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Mestrado e Doutorado

Efeito do Metimazol na Eficácia do Tratamento com Iodo Radiativo e nos Níveis Séricos do TRAb na Doença de Graves

Vânia Araújo Andrade

Orientadora: Profa. Dra. Ana Luiza Maia

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Vânia Araújo Andrade

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Este Trabalho é dedicado

A minha filha Vanessa, versão melhorada de mim.

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Novos Aspectos do Tratamento da Doença de Graves

Vânia Araújo Andrade, Jorge Luiz Gross, Ana Luiza Maia.

Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brasil

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Correspondência: Ana Luiza Maia

Serviço de Endocrinologia

Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos 2350

90035 –003 Porto Alegre, RS, Brasil

Phone: 55-51-316-8127; Fax: 55-51-332-5188; E-mail: almaia@vortex.ufrgs.br

RESUMO

O hipertireoidismo da doença de Graves é a forma mais comum de hipertireoidismo em pacientes entre 20-50 anos. Três abordagens terapêuticas são atualmente utilizadas, drogas antitireoidiana, cirurgia e iodo radioativo (^{131}I). O iodo radioativo tem sido cada vez mais aceito como primeira escolha terapêutica, porque é um tratamento seguro, definitivo e de fácil administração. O risco de piora do quadro de tireotoxicose após administração do ^{131}I, os fatores prognósticos de falência e o cálculo da dose administrada têm sido alguns dos aspectos discutidos na literatura recentemente, e constituem o foco desta artigo. Em pacientes com bócios pequenos (<30g), crianças e adolescentes, e em situações especiais como na gravidez, as drogas antitireoidianas ainda é a primeira escolha no tratamento para a maioria dos autores. O tratamento cirúrgico é, atualmente, quase um tratamento de exceção, com indicação restrita para os casos em que as terapias anteriores não possam ser utilizadas.

Unitermos: Doença de Graves, hipertireoidismo, drogas antitireoidianas, iodo radioativo.

ABSTRACT

Graves' disease is the most frequent cause of hyperthyroidism and current treatment options are antithyroid drugs, radioiodine (^{131}I) and surgery. Radioactive iodine is increasingly being used as definitive therapy, because it long has proven to be a safe, cheap and effective treatment. The risk of exacerbation of hyperthyroidism after ^{131}I administration, factors that may predict the response to radioiodine and the dose to be administrated have been discussed in the literature and we comment the controversies in this review. In patients with mild disease, small goiters, children, adolescents and in special situations, as pregnancy, antityhyroid drugs are still the first choice of treatment for most authors. Surgery is rarely employed, and it is indicated only in cases where antithyroid drugs have not been effective and radioiodine is contraindicated or not acceptable by the patients.

Keywords: Graves' disease, hyperthyroidism, antithyroid drugs, radioactive iodine.

INTRODUÇÃO

O hipertireoidismo da doença de Graves, a causa mais comum de hipertireoidismo entre 20-50 anos, é caracterizado por infiltração linfocitária da glândula tireóide e ativação do sistema imune com elevação dos linfócitos T circulantes, aparecimento de autoanticorpos que se ligam ao receptor do TSH (TRAb) e que estimulam o crescimento e a função glandular (1-3). Do ponto de vista clínico, a doença de Graves caracteriza-se por aumento difuso e hiperatividade da glândula tireóide, associada ou não a oftalmopatia infiltrativa e, mais raramente, ao mixedema localizado (4).

O excesso de hormônios tireoidianos é responsável por diversos efeitos deletérios em múltiplos orgãos, principalmente no sistema cardiovascular e ósseo. Esses hormônios têm efeitos cardioestimulatórios, causando aumento da freqüência cardíaca, pressão arterial sistólica (1/3 dos casos) e da massa e contração ventricular esquerda (5,6). O quadro de tireotoxicose pode levar ao desenvolvimento de complicações graves como insuficiência cardíaca congestiva, cardiomiopatia e arritmias, principalmente fibrilação atrial (10-30%) (7,8). O hipertireoidismo também está associado ao aumento da reabsorção óssea, elevação da excreção de cálcio e fósforo na urina e fezes, com conseqüente diminuição na densidade mineral óssea e risco de fraturas em mulheres idosas (9,10). De acordo, estudos de base populacional demonstram que pacientes com hipertireoidismo apresentaram maior risco de mortalidade devido a doenças cerebrovasculares, cardiovasculares e fraturas do colo do fêmur (11).

As opções terapêuticas utilizadas no tratamento do hipertireoidismo de Graves são as drogas antitireoidianas (DAT), a cirurgia e o iodo radioativo (^{131}I). Nenhuma delas é considerada ideal, visto que não atuam diretamente etiologia/patogênese da disfunção (12). A escolha do tratamento é influenciada por fatores, como idade do paciente, volume da tireóide, severidade do hipertireoidismo, preferência do paciente e do médico, recursos disponíveis e prática médica local (12). De acordo, o tratamento de primeira escolha difere entre os diferentes países ou regiões. Nos EUA 69% dos membros da American Thyroid Association (ATA), utilizam ^{131}I como primeira escolha (13), enquanto no Japão e na Europa, a primeira opção são as drogas antitireoidianas para os membros da European Thyroid Association (ETA) e da Japan Thyroid Association (JTA) (77% e 88%, respectivamente) (14). Na América do Sul, a utilização das drogas antitireoidianas constitui a primeira escolha para 73% dos membros da Sociedade Latino Americana de Tireóide (SLAT), sendo o ^{131}I a primeira opção para 26% desses profissionais (15).

IODO RADIOATIVO

O iodo radioativo foi empregado pela primeira vez em 1941 no Massachussets General Hospital, quando Hertz e Roberts trataram pacientes com hipertireoidismo. Esta forma de tratamento já vem sendo utilizada há quase 60 anos. O ^{131}I é um tratamento seguro, de fácil administração, efeito rápido e de baixo custo. A administração do ^{131}I causa uma tireoidite intensa secundária à radiação, seguida de fibrose intersticial progressiva e atrofia glandular, resultando em destruição da capacidade de síntese da glândula tireóide (35). Alguns estudos demonstram também que o tratamento com iodo radioativo pode induzir a alterações de resposta imune aos antígenos tireoidianos (36).

A indução de hipotireoidismo iatrogênico transitório ou permanente, é praticamente o único efeito colateral significativo do tratamento com iodo radioativo (37,38). Ward e cols. (34), em estudo comparativo entre custo de tratamento com drogas antitireoidianas, radioterapia com ^{131}I ou cirurgia, demonstraram que o tratamento com ^{131}I apresenta menor custo, melhores índices custo/eficácia e custo/efetividade, tanto em pacientes privados como no sistema público. No nosso serviço, o número de visitas médicas dos pacientes tratados com iodo radioativo foi de apenas 3±1, significativamente menor do que a média dos pacientes que receberam tratamento prévio com drogas antitireoidianas, 12 ± 4 (p<0,0)1)(53). O uso do isso apresenta ainda como vantagem a redução do volume glandular, dose dependente, observada no primeiro ano de tratamento (39).

