Comparison characteristics of mercazolilum and thyrozol in treatment of patients with diffuse toxic goiter

O.V. Rakov

SI «V.P. Komisarenko Institute of Endocrinology and Metabolism, Natl. Acad. Med. Sci. of Ukraine»

Summary. The aim of the work was to evaluate the therapeutic efficacy and safety of merkazolilum («Zdorovya» Ukraine) and thyrozol (Takeda) in the treatment of patients with diffuse toxic goiter (DTG). **Materials and methods.** 59 patients aged 20-73 years (mean age 43.17±1.85), 17 men (28.8%) and 42 women (71.9%) among them were examined in hospital for resolving determined tasks. Graves' disease of middle severity was diagnosed in all patients. The patients of study groups were matched by the age, sex, thyroid size and duration of thyrotoxicosis. The diagnosis of Graves' disease was verified on the basis of clinical characteristics, data of anamnesis, clinical examination, hormonal and immunological studies, ultrasound examination of the thyroid gland. The observation time from thyrostatic drug prescription consisted of 6 months. Such indices as TSH, fT_4, fT_3, TRAbs and thyroid gland ultrasound were monitored during the observation period — in 1, 3, 6 months after the treatment. All patients were treated by thyrostatic drugs (mercazolilum, thyrozol), β-blockers (bisoprolol, metoprolol), sedative means, and potassium drugs. The patients with DTG were divided into two groups by the nature of the conservative treatment: 30 patients who received mercazolilum were included in group 1, 29 patients who were taken thyrozol — in group 2. The daily dose of thyrostatic drugs was 20-30 mg for observed patients of both groups. No relationship between the manifestation of clinical symptoms of thyreotoxicosis, the levels of TSH, free T_3, free T_4, TRAbs in the peripheral blood and the degree of thyroid increase was revealed as a result of the examination. A decrease in the levels of thyroid hormones and TRAbs was observed in patients of both groups in a month after starting the medicamentous therapy, without a detection of significant differences between these parameters depending on the used thyrostatic drugs ($p>0.05$). Normalized levels of peripheral hormones such as fT_4, fT_3 under a low level of TSH were demonstrated in 100% of the subjects in both groups. Similar indices were determined in 3 and 6 months after beginning of thyrostatic therapy in patients of both groups later on. Euthyroid state was achieved in 100% (59 patients) patients of both groups against a background of thyrostatic therapy. No significant side effects (agranulocytosis, toxic hepatitis) were observed in patients of both groups in our case, in six months after treatment of patients with DTG by thyrostatic drugs. **Conclusions.** No difference in the timing of thyrotoxicosis compensation occurrence was found in patients receiving both mercazolilum and thyrozol. No differences in

* Адреса для листування (Correspondence): ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України», вул. Вишгородська, 69, м. Київ, 04114, Україна. E-mail: zdovado@ukr.net

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frequency of principal complications occurrence were also found as a result of medicamentous therapy with thyrostatic drugs. Merkazolilum and thyrozol can be considered equivalent drugs for their efficacy and safety.
Keywords: diffuse toxic goiter, thyrozol, mercazolilum.

In structure of endocrine pathology side by side with diabetes mellitus the significant increase in global incidence of thyroid disease consisting of 10-15% population is noted in recent years.

One of the pathologies, determining the frequency and importance of this disease group, is diffuse toxic goiter (DTG). Frequency of manifestation symptomatic form of the disease is approximately 2% in women and 0.2% in men [1, 2]. Currently, DTG is considered as a systemic disease of autoimmune origin, that is characterized by stable pathological hyperactivity of the thyroid gland with development of Graves' disease syndrome in combination with extrathyroidal pathology [3, 4]. According to scientific data, the general morbidity rate of DTG in Ukraine is gradually increased — from 101.5 cases per 100 thousand of population in 2006 to 128.8 cases in 2013 [5].

