

Propylthiouracil-induced agranulocytosis as a rare complication of antithyroid drugs in a patient with Graves' disease

 Patrícia Novais Rabelo¹
 Paula Novais Rabelo³
 Allyne Fernanda de Paula¹
 Samuel Amanso da Conceição²
 Daniela Pultrini Pereira de Oliveira Viggiano¹
 Daniela Espíndola Antunes¹
 Estela Muszkat Jatene¹
 Sílvia Leda França Moura de Paula¹
 Monike Lourenço Dias¹
 Maria Aparecida Lopes Reis¹

1. Division of Endocrinology & Metabolism, Intern Medicine Department, Hospital das Clínicas, Faculty of Medicine, Federal University of Goiás (HC-UFG), Goiás, GO, Brasil

2. Intern Medicine Department, Hospital das Clínicas, Faculty of Medicine, Federal University of Goiás (HC-UFG), Goiás, GO, Brasil

3. Faculty of Nutrition, Federal University of Goiás (HC-UFG), Goiás, GO, Brasil

<http://dx.doi.org/10.1590/1806-9282.65.6.755>

SUMMARY

INTRODUCTION: Graves' disease (GD) is an autoimmune disorder characterized by hyperthyroidism. Antithyroid drugs (ATDs) are available as therapy. Agranulocytosis is a rare but potentially fatal complication of this therapy. In this study, we report agranulocytosis induced by propylthiouracil (PTU) in a patient with GD and the difficulties of clinical management.

CASE: RNBA, male, 30 years old, with GD, treated with propylthiouracil (PTU). He progressed with pharyngotonsillitis. Then, PTU was suspended and antibiotic, filgrastim, propranolol, and prednisone were initiated. Due to the decompensation of hyperthyroidism, lithium carbonate, dexamethasone, and Lugol's solution were introduced. Total thyroidectomy (TT) was performed with satisfactory postoperative progression.

DISCUSSION: We describe here the case of a young male patient with GD. For the treatment of hyperthyroidism, thioamides are effective options. Agranulocytosis induced by ATDs is a rare complication defined as the occurrence of a granulocyte count $<500/\text{mm}^3$ after the use of ATDs. PTU was suspended, and filgrastim and antibiotics were prescribed. Radioiodine (RAI) or surgery are therapeutic alternatives. Due to problems with ATD use, a total thyroidectomy was proposed. The preoperative preparation was performed with beta-blocker, glucocorticoid, lithium carbonate, and Lugol solution. Cholestyramine is also an option for controlling hyperthyroidism. TT was performed without postoperative complications.

CONCLUSION: Thionamide-induced agranulocytosis is a rare complication. With a contraindication to ATDs, RAI and surgery are definitive therapeutic options in GD. Beta-blockers, glucocorticoids, lithium carbonate, iodine, and cholestyramine may be an adjunctive therapy for hyperthyroidism.

KEYWORDS: Graves disease. Propylthiouracil. Agranulocytosis. Hyperthyroidism.

DATE OF SUBMISSION: 20-Sep-2018

DATE OF ACCEPTANCE: 24-Nov-2018

CORRESPONDING AUTHOR: Patrícia Rabelo

Primeira Avenida S/N Setor Leste Universitário – Goiânia – Goiás
Brasil – 74075-150 – Tel:62 999653705

E-mail: pat.n.rabelo@hotmail.com

INTRODUCTION

Graves' disease (GD) is an autoimmune disease that predominantly affects women between the 2nd and 4th decades of life and is the most common cause of hyperthyroidism.¹ It consists of increased synthesis and secretion of thyroid hormones (THs), manifesting as nervousness, weight loss, polyphagia, tachycardia, heat intolerance, excessive sweating, tremors, and muscle weakness.²

Antithyroid drugs (ATDs), radioiodine (RAI), and surgery are available therapies for GD treatment. ATDs may be associated with toxic reactions such as rash, pruritus, hepatocellular injury and agranulocytosis.³ ATD-induced agranulocytosis is defined as the presence of granulocytes <500/mm³ following the use of ATDs and constitutes an absolute contraindication to the use of these medications; in this situation, RAI or surgery are therapeutic alternatives.

We describe here the case of a young male patient with GD which evolved as skin allergy and agranulocytosis induced by ATD, and discuss the challenges encountered in his clinical management.