Modo de Administração vs Eficácia da Radioiodoterapia

Não existe consenso sobre a melhor forma de administração do ^{131}I (40). Os esquemas terapêuticos são múltiplos, com variação da dose (50-300 μCi/g de tecido tireoidiano) ou associação com drogas antitireoidianas utilizadas antes, durante ou após o ^{131}I (41-45). Estudos comparando doses variadas de ^{131}I demonstraram que doses reduzidas estão associadas a menor incidência de hipotireoidismo, porém às custas de menor taxa de cura do hipertireoidismo e que doses altas do radioisótopo aumentam a incidência do hipotireoidismo (46).

A associação de drogas antitireoidianas e ^{131}I tem sido utilizada por cerca de 20-40% dos tireoidologistas americanos (13) e por 44.5% dos membros da SLAT (15). A principal razão para o tratamento prévio com drogas antitireoidianas seria a redução da quantidade de hormônios armazenados na tireóide e a liberação dos mesmos na circulação com o uso do ^{131}I, evitando o quadro de exacerbação do hipertireoidismo

conseqüente à tireoidite provocada pela radiação, ou mesmo a denominada “tempestade tireoidiana” (47). No entanto, uma criteriosa revisão da literatura nos mostra que os dados disponíveis sobre o tema são discordantes (48), alguns estudos evidenciando elevação (49), outros redução (50,51) ou mesmo não modificação nos níveis séricos dos hormônios tireoidianos após o tratamento (52).

O efeito do pré-tratamento com drogas antitireoidianas nos níveis séricos dos hormônios tireoidianos após administração do ^{131}I foi avaliado recentemente em estudo realizado no nosso Serviço (24) e concluímos que a interrupção do metimazol é responsável por aumento significativo das concentrações plasmáticas dos hormônios tireoidianos e que após administração de ^{131}I ocorre estabilização ou redução dos níveis séricos desses hormônios. De modo interessante, os pacientes tratados apenas com ^{131}I apresentaram melhora clínica significativa já a partir do segundo dia após uso do radioisótopo, avaliada através da aplicação do índice terapêutico de Wayne (53), que pode talvez ser explicada em parte pela diminuição dos níveis de T_3, fração hormonal que apresentou uma correlação quase perfeita com a sintomatologia clínica (figura 1) (24). Outra observação importante do estudo foi que, apesar da elevação dos níveis hormonais após a suspensão do metimazol nos pacientes que receberam pré-tratamento, houve estabilização ou declínio desses hormônios após a administração do ^{131}I, indicando não haver necessidade da reintrodução do medicamento (24).

Na discussão sobre a necessidade ou não da utilização prévia das drogas antitireoidianas no tratamento com ^{131}I, um aspecto importante a ser considerado é que, embora os pacientes tratados somente com ^{131}I tenham apresentado reduções dos níveis séricos dos hormônios tireoidianos, esses valores permaneceram significativamente mais elevados durante todo o período de acompanhamento, quando comparados com o grupo de pacientes previamente tratados com drogas antitireoidianas (24). Essa situação pode significar uma potencial desvantagem do tratamento com ^{131}I isolado, principalmente para pacientes com maior risco de complicações, como idosos e cardiopatas. Contudo, deve ser também considerado a necessidade de uso prolongado das drogas antitireoidianas para alcançar o eutireoidismo e da elevada taxa de abandono ao tratamento com drogas antitireoidianas. A elevação abrupta dos hormônios tireoidianos livres, que ocorre como conseqüência da suspensão das DAT também pode exacerbar o hipertireoidismo e aumentar o risco de complicações como tempestade tireoidiana (51). De modo geral, o emprego do ^{131}I em pacientes com hipertireoidismo de Graves sem uso prévio de drogas antitireoidianas pode representar uma alternativa de tratamento eficaz, pois tem desfecho

previsível, reduz a freqüência das consultas médicas e custo do tratamento, evita a elevada taxa de abandono ao tratamento clínico, além de evitar a exposição dos pacientes ao risco adicional dos efeitos colaterais das drogas antitireoidianas.

Vários fatores prognósticos têm sido associados com falência ao tratamento com ^{131}I, como bócio volumoso, não redução do bócio após a administração do radioisótopo, níveis basais de anticorpos elevados, associação com DAT (41-45). Recentemente demonstramos que pacientes com bócios volumosos (>50g), captação do ^{131}I em 24hs. >90% e/ou níveis séricos basais de T_3 >500ng/ml, apresentam taxas de falência ao tratamento com ^{131}I bem maiores que pacientes sem essas características (54).

A possibilidade do uso prévio das drogas antitireoidianas modificar a eficácia do tratamento com ^{131}I é um outro ponto controverso na literatura. Esses agentes inibem a organificação do iodo radioativo, reduzem a formação de radicais livres de O_2 pelas células mononucleares ativadas e podem limitar a eficácia do tratamento com ^{131}I (55). Vários trabalhos referidos na literatura exibem resultados discordantes, alguns concluindo que a eficácia do tratamento não é modificada (41), enquanto outros estudos evidenciam maior falência ao tratamento atribuída à radioresistência ao ^{131}I induzida pelas drogas antitireoidianas (42,43). Em recente estudo clínico, randomizado, avaliando 2 grupos de pacientes com hipertireoidismo de Graves, tratados apenas com ^{131}I ou previamente tratados com MMI, verificamos que não houve diferenças entre os grupos com relação às taxas de persistência de hipertireoidismo (15.6% *vs.* 13.8%), eutireoidismo (28.1% *vs.* 31.0%) ou hipotireoidismo (56.3% *vs*. 55.2%) após 1 ano de seguimento, indicando que o uso prévio de MMI não interfere na eficácia do tratamento com ^{131}I (54) (Figura 2). A taxa de cura 3 meses após ^{131}I, independente do paciente ter recebido ou não pré-tratamento, foi de aproximadamente 80%, sendo que 90% dos pacientes curados com dose única de ^{131}I, responderam nesse período. Esses resultados, no entanto, talvez não possam ser aplicados quando o propiltiouracil for a droga escolhida. Imseis e cols. (56) comparando o uso do propiltiouracil e do metimazol na eficácia do tratamento com ^{131}I demonstraram que a redução da eficácia do radioisótopo ocorre apenas nos pacientes tratados com propiltiouracil, devido, talvez, à permanência mais prolongada dessa droga na tireóide quando comparada com o metimazol.

O uso simultâneo de ^{131}I e de DAT parece reduzir de modo significativo a taxa de cura do hipertireoidismo. Sabri e cols. (44) realizaram um estudo envolvendo 207 pacientes tratados apenas com ^{131}I ou simultaneamente tratados com carbimazole e demonstraram que pacientes que utilizaram carbimazole apresentaram maior falência ao

radioisótopo. O menor sucesso do tratamento simultâneo foi verificado apesar da utilização de dose mais elevada do radioisótopo, para correção da menor captação e meia vida do ^{131}I relacionados com uso da medicação. Outros estudos têm demonstrado que a utilização de DAT após ^{131}I também pode reduzir a eficácia do tratamento (45).