As it is generally known, there are three main treatment methods of DTG: drug therapy with thyrostatic drugs, radioiodine therapy and surgical intervention.

Conservative therapy is realized with the use of thyrostatic drugs which principal mechanism is a suppression of the thyroid hormones synthesis. Thyrostatic drugs remain the fundamental ones in the treatment of Graves' disease patients. Thianomides such as thiamazole (tyrosol, methimazole, mercazolilum) carbimazole and propylthiouracil are used for drug therapy of DTG currently [6-14].

The key mechanism of thianomides is caused by their central effect — that is an inhibition of two stages of the thyroid hormones biosynthesis — the organification and condensation. Entering the thyroid gland, thianomides suppress the activity of thyroid peroxidase, which deficiency decreases the iodine oxidation, thyroglobulin iodination, and iodotyrosine condensation [15, 16].

It is known that thiamazole does not affect the release of the synthesized thyronines from the thyroid follicles. This explains the latent period of the drug effect, which is preceded by normal levels of T_3 and T_4 in the blood plasma and the clinical effect from thyrostatic drugs using occurs only in several weeks (as a rule, in 3-6 weeks) after beginning of its intake. That is, when earlier formed thyroid hormones, which are located in the follicle lumen as a complex connection with thyroglobulin, will be used up, and the synthesis of thyroid hormone new number does not occur because of the blockade of their bio-synthesis by thyrostatic drugs [16, 17].

It was proved that thianomides influence on immunological disorders arising in DTG — increasing the amount and activity of certain lymphocyte subpopulations, decreasing the immunogenicity of thyroglobulin as a result of reducing its iodination and synthesis of prostaglandins E_2, interleukin-1, interleukin-6, and the production of heat shock proteins by thyrocytes [2, 18-19]. Traditionally thyrostatic drugs are used in the dose titration mode: treatment starts with the highest possible therapeutic doses (30-40 mg per day) with gradually decreasing to maintaining dose (5-10 mg per day) [10, 11, 16]. The duration of thyrostatic drugs therapy is one of the important conditions to achieve thyreotoxicosis remission [6, 7, 10], since the short course of treatment with such therapy (during 3-6 months) is achieved persistent remission only in minority of patients (30-40%). A number of patients with the disease remission is greatly increased during long-term course of thyrostatic drugs intake (about 18-24 months) [7-11, 16]. Therefore, planning long-term therapy of DTG, there is arising a question for choice of one or another thyrostatic drugs, as there is the risk of complications and side effects of therapy (nausea, skin itch, joint pain, agranulocytosis, cholestasis, aplastic anemia) [2, 20-22].

It is shown that the high and low doses of thyrostatic drugs equally reduce the level of antibodies to TSH receptor, while the frequency of thyreotoxicosis relapse in 12 months after treatment is practically the same, and high doses of these drugs is much more likely cause agranulocytosis [2, 20-22].

According to the available data, propylthiouracil and thiamazole very seldom have the side effects. The general risk of these effects accounts only 3% for propylthiouracil and 7% for thiamazole, and the most severe reaction — agranulocytosis — is

respectively developed in 0.44 and 0.12% cases [23]. The risk of agranulocytosis development, while thiamazole taking, depends on the dose, whereas such dependence has not been identified for propylthiouracil [22, 24, 25]. Light leucopenia can be both a symptom of thyreotoxicosis and a sign of agranulocytosis beginning [16, 24, 26-28].

The most common side effect of thyrostatic drugs is light urticarial (occasionally hemorrhagic) rash. It often disappears without the discontinuation of treatment.

Less common side effects include pain and stiffness of joints, paresthesias, headache, nausea, skin pigmentation, and alopecia. Drug fever, liver and kidney damages are not often observed, even if the activity of hepatic enzymes is not frequently increased against a background of propylthiouracil intake [21, 22, 25-29].

