) received ablative doses of radioiodine.

However, the goal of the reported study was not the evaluation of corticosteroid therapy on the course of GO, but to find out whether their administration had any effect on radioiodine therapy of hyperthyroidism. The issue of corticosteroid application and of their effect on the outcome of radioiodine treatment in hyperthyroid patients has been approached but in just a few reports.

In our present study, prednisone, applied in hyperthyroid patients in the course of GD and accompany-

ing GO (Group IV), significantly increased the efficacy of ^{131}I therapy.

Jude et al. [25] described a case of two patients in whom it was difficult to compensate thyrometabolic state by means of applied antithyroid drugs, while only prednisone administration brought control over hyperthyroidism and enabled effective therapy with radioiodine. The authors suggest that corticosteroids may be used to bring about balanced thyroid functionality in combination with antithyroid drugs. However, Bartalena et al. [10] studied the effects of corticosteroids on the effects of radioiodine treatment of hyperthyroidism, finding that in both a group of patients receiving corticosteroids and in a group with no corticosteroid administration, the effectiveness of the basic (^{131}I) therapy was almost the same. Similar conclusions were obtained by Jensen et al. [26]. Kloza et al. [27] demonstrated in their study a significant correlation between hyperthyroidism recurrence and treatment with corticosteroids at the time of ^{131}I administration. The authors of the study reported that the use of corticosteroids at the time of radioiodine treatment was identified as an unequivocally bad prognostic factor for the therapy with radioactive iodine.

In our present investigation, the evaluation also encompassed the effect of the initial hormonal status on the final effect of ^{131}I therapy in Groups II, III, IV, and V. It appears from the performed evaluation that, taking into account Groups II and III, normal TSH values exert beneficial effects on the efficacy of radioiodine therapy, but in Groups IV and V the initial hormonal status had no effect on the efficacy of ^{131}I therapy.

It is worth some deliberation why, in the two groups of patients treated with radioiodine only (Groups III and V – the— control groups), the obtained results were not the same. In Group III the obtained status of metabolic euthyroidism had advantageous effects on the final outcome of ^{131}I therapy, while in Group V no such relationship was found. The divergence of the two results may have resulted from different absorbed doses applied in either group. The absorbed dose in Group III was 150–200 Gy, while the doses applied in Group V amounted to 250–350 Gy, the latter already being ablative doses. The median values of absorbed doses in Groups III and V were compared by means of U Mann-Whitney's test, revealing that they did not differ from each other at the level of statistical significance. Thus, it seems that the factors considered by many authors to influence the efficacy of therapy with radioactive iodine may be less important in cases when the applied therapeutic activities of ^{131}I are calculated on the basis of ablative absorbed doses.

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