As contra-indicações ao tratamento com ^{131}I incluem pacientes grávidas ou lactantes, níveis baixos da captação de ^{131}I, presença de nódulo tireoidiano maligno ou suspeito de malignidade.

Efeitos Colaterais

O tratamento com ^{131}I apresenta como principal efeito colateral uma alta incidência de hipotireoidismo permanente, cuja freqüência no primeiro ano de tratamento varia de acordo com a dose de ^{131}I administrada (46), enquanto que a incidência posterior (3% ao ano) depende de fatores imunológicos (57), da associação ou não com drogas antitireoidianas (41-45), tamanho do bócio, radiosensibilidade individual, homogeneidade da distribuição de iodo na glândula tireóide e duração do seguimento dos pacientes tratados (58). Hipotireoidismo transitório pode ocorrer no período de 2 a 5 meses após o uso do radioisótopo (9-58% dos casos) (37).

Estima-se que mais de 2 milhões de pacientes com a Doença de Graves já foram tratados com ^{131}I, sem evidências de elevação da freqüência de defeitos congênitos em crianças cujos pais realizaram esta forma de tratamento (59). A Comissão Internacional de Proteção Radiológica estima que o risco de dano genético associado com exposição ao tratamento com ^{131}I é de aproximadamente 0,005%, considerado menor que o risco espontâneo de tais anormalidades (59). O tratamento com iodo radioativo parece não afetar a fertilidade e doses de irradiação gonadal relacionadas com o tratamento (máximo de 3 rads) são similares ou menores que as doses utilizadas durante a realização de tomografia computadorizada de abdome, pielografia endovenosa ou enema baritado (60). Quanto à preocupação com a possibilidade do tratamento induzir carcinogênese, não existem evidências de haver aumento de risco de leucemia (61), câncer da tireóide ou outras malignidades (62,63). Os estudos prévios que observaram um possível aumento de risco de câncer de estômago e câncer de mama, após 10 e 30 anos de tratamento, respectivamente, são criticados pela ausência de grupos controles, delineamento retrospectivo e/ou não randomizados (64). Recentemente Franklyn e cols. (65), em estudo populacional envolvendo 7417 pacientes com hipertireoidismo tratados com ^{131}I, demonstraram uma redução na incidência e mortalidade por câncer em geral, com pequeno aumento de risco de câncer de tireóide e intestino delgado. Entretanto como não

houve relação entre essas neoplasias e dose de ^{131}I utilizada, tempo ou idade de tratamento, os autores sugerem que esse achado pode estar associados à tireotoxicose e não com exposição ao ^{131}I.

Um dos aspectos mais controversos do uso do iodo radioativo seria a possibilidade de desencadear ou interferir na evolução da oftalmopatia pré-existente (66,67). Outros autores, no entanto, observaram que o ^{131}I não influencia (68) ou que pode até melhorar a oftalmopatia pré-existente (66). Recentes estudos bem conduzidos, sugerem que a piora da oftalmopatia relacionada ao tratamento é transitória e pode ser prevenida pelo uso concomitante de glicocórticoides (69).

DROGAS ANTITIREOIDIANAS

Propiltiouracil e metimazol são as drogas utilizadas no tratamento da doença de Graves há mais de 60 anos (16). Esses compostos, pertencentes à classe das tionamidas, têm como mecanismo de ação primário a redução da síntese de T3 e T4 nas células foliculares (17). Embora ainda controverso, postula-se que as DAT também apresentem uma ação na autoimunidade (17,18). O propiltiouracill (PTU) apresenta um mecanismo de ação adicional que consiste na redução da conversão de T4 para T3, através da inibição da deiodinase tipo 1, presente nos tecidos periféricos e na tireóide (17).

A escolha das DAT depende da preferência e experiência do médico assistente. O uso do metimazol (MMI) apresenta a grande vantagem da dose única diária (19), os efeitos colaterais são dose dependentes (raros com dose <20mg/dia) (20) e hepatotoxicidade menos grave (20). Alguns autores sugerem que o PTU deve ser a droga de escolha na gravidez e na lactação, porque atravessa menos a barreira placentária e é encontrada em menor quantidade no leite materno que o MMI (21). Outros autores, no entanto, questionam as restrições ao uso do MMI, porque os estudos não demonstram efeitos indesejáveis para o feto, exceto, talvez, pela aplasia cutis (17,22,23). O PTU deve ser a droga de escolha no tratamento do hipertireoidismo grave ou tempestade tireoidiana, visto que em altas doses inibe a conversão de T4 para T3 (17). Pacientes que utilizam doses mais elevadas apresentam resposta mais rápida ao tratamento (16). Na nossa experiência, praticamente todos os pacientes evoluem para eutireoidismo dentro de 6 a 12 semanas após início do tratamento com metimazol (30mg/dia) (24).

A mais importante decisão terapêutica na escolha das DAT como tratamento de primeira escolha, deve ser a probabilidade de remissão da doença. Estudos prévios demonstraram que 40% a 50% dos pacientes tratados com DAT apresentaram remissão da doença (eutireoidismo bioquímico após 1 ano de suspensão da medicação) (16). Dados sobre chance de remissão em pacientes do sexo masculino, jovens, tabagistas ou com bócios volumosos são controversos (25,26), entretanto a maioria dos estudos mostra que níveis muito elevados de T3 se associam com maior chance de recidiva da doença (27). O uso de doses mais elevadas das DAT, embora levem ao controle mais rápido da tireotoxicose, parece não elevar a chance de remissão, aumentando, no entanto, a incidência de efeitos colaterais (28). Outros pontos controversos referem-se à taxa de remissão relacionada aos níveis basais baixos de TRAb ou diminuição desses anticorpos após suspensão das DAT (29). O papel de outros fatores possivelmente relacionados à taxa de cura com DAT, como duração do tratamento (30) e quantidade de iodo ingerido (31) também ainda são questionáveis. A grande desvantagem do uso das DAT são os efeitos colaterais, presentes em até 7% dos pacientes, alguns potencialmente fatais como a hepatite tóxica e agranulocitose (32,33). Além disso, a aderência dos pacientes ao uso das drogas antitireoidianas é baixa e a taxa de abandono (40-68%) reduz a efetividade do tratamento (34).

Apesar das controvérsias na literatura, é razoável supor que pacientes com bócios volumosos, aumento da razão T3/T4 e níveis de T3 acima de 500 ng/dL, apresentem menor chance de remissão da doença após uso de DAT, e, nesses casos, o tratamento definitivo deve ser considerado como primeira escolha. Os candidatos ideais para tratamento com DAT seriam pacientes com doença leve e bócios pequenos, crianças e adolescentes (17).

Tratamento Cirúrgico do Hipertireoidismo de Graves

A terapia cirúrgica tem indicações bem limitadas na doença de Graves, sendo considerado quase que um tratamento de exceção atualmente. Embora associado a maior probabilidade de eutireoidismo a longo prazo (70), apresenta como principal desvantagem o risco de complicações cirúrgicas, diretamente relacionadas com a experiência do cirurgião que realiza o procedimento. Essa modalidade de tratamento é preferida por apenas 1,3% dos profissionais membros da SLAT (15).