CASE REPORT

RNBA, male, 30 years old, diagnosed with GD and presenting with sarcopenia, large diffuse goiter, and free T4 level >7.7 ng/dL. He started treatment with methimazole (MMI) 10 mg/day and propranolol 80 mg/day and developed a skin allergy 1 month later when the treatment was then switched to propylthiouracil (PTU) 200 mg/day. The patient used low and irregular doses of PTU, but his allergy persisted even with the use of antihistamines.

Due to problems with ATD use, total thyroidectomy was proposed. The patient was admitted to the Hospital das Clínicas da Universidade Federal de Goiás (HC/UFG) with fever, tachycardia, and normal hematological (Table 1) and hepatic evaluations. He progressed with pharyngotonsillitis when PTU was then suspended and an antibiotic was initiated. On the 4th day, he developed neutropenia (495 cells/mm³). Granulocyte colony-stimulating factor (G-CSF) 300 µg was initiated for 2 days, which resolved the neutropenia, and propranolol 320 mg/day and prednisone 20 mg/day were prescribed.

The patient was discharged with the prescribed medications while awaiting surgery. He returned after 7 days with decompensated hyperthyroidism, when he was prescribed lithium carbonate (LC) 300

mg 6/6h and dexamethasone 8 mg/day. He was admitted for the surgical procedure and received pre-operative preparation with potassium iodide 10% and metalloid iodine 5%, 7 drops 8/8h for 3 days, which decreased his hormone levels (Table 2).

He underwent total thyroidectomy with satisfactory postoperative progression and was discharged without complications and in regular use of levothyroxine. He currently presents compensated postsurgical hypothyroidism.

DISCUSSION

GD is the main cause of hyperthyroidism, affecting 1.0-1.6% of the population.¹ It may present as goiter, ophthalmopathy, and pretibial myxedema. We described here the case of a young male patient with GD, diffuse goiter, and sarcopenia. Evidence suggests that male gender and goiter are associated with GD severity. Goiter is also associated with a diagnosis in younger individuals.⁴ Therapeutic options include ATDs, RAI, and surgery. In the described case, the drug was initially chosen until the definitive surgical treatment.

ATDs (PTU and MMI) inhibit thyroid peroxidase. PTU additionally inhibits the conversion of T4 into T3 in peripheral tissues.⁵ The use of ATDs is associated with reduced titers of antithyroid antibodies and anti-TSH receptor antibodies.³ Younger patients with recent disease onset who require faster biochemical control are candidates for ATD use.⁵

The use of ATDs can be associated with toxic reactions in 3 to 12% of the patients,^{3,6} including rash

TABLE 1 - LABORATORY TESTS ON THE FIRST AND FOURTH DAY OF HOSPITALIZATION

Hemogram	1st day of hospitalization	4th day of hospitalization
Hemoglobin (12-16 g/dL)	13.9 g/dL	13.5 g/dL
Hematocrit (36-45%)	40.8%	39%
Leukocytes (4,000-10,000 cells/mm ³)	4,300 cells/mm ³	1,500 cells/mm ³
Neutrophils (40-75%)	58% (3,480 neutrophils)	33% (495 neutrophils)
Lymphocytes (20-40%)	21% (1,260 lymphocytes)	37% (555 lymphocytes)
Monocytes (2-10%)	15% (900 monocytes)	24% (360 monocytes)
Eosinophils (1-5%)	0% (zero)	0% (zero)
Basophils (0-2%)	0% (zero)	1% (15 basophils)
Platelets (150,000-450,000)	219,000	65,000

TABLE 2 - EVOLUTION OF LABORATORY TESTS FOR THYROID FUNCTION

Date	Free T4	TSH	Diagnosis
19/Sep./2015	> 7.7 ng/dL*	<0.005 µIU/ mL§	
04/Jan./2016	2.31 ng/dL* 1.25 x ULM	0.005 µIU/ mL§	Propylthiouracil Propranolol
18/Apr./2016	7.5 ng/dL* 4.4x ULM	<0.005 µIU/ mL§	Prednisone Propranolol
02/May/2016	1.97 ng/dL** 1.33x ULM	0.00 µIU/ mL#	Lithium carbonate Dexamethasone Propranolol Lugol's solution
05/Oct./2016	1.39 ng/dL*	2.870 µIU/ mL§	Levothyroxine