The main thianomides used in Ukraine for the treatment of Graves' disease are mercazolilum («Zdorovya» Ukraine) and thyrozol (Takeda). In recent years, more often clinicians give prefeverence to import drugs for the thyreotoxicosis treatment, such as thyrozol, considering it more safe and efficient [16, 30].

Thus, the aim of our study was to compare the efficiency, safety of using mercazolilum («Zdorovya» Ukraine) and thyrozol (Takeda) for the treatment of Graves' disease.

Materials and methods

The study was conducted in the clinic of SI «V.P. Komisarenko Institute of Endocrinology and Metabolism, Natl. Acad. Med. Sci. of Ukraine» in the certificated department of functional diagnostics, which has a Certificate of Attestation № 2604/4692, issued 27.07.11. To perform those tasks, 59 patients aged 20 to 73 years (mean age 43.17±1.85), 17 of which were male (28.8%), and 42 women (71.9%) were examined. Graves' disease of middle severity was diagnosed in all patients under hospital conditions. The diagnosis of Graves' disease was verified on the basis of clinical characteristics, data of anamnesis, clinical examination, hormonal and immunological studies, ultrasound examination of the thyroid gland.

All patients were divided into 2 groups, depending on the use of thyrostatic drugs. The observation time from the thyrostatic drugs prescription was 6 months. In the first group (n=30) patients were received mercazolilum in initial dose 20-30 mg per day. Patients of the second group (n=29) were prescribed thyrozol in dose of 20-30 mg per day. The thyroid size (according to thyroid palpation and ultrasound examination) and indices of thyroid status (TSH, free T_3, free T_4, TRAbs) were controlled in all patients, and were also fixated complications occurring in some patients as a result of conducted therapy (urticarial rash, joint pain, headache, nausea).

The ultrasound examination was conducted to determine the thyroid size and structure, by standard methods (with apparatus «Toshiba» SSA-580A and «Ultima» PA GRIS. 941217.01343 IZ).

Thyroid status was assessed by the level of free fractions of thyroid hormones (fT_4, fT_3) and TSH in venous blood serum by radioimmunoassay with the help of standard kits of «Immunotech» company (Czech Republic), intended for the quantitative determination of these hormones. Reference values for fT_4 consisted of 11.5-23.0 pmol/l and fT_3 — 2.5-5.8 pmol/l, and normal TSH values were in the range of 0.17-4.05 mIU/mL.

The method of immunoenzyme assay using standard kids of «Medizim» firm (Germany) was used to determine the level of antibodies to the TSH receptor (TRAbs) in the blood serum. The indices that do not exceed 1.5 mIU/l are considered as the normal values of TRAbs.

Level of TSH, thyroid hormones (fT_4, fT_3) and TRAbs was evaluated in patients before treatment, and then in 1, 3 and 6 months after thyrostatic drug therapy.

The total blood count was also determined in all patients 1 time every 10 days, and during transition to maintening doses of thyrostatic drugs (5-10 mg) later — 1 time per month.

Ultrasound examination of the thyroid gland was performed before the appointment of thyrostatic drugs, as well as in 3 and 6 months after beginning of anti-thyroid therapy.

In addition to anti-thyroid therapy, all patients were treated with β-blockers (bisoprolol, metoprolol), sedatives, and potassium supplements.

Criteria of thyrostatic drugs effectiveness, with the exception of an elimination of the clinical picture of thyreotoxicosis, was normalization of such laboratory indices such as fT_4, fT_3, TSH and TRAbs.

Materials were statistically processed using the Student t-test (determination of significance of index P) and the non-parametric method of Pearson's chi-squared test (χ^2)

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Results and discussion

The increased thyroid sizes were determined in both groups of patients before starting thyrostatic drugs therapy that corresponded to II degree of goiter by the results of palpation study. At the ultrasound examination an increase in the thyroid volume was revealed, upon the average of 90% with respect to the upper limit of patients' age norm. Thus, the average volume of the thyroid gland, amounted 39.54±3.47 cm^3 in patient population of group I and 37.84±2.1 cm^3 — in patients of group II.