De acordo com a literatura, essa modalidade de tratamento seria indicada a crianças e gestantes que apresentem efeitos colaterais às medicações antitireoidianas ou

que não apresentem aderência ao tratamento, pacientes com bócios volumosos ou que desejam tratamento definitivo e recusam o uso do iodo radioativo (16).

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REFERÊNCIAS BIBLIOGRÁFICAS

1. Jacobson D.L, Gange S.J, Rose N.R., Graham N.M. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997; 84:223-43.
2. Tunbridge WMG, Evered DC, Hall R. The spectrum of thyroid disease in a community: the Wickham Survey. Clin Endocrinol 1977; 7:481-93.
3. Paschke R, Ludgate M. The thyrotropin receptor in thyroid diseases. N Engl J Med 1997; 337:1675-81.
4. Dabon-Almirante C.L., Surks M.I. Clinical and laboratory diagnosis of thyrotoxicosis. Endocrinol Metab Clin North Am 1998; 27:25-35.
5. Klein I, Ojama K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344:501-09.
6. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation 1993; 87:1435-41.
7. Koshiyama H, Sellitti D. F., Akamizu T, Doi S. Q , Takeuchi Y, Inoue D. et al. Cardiomyopathy associated with Graves'disease. Clin Endocrinol 1996; 45:111-16.
8. Gross J.L., Caramori M.L., Ribeiro J.P. Hipertireoidismo com fibrilação atrial: é necessário anticoagular todos os pacientes? Arq Bras Endocrinol Metab 1996; 40: 54-7.
9. Franklin J, Betterridge J, Holder R, Daykin J, Lilley J and Sheppard M. Bone mineral density in thyroxine treated females with or without a previous history of thyrotoxicosis. Clin Endocrinol 1994; 41:425-32.
10. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE et al. Risk factors for hip fracture in white women. N Engl J Med 1995; 332:767-73.
11. Franklyn J.A, Maisonneuve P., Sheppard M.C., Betteridge J.and Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. N Engl J Med 1998; 338:712-8.
12. Singer P.A., Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995; 273:808-12.
13. Solomon B, Glinoer D, Lagasse R, and Wartofsky L. Current trends in the management of Graves' disease. J Clin Endocrinol Metab 1990; 70:1518-24.

14. Wartofsky L, Glinoer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. Thyroid 1991; 1:129-35.
15. Romaldini J.H. Case selection and restrictions recommended to patients with hyperthyroidism in South America. Thyroid 1997; 7:225-28.
16. Cooper D.S. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. Endocrinol Metab Clin North Am 1998; 27:225-47.
17. Weetman A P. Graves' Disease. N Engl J Med 2000;343:1236-48.
18. Volpé R. Evidence that the immunosuppressive effects of antithyroid drugs are mediated through actions on the thyroid cell, modulating thyrocyte-immunocyte signaling: a rewiew. Thyroid 1994; 4:217-23.
19. Nicholas W.C., Fischer R.G., Steveseon R.A., Bass J. D. Single daily dose of methimazole compared to every 8 hours propylthiouracil in the treatment of hyperthyroidism. South Med J 1995; 88:973-76.
20. Cooper D.S. Which anti-thyroid drug? Am J Med 1986; 80:1165-68.
21. Cooper DS. Antithyroid drugs: to breastfeed or not to breastfeed. AM J Obstet Gynecol 1987; 157:234-5.
22. Momotani N, Noh Jy, Isikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. J Clin Endocrinol Metab 1997; 82:3633-6.
23. Wing DA., Miller LK, Koonings PP, Montoro NM, Mestman JH. A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. Am J Obstet Gynecol 1994; 170:90-5.
24. Andrade V. A, Gross J. L. and Maia A. L. Effect of methimazole pretreatment on serum thyroid hormone levels after radioactive treatment in Graves' hyperthyroidism. J Clin Endocrinol Metab 1999; 84:4012-16.
25. Vitti P, Rago T, Chiovato L. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid 1997;7:369-75.
26. Benker G., Vitti P, Kahaly G, Raue F, Tegler L, Hirche H et al. Response to methimazole in Graves' disease. Clin Endocrinol 1995; 43:25-63.
27. Young ET, Steel NR, Taylor JJ, Stephenson AM, Stratton A, Holcombe M et al. Prediction of remission after antithyroid drug treatment in Graves' disease. Q J Med 1988; 250:175-89.

28. Reinwein D., Benker G., Lazarus J.H., Alexander W.D., and the European Multicenter Study Group on antithyroid drug treatment. A prospective randomized trial of antithyroid drug dose in Graves' disease therapy. J Clin Endocrinol Metab 1993; 76:1516-21.
29. Feldt-Rasmussen U, Schleusener H, Carayon P. Meta-analyses evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. J Clin Endocrinol Metab 1994; 78:98.
30. Allanic H, Fauchet R, Orgiazzi J, Madec AM, Genetet B, Lorcy Y. et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 1990; 70:675-79.
31. Solomon B.L., Evaul J.E., Burman K. D. and Wartofsky L. Remission rates with antithyroid drug therapy: continuing influence of iodine intake? Ann Intern Med 1987; 107:510-12.
32. Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid Drug-Induced Agranulocytosis. The Usefulness of Routine White Blood Cell Count Monitoring. Arch Inter Med 1990;150: 621-24.
33. Williams KV, Nayak S, Becker D, Reyes I, Burmeister LA. Fifty years of experience with propylthiouracil associated hepatotoxicity: what have we learned? J Clin Endocrinol Metab 1997; 82:1727-33.
34. Ward L.S., Filho AC., Menabó E., Ribeiro SRR., Lima MC., Maciel R.M.B. Estudo da relação custo/efetividade no tratamento da doença de Basedow-Graves. Rev Ass Med Brasil 1986; 32:147-54.
35. Dobyns BM, Vickery AL, Maloof F, Chapman EM. Functional and histologic effects of therapeutic doses of radioactive iodine on the thyroid of man. J Clin Endocrinol Metab 1953; 13:548.
36. DeGroot L. J. Radioiodine and the immune system. Thyroid 1997:7:259-63.
37. Aizawa Y., Yoshida K, Kaise N, Fukazawa H, Kiso Y, Sayama N et al. The development of transient hypothyroidism after iodine-131 treatment in hyperthyroid patients with Graves' disease: prevalence, mechanism and prognosis. Clin Endocrinol 1997; 46:1-5
38. Cunnien A.J., Hay I.D., Gorman C.A., Offord K.P. and Scalon P.W. Radioiodine-induced hypothyroidism in Graves' disease: factors associated with the increasing incidence. J Nucl Med 1982; 23:978-83.