* Reference value free T4: 0.93-1.7 ng/dL, ** Reference value free T4: 0.7-1.48 ng/dL, § Reference value TSH: 0.27-5.0 µIU/mL, # Reference value TSH: 0.35-5.0 µIU/mL, ULM: upper limit of the method

and pruritus as the most common ones. Upon development of rash, the drug may be continued with the association of an antihistamine or exchange for another thiocarbamide.³ The reaction often resolves spontaneously.³ Our patient presented skin allergy after 30 days of MMI use, and MMI was then switched to PTU and dexchlorpheniramine until the day scheduled for surgery. The use of PTU was limited to a dose lower than the necessary to control hyperthyroidism since the patient presented allergy with an increased dose.

More severe reactions (vasculitis, hepatocellular injury, cholestatic jaundice, agranulocytosis) are rare and comprise definitive contraindications for ATD use.⁵ Close to the surgery date, the patient was admitted at HC/UFG with fever and tachycardia, and a normal hematological and hepatic evaluation. He evolved with pharyngotonsillitis on the second day, when PTU was then suspended. On the fourth day, he presented agranulocytosis (neutrophils 495/mm³) and thrombocytopenia.

Agranulocytosis induced by ATDs is defined as the occurrence of a granulocyte count <500/mm³ after use of ATDs.⁷ Fever, prostration, and odynophagia are common complaints, although hematopoietic damage may occur, even in asymptomatic patients.^{8,9} Our patient presented with febrile pharyngotonsillitis, one of the main clinical manifestations of ATD-induced agranulocytosis.

The incidence of ATD-induced agranulocytosis is 0.3-0.6%.^{3,8} Pancytopenia is 10 times less common.⁸ MMI was responsible for a minor side effect, while PTU caused a major severe adverse event in our pa-

tient. Some studies have shown that agranulocytosis is more likely to occur with PTU.⁵

With the use of ATD's, agranulocytosis occurs mainly within the first months, with high doses, intermittent use, and in elderly individuals; however, it may occur regardless of treatment duration or age.³ Our patient used low doses of antithyroid therapy irregularly for 5 months.

Agranulocytosis has a high mortality rate (2-10%).¹⁰ Factors indicating poor prognosis (age >65 years, pancytopenia, hepatic insufficiency, and renal failure)⁸ were not present in the described case.

ATDs can lead to neutrophil destruction by an immune mechanism and idiosyncrasy.¹¹ The presence of autoantibodies directed against granulocytes due to the interaction neutrophil-drug and antibodies against ATD can cause granulocyte destruction.⁸ However, the pathogenesis of ATD-induced neutropenia is not fully understood.¹¹ Development of hematopoietic damage may not be predetermined,^{8,12} although some studies have associated agranulocytosis with HLA-B*27:05 in Europe and HLA-B*38:02 and HLA-DRB1*08:03 in Asia.⁷

Management of agranulocytosis includes suspension of ATDs and antibiotics.⁹ G-CSF accelerates neutrophil recovery and is used when neutrophils are <500/mm³.¹³ Despite G-CSF use, mortality remains high.⁸ In the described case, PTU was discontinued and amoxicillin-clavulanate and G-CSF were initiated. Corticosteroids may have anti-inflammatory effects on hematopoietic cells recovery, but no consensus exists on their use in agranulocytosis.¹⁴ Recovery from agranulocytosis is defined as a granulocyte count ≥500/mm³. The mean time to hematologic recovery varies from 5 to 7 days.¹⁰ In our patient, agranulocytosis resolved within 2 days.

With a contraindication for the use of ATDs, RAI or surgery are therapeutic alternatives. RAI is used in patients with a high surgical risk, operated or irradiated neck, or with failure or contraindications to ATDs. Contraindications include pregnancy, lactation, suspected or coexisting thyroid cancer, active exophthalmos, and large goiter.⁵ RAI was not chosen in the described case because large goiters often do not decrease in size after RAI, in addition to a risk of hyperthyroidism decompensation immediately after the procedure in the absence of the possibility of use of ATDs for control.