As it is shown in the **Table 1**, the following results were obtained studying the hormonal status in patients of both groups: average quantities of fT_3 and fT_4 were expectedly increased in comparison with the indices of healthy individuals, and TSH serum concentration was reduced and, on average, amounted 0.025±0.01 mIU/l ($p<0.001$) in the Ist group of patient population, and 0.017±0.04 mIU/l — in the IInd group ($p<0.001$). Indices of blood serum TRAbs were significantly increased ($p<0.001$) comparing to the respective indices of healthy individuals and, on average, amounted 20.19±2.8 IU/l in the Ist group of patients and 17.86±2.16 IU/l in the IInd group of patients.

While controlling in a month after the beginning of drug therapy the received results of TSH thyroid hormones and TRAbs examinations are presented in the **Table 2**.

As it is demonstrated with the data of the Table 2, the decreased level of thyroid hormones and TRAbs was observed in both groups of patients, while significant differences between these indices were not detected ($p>0.05$), depending on used thyrostatic drugs. The disease compensation occurs within a month after the beginning of thyrostatic drugs therapy. The normalization in the levels of peripheral hormone (fT_4, fT_3) was observed in 100% patients of both groups. At the same time the TSH level was remained low and amounted 0.15±0.02 mIU/l in patients of group I and 0.12±0.05 mIU/l in patients of group II.

In the future, similar indices were determined in 3 and 6 months after the beginning of thyrostatic drug therapy. The results are shown in the **Table 3**.

As it is indicated in the Table 3, euthyroid status was achieved in 100% (59 patients) in both groups against a background of thyrostatic therapy.

Analyzing the results of thyroid volume changes in patients of both groups in 6 months after treatment, one can concluded that the thyroid gland was decreased in patients of group I from 39.54±3.47 cm^3 to 34.96±2.5 cm^3 ($p>0.05$) and in group II — from 37.84±2.1 cm^3 to 33.96±3.4 cm^3 ($p>0.05$). No significant differences were observed between the indices of the average volumes in the patients of both groups.

Normalization of the levels of TSH and thyroid hormones was registered in all observed patients. The TRAbs levels were significantly decreased during 6 months of therapy, reaching the minimum

Table 1. Main examination results of patients' two groups at the thyrotoxicosis decompensation period

Main indices		group I (n=30)	group II (n =29)	p
Age (years)		43±2.4	44±2.1	>0.05
Sex	men	7	9	
	women	23	20	
TSH, mIU/l		0.025±0.01	0.017±0.04	>0.05
fT_3, pmol/l		31.86±1.95	33.12±1.81	>0.05
fT_4, pmol/l		36.4±2.42	35.29±2.67	>0.05
TRAbs, IU/l		20.19±2.8	18.86±2.16	>0.05
The thyroid gland volume, cm^3		39.54±3.47	37.84±2.1	>0.05

Note. P — significance of differences between groups.

Table 2. Indices of thyroid hormones, TSH, TRAbs and thyroid volume in 1 month after conservative treatment of patients with Graves' disease

Groups of patients	fT_3, pmol/l	fT_4, pmol/l	TSH, mIU/l	TRAbs, IU/l
I group (n=30)	5.49±0.45	20.52±0.79	0.15±0.02	12.39±1.74
II group (n= 29)	5.8±0.15	19.94±0.66	0.12±0.05	11.81±1.64
P	>0.05	>0.05	>0.05	>0.05

Note. P — significance of differences between groups.