39. Peters H., Fischer C., Bogner U., Reiners C., Schleusener H. Reduction in thyroid volume after radioiodine therapy of Graves' hyperthyroidism: results of a prospective, randomized, multicentre study. Eur J Clin Invest 1996; 26:59-63.
40. Jarlov AE, Hegedüs L., Kristensen L., Nygaard B. and Hansen JM. Is calculation of the dose in radioiodine therapy of hyperthyroidism worth while? Clin Endocrinol 1995; 43:325-29.
41. Marcocci C., Gianchecchi D, Masini I, Golia F, Ceccarelli C, Bracci E et al. A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. J Endocrinol Invest 1990; 13:513-20.
42. Tuttle RM, Patience T, Budd S. Treatment with propyltiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995, 5:243-47.
43. Hancock L., Tuttle M., LeMar H., Bauman J., and Patience T. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves' disease. Clin Endocrinol 1997; 47:425-30.
44. Sabri O., Zimny M, Schulz G, Schreckenberger M, Reinartz P, Willmes K et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab 1999; 84:1229-33.
45. Velkeniers B., Vanhaelst L., Cytryn R., Jonckheer M.H. Treatment of hyperthyroidism with radioiodine: adjunctive therapy with antithyroid drugs reconsidered. Lancet 1988:1127-29.
46. Sridama V, McCormick M, Kaplan E L, Fauchet R, DeGroot L J. Long-term follow-up study of compensated low-dose ^{131}I therapy for Graves'disease. N Engl J Med 1984; 311:426-32.
47. Perros P. Anti-thyroid drug treatment before radioiodine in patients with Graves' disease: soother or menace? Clin Endocrinol 2000; 53:1-2.
48. McDermott MT, Kidd GS, Dodson LE, Hofeldt FD. Radioiodine-induced thyroid storm. Case report and literature review. Am J Med 1983; 75:353-59.
49. Shafer RB, Nuttall FQ. Acute changes in thyroid function in patients treated with radioactive iodine. Lancet 1975; 2:635-7.
50. Wise PH, Burnet RB, Ahmad A, Harding PE. Intentional radioiodine ablation in Graves' disease. Lancet 1975; 231-33.

51. Burch H.B., Solomon B.L., Wartofsky L.and Burman K D. Discontinuing antithyroid drug therapy before ablation with radioiodine in Graves' disease. Ann Inter Med 1994; 121: 553-59.
52. Tamagna E.I., Levine GA and Hershman J.M. Thyroid hormone concentrations after radioiodine therapy for hyperthyroidism. J Nucl Med 1979; 20:387-91.
53. Wayne E.J. Clinical and metabolic studies in thyroid disease. Br Med J 1960; 5165-172.
54. Andrade V.A, Gross J.L. and Maia AL.The Effect of Methimazole Pretreatment on the Efficacy of Radioactive Iodine Therapy in Graves' Hyperthyroidism: One-Year Follow-Up of a Prospective, Randomized Study. J Clin Endocrinol Metab 2001; 86:3488-93.
55. Weetman A.P., Holt M. E., Campbell A.K., Hall R., McGregor A.M. Methimazole and generation of oxygen radicals by monocytes: potential role in immunosuppression. Br Med J 1984; 288:518-20.
56. Imseis R.E, Vanmiddlesworth L., Massie J.D, Bush AJ and Vanmiddlesworth NR. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab 1998; 83:685-87.
57. Chiovato L., Fiore E, Vitti P, Rocchi R, Rago T, Dokic D et al. Outcome of thyroid function in Graves' patients treated with radioiodine: role of thyroid-stimulating and thyrotropin-blocking antibodies and of radioiodine-induced thyroid damage. J Clin Endocrinol Metab 1998; 83:40-46.
58. Tsuruta M., Nagayama Y., Yokoyama N., Izumi M., and Nagataki S. Long-term follow-up studies on iodine-131 treatment of hyperthyroid Graves' disease based on the measurement of thyroid volume by ultrasonography. Ann Nucl Med 1993; 7:193-97.
59. Graham G.D., Burman K.D. Radioiodine treatment for Graves' disease. An assessment of its potential risks. Ann Intern Med 1986; 105:900-05.
60. Robertson J.S and Gorman C.A. Gonadal radiation dose and its genetic significance in radioiodine therapy of hyperthyroidism. J Nucl Med 1976; 17:826-35.
61. Hall P., Bjelkengren G., Lidberg M, Tennvall J, Boice J.D., Ericsson U-B et al. Leukemia incidence after iodine-131 exposure. Lancet 1992;340:1-4.

62. Ron E., Doody M.M., Becker D. V., Brill B., Curtis R.E., Goldman M.B. et al. Cancer mortality following treatment for adult hyperthyroidism. JAMA 1998; 280:347-55.
63. Hall P. and Holm L-E. Late consequences of radioiodine for diagnosis and therapy in Sweden. Thyroid 1997; 7:205-8.
64. Goldman MB., Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC. Radioactive iodine therapy and breast cancer:a follow-up study of hyperthyroid women. Am J Epidemiol 1988;127:969-80
65. Franklin JA, Maisonneuve P., Sheppard M. Betterridge J. and Boyle P. Cancer incidence and mortality after radioiodine treatment for hyperthyroidismi: a population- based cohort study. Lancet 1999; 353:2111-15.
66. DeGroot L.J., Gorman C A, Pinchera A, Bartalena L, Marocci C, Wiersinga WM, et al. Radiation and Graves' ophthalmopathy. J Clin Endocrinol Metab 1995; 80:339-49.
67. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998; 338:73-78.
68. Manso P. G., Furlanetto R.P., Wolosker A M, Paiva E. R, Abreu M.T. and Maciel R.M.B. Prospective and controlled study of ophthalmopathy after radioiodine therapy for Graves' hyperthyroidism. Thyroid 1998; 8:49-52.
69. Bartalena L., Maracocci C., Bogazzi F., Panicucci M.Lepri A. and Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med 1989; 321:1349-52.
70. Franklin JA, Daykin J, Drolc Z, Farmer M and Sheppard MC. Long-term follow-up of treatment of thyrotoxicosis by three different methods. Clin Endocrinol 1991; 34:71-6.
71. Weetman A. P. Graves' Disease. N Engl J Med. 2000; 343:1236-48.
72. Mandel SJ, Brent GA, Larsen PR. Review of antithyroid drug use during pregnancy and report of a case of aplasia cutis. Thyroid 1994; 4:129-33.
73. Kung AWC, Jones BM. A change from stimulatory to blocking antibody in Graves' disease during pregnancy. J Clin Endocrinol Metab 1988; 83:514-18.
74. Stoffer SS., Hamburger JL. Inadvertent ^{131}I therapy for hyperthyroidism in the first trimester of pregnancy. J Nucl Med 1976; 17:146-49.