Surgical treatment has the ultimate advantage of offering definitive control of hyperthyroidism and is

indicated in patients with large goiters (80 g),¹⁵ as in the case described. Other indications include failure or contraindications to ATDs and presence of suspect thyroid nodules.¹⁶ Contraindications include comorbidities with prohibitive surgical risk, final stage cancer, or lack of access to experienced surgeons.⁵

The proposed surgery was total thyroidectomy, aiming to avoid GD recurrence due to the severity and challenges of pharmacological and RAI treatment in the present case. The most common complications are hypoparathyroidism, recurrent or superior laryngeal nerve injury, and postoperative bleeding. No complications occurred in our patient. Levothyroxine was started at a dose of 1,6 µg/kg.⁵

Until the surgery date, beta-blocker was optimized, and glucocorticoid was introduced. Beta-blockers are an adjunct therapy in the symptomatic control of hyperthyroidism, attenuating the peripheral action of THs.¹⁷ Glucocorticoids inhibit the peripheral conversion of T4 into T3, but their side effects limit their chronic use.³ Potassium perchlorate has antithyroid action, preventing the concentration of iodine by the thyroid.³ Currently, it is no longer used due to toxicities, such as bone marrow depression.

Despite the use of propranolol and prednisone, the patient was unable to achieve adequate biochemical control of the hyperthyroidism and was prescribed lithium carbonate (LC) 1.200 mg/day and had prednisone switched for dexamethasone 8 mg/day.

LC may decrease TH levels.^{18,19} Rates of hypothyroidism vary from 0 to 47% during treatment with lithium²⁰ and, for this reason, lithium has been used as a second line of treatment drug for hyperthyroidism.²⁰ It concentrates on follicular thyroid cells, inhibits synthesis and release of hormones, decreases iodine uptake, and interferes with tyrosine iodination, thyroglobulin structure, and iodotyrosine coupling and inhibits peripheral deiodinases.²¹

The failure of LC treatment may be related to high levels of THs, the presence of TRAB, and thyroiditis.²⁰ Although these factors were present in our case, the patient had a good response to LC, beta-blocker, and glucocorticoid. This observation is corroborated by data in the literature showing improvement in TH levels in patients with GD after treatment for 36 weeks with LC 500 to 750 mg/day, associated or not with glucocorticoid and/or beta-blockers.²⁰

LC is safe to treat patients with preoperative hyperthyroidism when ATDs are contraindicated.²⁰ There are few cases in the literature describing the

use of lithium to treat thyrotoxicosis without planning for definitive treatment.²¹ Lithium salts may modulate granulocytopoiesis and are a beneficial option for patients with neutropenia induced by thioamides.²²

Another option for management of hyperthyroidism is cholestyramine, an adjuvant resin in lipid-lowering therapy.²³ It interferes with the endogenous absorption of THs, increasing their fecal excretion and decreasing their serum levels.^{24,25}

Cholestyramine associated with ATDs provides a faster decline in THs, normalizing their levels within 1 week of use.²⁶ Most studies suggest that the required dose of cholestyramine is 12 g/day divided into 2 to 4 doses for 4 weeks.^{23,25,26} However, the use of cholestyramine at a low dose (4 g/day) may also be effective in GD treatment.²⁴ Cholestyramine was not used in the present case due to unavailability. The use of this medication may be beneficial in thyrotoxic storm since 3,000 µg of T4 can bind to 50 mg of cholestyramine.²⁶

Lugol's solution was used in the preoperative management of our patient. Iodine is the oldest thyrostatic agent and reduces their secretion of THs by inhibition of cyclic AMP and organification.²⁷ Iodine at supraphysiological doses temporarily inhibits TH synthesis (Wolff-Chaikoff effect) for 10-14 days, with possible hyperthyroidism worsening after this period (Jod-Basedow effect).¹⁷ Prior to the introduction of ATDs, iodine was commonly used to treat hyperthyroidism. Current guidelines suggest the use of iodine associated with thioamide in the immediate preoperative preparation of patients with GD. This preparation is performed with administration of MMI or PTU until euthyroidism is obtained, then iodine is administered for 7-10 days before surgery.³

The therapeutic response to iodine begins within 2 to 7 days of use and induces involution of the gland, decreasing its vascularization.⁵ Iodine should be administered only when the patient is under the effect of ATD to avoid exacerbation of the thyrotoxicosis.³