Table 3. Indices of thyroid hormone, TSH, TRAbs and thyroid volume in 3 and 6 months after conservative treatment of patients with Graves' disease

Indices	3 months after treatment		6 months after treatment		P
	Group I (n=30)	Group II (n=29)	Group I (n=30)	Group II (n=29)	
TSH	0.68±0.17	0.71±0.01	0.98±0.26	1.2±0.56	>0.05
fT3	3.16±0.25	2.99±0.14	4.12±0.5	3.02±1.2	>0.05
fT4	15.18±1.29	14.67±1.12	14.28±2.2	14.11±3.4	>0.05
TRAbs	8.94±1.17	9.36±1.32	3.69±1.6	4.54±1.5	>0.05
Thyroid Gland Volume, cm^3	35.6±2.1	34.21±2.8	34.96±2.5	33.96±3.4	>0.05

Note. P — significance of differences between groups.

values in 6 months after the beginning of thyrostatic drugs therapy.

No significant differences were also observed in the levels of TSH, thyroid hormones (fT_3, fT_4) and TRAbs in patients of groups I and II (Table 3).

Based on the aims of the study, the complications that were noted during anti-thyroid therapy are presented in the **Table 4**.

Table 4. Complications of medicamentous therapy as a result of imidazole drug therapy

Complications of drug therapy	Group I (n=10)	Group II (n=8)	χ^2
Urticarial rash	3	1	0.3169
Joint pain	2	2	0.6121
Headache	2	3	0.9719
Nausea	3	2	0.6687

Note. P — in accordance with the criterion χ^2.

For six months of treating patients with Graves' disease with mercazolilum and thyrozol, no significant side effects were observed in patients of both groups (Table 4). As a rule, registered headaches, nausea, joint pain, and urticarial rash were independently without the discontinuation of therapy. No significant differences in the occurrence of major complications from drug therapy were observed in patients of I and II groups.

Conclusions

No differences were found in the timing of thyrotoxicosis compensation occurrence in patients taking both mercazolilum and thyrozol.

Also, no significant differences were found in the frequency of main complications occurrence as a result of drug therapy by anti-thyroids.

Mercazolilum and thyroszl can be considered equivalent drugs for their efficacy and safety.

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Порівняльна характеристика ефективності мерказолілу й тиразолу у лікуванні хворих на дифузний токсичний зоб

О.В. Раков

ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України»

Резюме. Метою роботи була оцінка терапевтичної ефективності та безпеки застосування мерказолілу («Здоров'я» України) й тирозолу (Takeda) у лікуванні хворих на дифузний токсичний зоб (ДТЗ). **Матеріали та методи.** В умовах стаціонару обстежено 59 хворих віком від 20 до 73 років (43,17±1,85 року), серед яких 17 (28,8%) чоловіків і 42 (71,9%) жінки . В усіх пацієнтів діагностували ДТЗ середньої тяжкості. Групи обстежуваних були порівнянними за віковим, статевим складом, розмірами щитоподібної залози (ЩЗ) і тривалістю тиреотоксикозу. Діагноз ДТЗ верифіковано на підставі характерної клінічної картини, даних анамнезу, клінічного огляду, гормонального, імунологічного обстеження та УЗД ЩЗ. Термін спостереження — 6 місяців. Через 1, 3, 6 місяців лікування здійснювали контроль ТТГ, T_4в., T_3в., АТ-рТТГ, УЗД ЩЗ. Усім хворим проводили лікування ТСТ (мерказоліл, тирозол), β-блокаторами (бісопролол, метопролол), седативними засобами та препаратами калію. Хворих на ДТЗ розподілили на дві групи: пацієнти I групи (30 осіб) отримували мерказоліл, II групи (29 осіб) — тирозол. Добова доза тиреостатиків складала 20-30 мг. За результатами обстеження не було виявлено взаємозв'язку між вираженістю клінічних симптомів тиреотоксикозу, рівнями ТТГ, T_4в., T_3в., АТ-рТТГ у периферичній крові та ступенем збільшення ЩЗ. Через місяць від початку медикаментозної терапії у пацієнтів обох груп спостерігалося зниження рівнів тиреоїдних гормонів й АТ-рТТГ без вірогідної залежності від застосовуваного ТСТ. В обох групах у 100% випадків відбулася нормалізація рівнів T_4в., T_3в. на тлі низького вмісту ТТГ. Далі показники визначали через 3 і 6 місяців від початку тиреостатичної терапії. На тлі тиреостатичної терапії евтиреоїдного стану досягнуто у 100% випадків. Впродовж 6 місяців лікування не відзначено значущих побічних ефектів (агранулоцитоз, токсичний гепатит) у пацієнтів обох груп. **Висновки.** У пацієнтів, які лікувались мерказолілом або тирозолом, не виявлено різниці у термінах компенсації тиреотоксикозу. Також не спостерігалося значущих ускладнень медикаментозної терапії даними ТСТ. Мерказоліл і тирозол за ефективністю та безпечністю можна вважати рівноцінними препаратами.