75. Gorman CA. Radioiodine and pregnancy. Thyroid 1999; 9:721-26.
76. Zimmerman D, Lteif AN. Thyrotoxicosis in children. Endocrinol Metab Clin North Am 1998; 27:109-26.
77. Rivkees S. A, Sklar C. and Freemark M. The management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab 1998; 83:3767-76.
78. Nordyke RA, Gilbert FI Jr, Harada ASM. Graves' disease: influence of age on clinical finding. Arch Intern Med 1988; 148:626-31.
79. Kahaly G J, Nieswandt J, and Mohr-Kahaly S. Cardiac risks of hyperthyroidism in the elderly. Thyroid 1998; 8:1165-69.
80. Delit C., Silver S., Yohalem S., Segal R. Thyrocardiac disease and its management with radioactive iodine. JAMA 1961; 262-67.
81. Sawin CT, Geller A, Wolf PA, Belanger A J, Baker E, Bacharach P et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331:1249-52.

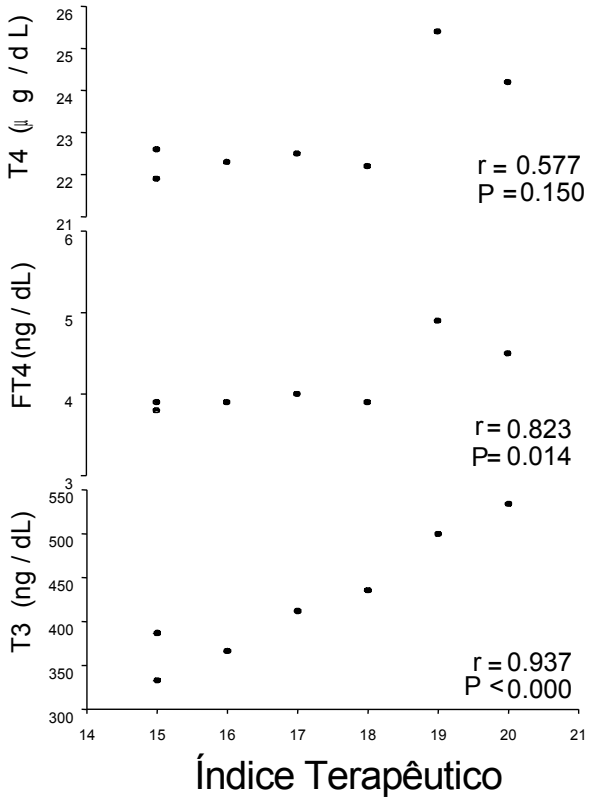
Tabela 1. Efeitos Colaterais das Drogas Antitireoidianas

Leves	Graves
Comuns (1-5%)	**Raros** (0.25-0.5%)
Eritema cutâneo	Agranulocitose
Urticária	**Muito Raros**
Artralgia	Anemia aplástica
Febre	Hepatite (PTU)
Leucopenia transitória	Hepatite colestática (MMI)
Raros	Hipoglicemia (anticorpos anti- insulina)
Artrite	Trombocitopenia

Adaptado das referências 25, 44,45

Figura 1. Correlação entre alterações no índice terapêutico de Wayne e níveis séricos dos hormônios tireoidianos em pacientes com hipertireoidismo da Doença de Graves tratados com iodo radioativo. r = coeficiente de correlação de *Sperman*.

Figura 2. Curva de Kaplan-Meier .ilustra a proporção de pacientes curados após administração de dose única de ^{131}I. O tempo necessário para a cura foi avaliado através do teste de Breslow (P=0.628). (Adaptado referência 54).


T4 (µ g / d L)
26
25
24
23
22
21
r = 0.577
P = 0.150
FT4 (ng / dL)
6
5
4
3
r = 0.823
P= 0.014
T3 (ng / dL)
550
500
450
400
350
300
r = 0.937
P < 0.000
14
15
16
17
18
19
20
21
Índice Terapêutico

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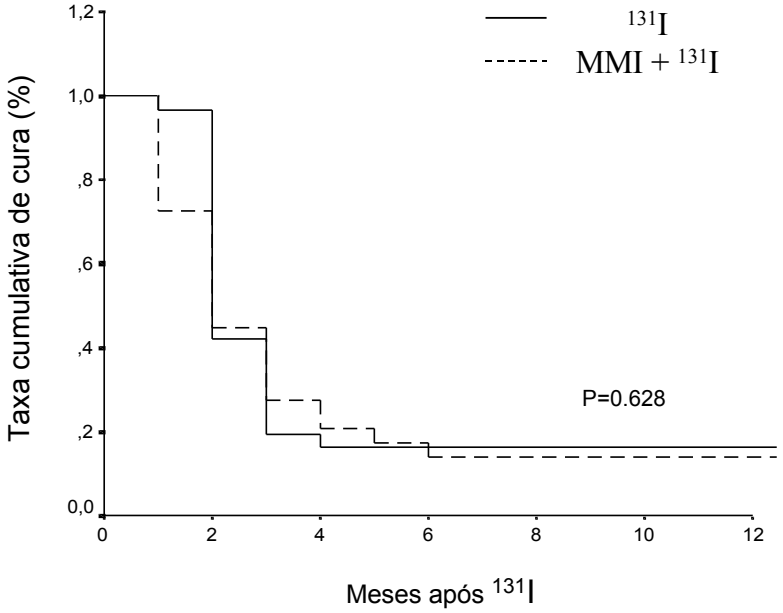
131I
MMI + 131I
Taxa cumulativa de cura (%)
1,2
1,0
,8
,6
,4
,2
0,0
P=0.628
0
2
4
6
8
10
12
Meses após 131I

The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: 1-year follow up of a prospective, randomized study

Vânia A. Andrade, M.D.,* Jorge L. Gross, M.D, Ph.D.,* Ana Luiza Maia, M.D., Ph.D.*

*Endocrine Division, Hospital de Clínicas de Porto Alegre,
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

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Correspondence and Reprints: Ana Luiza Maia, M.D., Ph.D.

Serviço de Endocrinologia

Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos 2350

90035 –003 Porto Alegre, RS, Brazil

Phone: 55-51-316-8127; Fax: 55-51-332-5188; E-mail: almaia@vortex.ufrgs.br

Abstract

The effect of antithyroid drugs on the efficacy of radioiodine (^{131}I) treatment is still controversial. This study aimed at evaluating methimazole pretreatment effect on the efficacy of ^{131}I therapy in Graves' hyperthyroidism. Sixty-one untreated patients were randomly assigned to receive ^{131}I alone (32 patients) or ^{131}I plus pretreatment with methimazole (30 mg/day; 29 patients). ^{131}I was administered 4 days after drug discontinuation. Calculated ^{131}I dose was 200 μCi/g of thyroid tissue as estimated by ultrasound, corrected by 24-hour radioiodine uptake (RAIU). Serum TSH, T_4 and free T4 (FT_4) were measured 4 days before ^{131}I therapy, on the day of treatment and then monthly during 1 year. Considering cure as euthyroidism or hypothyroidism, based on FT_4 measurement, approximately 80% of patients from both groups were cured 3 months after ^{131}I dosing. After 1 year, the groups were similar concerning persistent hyperthyroidism (15.6% *vs.* 13.8%), euthyroidism (28.1% *vs.* 31.0%) or hypothyroidism (56.3% *vs*. 55.2%). Relapsed patients presented larger thyroid volume (P=0.002), higher 24h RAIU (P=0.022) and T_3 levels (P=0.002). Multiple logistic regression analysis identified T_3 values as an independent predictor of therapy failure. In conclusion, pretreatment with methimazole had no effect either on the time required for cure or on the 1-year success rate of ^{131}I therapy.