Severe reactions to ATDs require another form of preoperative preparation, but no alternative is entirely satisfactory as the use of thioamides associated with iodine. One option is to use iodide and propranolol before surgery.²⁸ This preoperative preparation should only be used when ATDs are not an option and surgery is preferred to RAI treatment.²⁹

In view of the above, it should be emphasized that the clinical follow-up of patients using thioamides is important. These patients should be advised on signs and symptoms related to agranulocytosis,

as well as suspension of medication and medical care if they present with fever or odynophagia. With absolute contraindication to ATDs, thioamide-free regimens are required to control hyperthyroidism until definitive treatment. In the present case, the combined use of LC, propranolol, dexamethasone, and Lugol's solution presented good results for clinical and laboratory control until total thyroidectomy was performed, with a favorable outcome for the case.

RESUMO

INTRODUÇÃO: A doença de Graves (DG) é uma doença autoimune caracterizada por hipertireoidismo. As drogas antitireoidianas (DAT) são opções terapêuticas disponíveis. A agranulocitose é uma complicação rara, potencialmente fatal desta terapia. Neste estudo, relatamos um caso de agranulocitose induzida por propiltiouracil (PTU) em paciente com DG e as dificuldades do manejo clínico.

RELATO DE CASO: RNBA, sexo masculino, 30 anos, com DG, tratado com PTU. Evoluiu com faringoamigdalite, sendo o PTU suspenso e antibióticos, filgrastim, propranolol e prednisona, iniciados. Devido à descompensação do hipertireoidismo, iniciou carbonato de lítio (CL), dexametasona e a solução de Lugol. A tireoidectomia total (TT) foi realizada com boa evolução pós-operatória.

DISCUSSÃO: Descrevemos caso de paciente jovem, sexo masculino, com DG. Para o tratamento do hipertireoidismo, as tionamidas são opções efetivas. A agranulocitose induzida por DATs é uma complicação rara, definida como a ocorrência de contagem de granulócitos <500/mm³ após uso de dats. PTU foi suspenso e foram prescritos filgrastim e antibiótico. O radioiodo (RAI) ou a cirurgia são alternativas terapêuticas. Devido a problemas com o uso de DAT, a TT foi proposta. A preparação pré-operatória foi realizada com betabloqueador, glicocorticoide, CL e solução de Lugol. A colestiramina também é uma opção para controlar o hipertireoidismo. A TT foi realizada sem complicações pós-operatórias.

CONCLUSÃO: A agranulocitose induzida por drogas antitireoidianas é uma complicação rara. Com a contraindicação às DATs, RAI e cirurgia são opções terapêuticas definitivas para DG. Os betabloqueadores, glicocorticoides, CL, iodo e a colestiramina podem ser uma terapia adjuvante para o hipertireoidismo.

PALAVRAS-CHAVE: Doença de Graves. Propiltiouracila. Agranulocitose. Hipertireoidismo.

CONCLUSION

Thionamide-induced agranulocytosis is a rare complication, and its consequences can be minimized with an early diagnosis. Alerting the patient of the symptoms of this complication is fundamental. With a contraindication to ATDs, RAI and surgery are definitive therapeutic options in GD. Beta-blockers, glucocorticoids, LC, iodine, and cholestyramine may be an adjunctive therapy for hyperthyroidism in this context.