Ключові слова: дифузний токсичний зоб, тирозол, мерказоліл.

Сравнительная характеристика эффективности мерказолила и тирозола в лечении больных диффузным токсическим зобом

О.В. Раков

ГУ «Институт эндокринологии и обмена веществ им. В.П. Комиссаренко НАМН Украины»

Резюме. Целью работы была оценка терапевтической эффективности и безопасности применения мерказолила («Здоровье» Украины) и тирозола (Takeda) в лечении больных диффузным токсическим зобом (ДТЗ). **Материалы и методы.** В условиях стационара обследованы 59 больных в возрасте от 20 до 73 лет (43,17±1,85 года), среди них 17 (28,8%) мужчин и 42 (71,9%) женщины. У всех пациентов диагностировали ДТЗ средней тяжести. Группы не различались по возрастному, половому составу, размерам щитовидной железы (ЩЖ) и длительности тиреотоксикоза. Диагноз ДТЗ верифицирован на основании характерной клинической картины, данных анамнеза, клинического осмотра, гормонального и иммунологического обследования, УЗИ ЩЖ. Время наблюдения от момента назначения тиреостатических препаратов составило 6 месяцев. Через 1, 3, 6 месяцев лечения осуществляли контроль ТТГ, T_4св., T_3св., АТ-рТТГ, УЗИ ЩЖ. Всем больным проводили лечение ТСТ (мерказолил, тирозол), β-блокаторами (бисопролол, метопролол), седативными средствами и препаратами калия. Больных ДТЗ разделили на две группы: пациенты I группы (30 человек) получали мерказолил, II группы (29 больных) — тирозол. Суточная доза тиреостатиков составляла 20-30 мг. По результатам обследования не выявлено взаимосвязи между выраженностью клинических симптомов тиреотоксикоза, уровнями в периферической крови ТТГ, T_4св., T_3св., АТ-рТТГ и степенью увеличения ЩЖ. Через месяц у пациентов обеих групп наблюдалось снижение уровней тиреоидных гормонов и АТ-рТТГ, при этом достоверного различия между этими показателями в зависимости от применяемого тиреостатика выявлено не было. В обеих группах в 100% случаев наблюдалась нормализация уровней T_4св., T_3св. при низком уровне ТТГ. В дальнейшем аналогичные показатели определяли через три и шесть месяцев. На фоне тиреостатической терапии эутиреоидное состояние достигнуто в 100% случаев (59 человек). За шесть месяцев лечения больных ДТЗ тиреостатиками мы не наблюдали значимых побочных эффектов (агранулоцитоз, токсический гепатит) у пациентов обеих групп. **Выводы.** У пациентов, принимающих мерказолил или тирозол, не обнаружено разницы в сроках компенсации тиреотоксикоза. Также не обнаружено разницы в частоте возникновения основных осложнений в результате медикаментозной терапии тиреостатиками. Мерказолил и тирозол по эффективности и безопасности можно считать равноценными препаратами.

Ключевые слова: диффузный токсический зоб, тирозол, мерказолил.