Introduction

Graves' disease is one of the most prevalent autoimmune disorders in the United States and the most frequent cause of hyperthyroidism in adults aged 20-50 years [1,2]. Antithyroid drugs have been one of the standard modalities of therapy for Graves' hyperthyroidism either as first choice therapy or as pretreatment prior radioactive iodine in selected patients. The most important effect of antithyroid drugs on hyperthyroidism control is the inhibition of thyroid peroxidase, yet some studies also indicate a possible effect on modulation of the immunologic process [3-5]. Pretreatment with antithyroid drugs before radioactive therapy is usually recommended in order to deplete preformed stores of thyroid hormones and to decrease the risk for hyperthyroidism exacerbation [6], although recent studies have shown that thyroid hormone levels do not increase after radioiodine dosing [7,8].

The influence of pretreatment with antithyroid drugs on the efficacy of radioactive iodine therapy (RAI) is controversial. While some studies associate antithyroid drugs with higher rates of RAI treatment failure [9-14], others do not report this association [15-17]. In addition, it has been suggested that propylthiouracil, but not methimazole, may reduce the effectiveness of radioiodine therapy [18]. In any case, the possible radioprotective properties of antithyroid drugs are the basis for an empirical increase in the dose of ^{131}I. However, so far the association between antithyroid drugs and RAI has been analyzed by retrospective or non-randomized studies whose conclusions may have been influenced by both selection bias and differences in the time interval between antithyroid drug discontinuation and radioactive therapy. Therefore, the purpose of the present randomized study was to evaluate the effect of pretreatment with methimazole on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism.

Methods

Subjects

The study was carried out between February 1997 and March 2000. Consecutive patients with a recent diagnosis of Graves' disease attending the Endocrine Division at Hospital de Clínicas de Porto Alegre were eligible. Graves' hyperthyroidism was diagnosed on the basis of suppressed thyroid-stimulating hormone levels by sensitive

assay, elevated serum thyroid hormone levels, 24-hour radioiodine uptake, and detectable levels of anti-TSH receptor antibody. Exclusion criteria were previous treatment with radioiodine or thyroidectomy, signs of moderate or severe ophthalmopathy (proptosis > 22 mm, ophthalmoplegia, chemosis or lagophthalmos), severe heart disease (symptomatic coronary heart disease, class III heart failure, New York Heart Association criteria), debilitating conditions, and large and compressive goiters (>150 g). Patients previously treated with antithyroid drugs whose treatment had been interrupted at least 3 months before the study were included.

Sixty-seven patients were enrolled. Five patients were lost to follow-up; one was excluded because of pregnancy. Thus, 61 patients participated in the study. During the enrollment period the patients underwent a complete physical examination, including ocular examination and EKG. Data about duration of the disease, previous antithyroid drug therapy, and history of smoking were recorded, and thyroid volume was assessed by ultrasound, always by the same observer. The study protocol was approved by the Ethics Committee at the Hospital, and all patients gave their written, informed consent.

Treatment protocol and serial evaluation

Patients were randomly assigned to receive RAI alone (32 patients) or to receive pretreatment with antithyroid drugs in addition to RAI therapy (29 patients). In the first group, patients received a single dose of radioiodine on the day of treatment (200 μCi/g of thyroid tissue as estimated by ultrasound, divided by the fractional 24 hour uptake value). A clinical and laboratory assessment was performed on the day of treatment and monthly for 1 year after treatment.

In the second group, patients were treated with methimazole (30 mg daily) until biochemical euthyroidism was achieved. Patients were considered to have reached euthyroidism when serum thyroid hormone levels were within the laboratory reference range. Patients received ^{131}I 4 days after antithyroid drugs discontinuation. ^{131}I dose was calculated in the same way as for the first group, based on a second 24-hour radioiodine uptake performed on the day of treatment. A clinical and laboratory assessment was carried out 4 days before radioiodine therapy; on the day of RAI treatment and then monthly for 1 year after RAI therapy.

The degree of thyrotoxicosis was evaluated always by the same physician, who did not know whether the patient had received methimazole, using the Wayne' s questionnaire (euthyroidism, ≤10; suspicion of hyperthyroidism, 11-19; hyperthyroidism, ≥20) [19]. Serum levels of thyroxine (T_4), free thyroxine (FT_4), TSH and TRAb were measured in the morning on the days scheduled for clinical and laboratory assessment, as described above. None of the patients received antithyroid drug therapy after radioiodine therapy. The β-adrenergic blocking agent propranolol (80-120 mg/day) was given to patients if tachycardia > 120 bpm.

Successful therapy was defined as euthyroidism or permanent hypothyroidism based on FT_4 measurements obtained at each monthly visit. To avoid misclassification of the thyroid status, we used two consecutive serum FT4 measurements in normal or low range, or, in cases of borderline upper range values, three serum FT4 values. The time of cure (month) was considered when the first serum FT4 measurement reached and persisted in the normal or low range. Therapy failure was defined as the need to repeat ^{131}I treatment or as persistent elevated thyroid hormone levels after 1 year of ^{131}I dosing.

Serum hormone measurements

Assays were performed on batched serum samples (duplicates) that had been stored at –20 ºC pending study completion. Serum T_4 and T_3 levels were measured using radioimmunoassay (Diagnostic Products, Los Angeles, CA; Immunotech, Marseille, France), and serum FT_4 was measured using Coat-a-Count (Immunotech, Marseille, France). Intra-assay coefficients of variation were as follows in euthyroid controls: T_4, 3-8%; T_3, 7-10%; and FT_4, 3-6%. For values in the hyperthyroid and hypothyroid ranges, intra-assay coefficients of variation were: T_4, 6-9%; T_3, 6-12%; and FT_4, 4-8% and T_4, 5-7 %; T_3, 6-10%; and FT_4, 4-6%, respectively. Interassay coefficients of variation were as follows (euthyroid controls): T_4, 10%; T_3, 12%; and FT_4, 7%. TSH level was measured by a double-antibody sensitive assay (Immulite, Diagnostic Products). Plasma levels of thyroid-stimulating hormone antibodies were determined by radioreceptor assay (CIS-Bio International, Cardiff, France). The reference ranges for each of these assays is shown in Table 1.

Statistical Analysis

The baseline characteristics of the two groups of patients were compared using the χ^2 test or Fisher's exact test for qualitative variables, or by Student's t-test or Mann-Whitney's U-test for quantitative variables. The differences in the cumulative cure rate between the groups were tested by Kaplan Meier curves; comparisons between nonremission curves were performed using the Beslow-Gean-Wilcoxon test. Stepwise multiple logistic regression analysis was used to identify independent predictors of treatment failure. Only variables showing statistical significance ($P \leq 0.05$) in the univariate analysis were included in the model as potential independent predictors of treatment failure. The correlation between changes in thyroid volume, 24-hour RAIU, calculated radioiodine dose and serum T_3 levels was assessed using Spearman's rank correlation. The Statistical Package for the Social Sciences 7.5 (SPSS, Chicago, IL) was used for the statistical analysis.