REFERENCES

- Chen PL, Shih SR, Wang PW, Lin YC, Chu CC, Lin JH, et al. Genetic determinants of antithyroid drug-induced agranulocytosis by human leukocyte antigen genotyping and genome-wide association study. *Nat Commun.* 2015;6:7633.
- DeGroot LJ, Quintans J. The causes of autoimmune thyroid disease. *Endocr Rev.* 1989;10(4):537-62.
- DeGroot LJ, New M, Rebar R, Singer F, Vinik A, Weickert MO. Diagnosis and treatment of Graves' disease. *Endotext.* South Dartmouth: MDText.com; 2012.
- Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, Chatterjee VK, et al. Influences of age, gender, smoking, and family history on autoimmune thyroid disease phenotype. *J Clin Endocrinol Metab.* 2006;91(12):4873-80.
- Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016;26(10):1343-421.
- Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. *Arch Intern Med.* 1990;150(3):621-4.
- Cheung CL, Sing CW, Tang CS, Cheng VK, Pirmohamed M, Choi CH, et al. HLA-B*38:02:01 predicts carbimazole/methimazole-induced agranulocytosis. *Clin Pharmacol Ther.* 2016;99(5):555-61.
- Chaudhry LA, Mauzen KF, Ba-Essa E, Robert AA. Antithyroid drug induced a granulocytosis: what still we need to learn? *Pan Afr Med J.* 2016;23:27.
- Andrès E, Weitten T, Mourot-Cottet R, Keller O, Zulfiqar AA, Serraj K, et al. Antithyroid agents related agranulocytosis: literature review. *Rev Med Interne.* 2016;37(8):544-50.
- Mourot-Cottet R, Maloisel, F, Séverac, F, Keller O, Vogel T, Tebacher M, et al. Idiosyncratic drug-induced severe neutropenia and agranulocytosis in elderly patients (≥75 years): a monocentric cohort study of 61 cases. *Drugs Real World Outcomes.* 2016;3(4):393-9.
- Ferreira AL, Rocha CP, Vieira LM, Dusse LMS, Junqueira DRG, Carvalho MG. Alterações hematológicas induzidas por medicamentos convencionais e alternativos. *Rev Bras Farm.* 2013;94(2):94-101.
- Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. *J Clin Endocrinol Metab.* 2013;98(12):4776-83.
- Fukata S, Kuma K, Sugawara M. Granulocyte colony-stimulating factor (G-CSF) does not improve recovery from antithyroid drug-induced agranulocytosis: a prospective study. *Thyroid.* 1999;9(1):29-31.
- Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: how has granulocyte colony-stimulating factor changed therapy? *Thyroid.* 2005;15(3):292-7.
- Palit TK, Miller CC 3rd, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. *J Surg Res.* 2000;90(2):161-5.

16. Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, et al. Surgical treatment of Graves' disease: subtotal or total thyroidectomy? *Surgery*. 1996;120(6):1020-4.
17. Fischli S, Lucchini B, Müller W, Slahor L, Henzen C. Rapid preoperative blockage of thyroid hormone production / secretion in patients with Graves' disease. *Swiss Med Wkly*. 2016;146:w14243.
18. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. *J Clin Psychiatry*. 1998;59(Suppl 6):13-9.
19. Parker PE, Walter-Ryan WG, Pittman CS, Folks DG. Lithium treatment of hyperthyroidism and mania. *J Clin Psychiatry*. 1986;47(5):264-6.
20. Zheng R, Liu K, Chen K, Cao W, Cao L, Zhang H, et al. Lithium carbonate in the treatment of Graves' disease with ATD-induced hepatic injury or leukopenia. *Int J Endocrinol*. 2015;2015:694023.
21. Prakash I, Nylen ES, Sen S. Lithium as an alternative option in Graves thyrotoxicosis. *Case Rep Endocrinol*. 2015;2015:869343.
22. Petrini M, Azzarà A. Lithium in the treatment of neutropenia. *Curr Opin Hematol*. 2012;19(1):52-7.
23. Alswat KA. Role of cholestyramine in refractory hyperthyroidism: a case report and literature review. *Am J Case Rep*. 2015;16:486-90.
24. Kaykhaei MA, Shams M, Sadegholvad A, Dabbaghmanesh MH, Omrani GR. Low doses of cholestyramine in the treatment of hyperthyroidism. *Endocrine*. 2008;34(1-3):52-5.
25. Ha J, Jo K, Kang B, Kim MH, Lim DJ. Cholestyramine use for rapid reversion to euthyroid states in patients with thyrotoxicosis. *Endocrinol Metab (Seoul)*. 2016;31(3):476-9.
26. Lin D, Suwantarat N, Bornemann M. Cholestyramine for thyrotoxicosis? *J Fam Pract*. 2013;62(4):E1-2.
27. Erbil Y, Ozluk Y, Giriş M, Salmaslioglu A, Issever H, Barbaros U, et al. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. *J Clin Endocrinol Metab*. 2007;92(6):2182-9.
28. Feek CM, Sawers JS, Irvine WJ, Beckett GJ, Ratcliffe WA, Toft AD. Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. *N Engl J Med*. 1980;302(16):883-5.
29. Sundaresh V, Brito JP, Wang Z, Prokop LJ, Stan MN, Murad MH, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2013;98(9):3671-7.