Results

Subjects

The characteristics of the 61 patients with Graves' hyperthyroidism that were randomly assigned to receive RAI alone or RAI plus antithyroid drug treatment are shown in Table 1. There were no significant differences between the two groups with respect to any of the characteristics listed.

The median for the period of time required to achieve biochemical euthyroidism in the group of patients pretreated with antithyroid drugs was 12 weeks (2 to 48 weeks). The mean dose of RAI (10.6 ± 5.7 vs. 8.9 ± 4.6) and the number of patients using propranolol (3 vs. 2) and/or oral contraceptives (9 vs. 8) were similar in both groups. Methimazole was replaced with propylthiouracil (300 mg/day) in three patients who developed a cutaneous rash.

Patient follow-up

Kaplan Meier estimates of cumulative cure rate yielded nearly identical curves for the two treatment groups (Figure 1). The successful cure rate in 2 and 3 months after ^{131}I therapy in patients from both groups was approximately 57 and 77%, respectively. About

90% of all patients cured with a single RAI dose responded in the 3 first months after ^{131}I dosing. One patient in the methimazole group required a second dose of ^{131}I before 1 year due to persistently elevated serum levels of thyroid hormone and development of atrial fibrillation.

One year after RAI administration, no statistical differences were observed between pretreated or not-pretreated patients with respect to permanent hypothyroidism (55.2% versus 56.3%), euthyroidism (31.0% vs. 28.1%) or persistent hyperthyroidism (13.8% *vs.* 15.6%).

Prognostic factors for radioiodine therapy failure

In view of the lack of difference between the two treatment groups concerning the thyroid function outcome, all patients were grouped for analysis of possible prognostic factors for therapy failure. Table 2 compares clinical and laboratory data from patients who were successfully treated with data from subjects who remained thyrotoxic after a single dose of RAI. Age (P=0.940), gender (P=0.283), BMI (P=0.166), duration of disease (P=0.533) or TRAb titers (P=0.748) were not associated with therapy failure. Male patients at presentation had, however, larger goiters (47.6±23.2 Vs 33.7±17.0, P=0.071), higher concentrations of T_3 (578±52.4 *vs.* 455±202; P=0.002) and FT_4 than females (7.7±1.77 vs. 4.1±1.4, P=0.0001). Although the percentage of smokers appeared to be higher in the failure group, the difference was not significant (P=0.460). At baseline, patients in the treatment failure group presented larger goiter (P=0.002), higher 24-hour RAIU (P=0.022), and higher basal serum T_3 levels (P=0.002) than patients who were cured after a single dose of radioiodine. Nevertheless, multiple logistic regression analysis with radioactive therapy failure as the dependent variable and thyroid volume, 24h RAIU, and serum T_3 level as independent variables identified only serum T_3 levels as an independent predictor of failure (estimated OR: 1.0058; 95% CI: 1.0014-1.0102; P<0.01), presumably because of the high co-linearity between the variables included in the model. Therefore, we also analyzed the correlation between thyroid volume, 24h RAIU and serum T_3 levels in successfully and unsuccessfully treated patients.

Thyroid volume, 24h RAIU, and serum T_3 levels were significantly correlated in the subjects included in the present study (Fig 2A-C). Nevertheless, when patients were analyzed in terms of therapy outcome, a significant correlation was found only in the successfully treated group (results not shown). Another interesting finding was that

combinations of these pretreatment variables could be strong predictors of therapy failure (Figure 2). We observed that only 4 out of 61 patients (6.6%) presented 24h RAIU values ≥ 90% and thyroid volume ≥ 50 ml, and all of them had to be treated again (100% treatment failure) (Fig.2A). Six of 9 (67%) subjects who did not respond to a single dose of radioiodine had 24h RAIU values ≥ 90% with basal serum T_3 levels exceeding 7.68 nmol/L (500 ng/dL) at presentation compared to only 6 of 52 (12%) successfully treated patients ($P<0.02$) (Fig.2B). Patients with serum T_3 levels exceeding 7.68 nmol/L (500 ng/dL) and goiter ≥ 50 ml (7 of 61 patients) presented a higher therapy failure rate compared to patients with smaller goiter and lower serum T_3 values (33% vs. 8% treatment failure, $P<0.02$) (Fig.2C). On the other hand, the cure rate of ^{131}I treatment was 96% in patients who did not present any of these pretreatment characteristic (28 patients, 1 treatment failure).

Discussion and conclusions

After 1 year of follow up, we did not observe any differences in the thyroid function outcome after RAI treatment between patients pretreated or not treated with methimazole. Furthermore, the period of time required to achieve cure was virtually identical in both groups. Persistent hyperthyroidism was associated with larger goiters, higher 24h RAIU, and serum T_3 levels at baseline. Subsequent analysis by multiple logistic regression analysis identified serumT_3 values as an independent predictor of therapy failure.

The effect of antithyroid drugs on RAI therapy has long been the focus of discussion and it is still a matter of debate [20]. Some studies have reported that previous use of antithyroid drugs increases the rate of radioactive therapy failure due to a possible protective effect of antithyroid drugs to radioiodine [9-14] while others did not observed similar effects of these compounds [15-17]. Since Einhorn and Säterborg have proposed that the radioresistance associated with thiourea resulted from the presence of a sulfhydryl group [21], it has been suggested that methimazole and carbimazole would not present this property because they do not present sulfhydryl groups [22]. In the present study, the proportion of patients who were cured by RAI administration was not influenced by methimazole. However, one other explanation for our results would be that the four days of antithyroid drug interruption was enough to vanish the methimazole effect on effective ^{131}I half-life and RAIU values [8, 23-25]. Accordingly, it has been recently shown that RAI administration during use of carbimazole results in a 5-fold increase in the possibility of treatment failure, although the radioprotective effect of these drugs was overcome by drug discontinuation a few days before radioiodine dosing [26]. Other possibility would be that the relative high ^{131}I dose per gram of thyroid used in our protocol had overcame or obscured a methimazole effect on the response to lower ^{131}I doses.

The cumulative cure rate observed in this study was virtually identical in both treatment groups and supports the absence of a methimazole effect on the efficacy of RAI therapy as well on the period of time required for disappearance of the hyperthyroid state. In fact, about 80% of patients from both groups were cured 3 months after radioiodine dosing. At least two inferences arise from this observation. First, Graves' hyperthyroidism was cured faster in patients who received radioiodine alone if we consider the median period of 12 weeks required to achieve biochemical euthyroidism with pretreatment with antithyroid drugs [8]. Also, it seems that patients who did not respond 4 months after RAI administration have a very low probability of cure, and therefore a second dose of radioiodine should be considered.

Because RAI is increasingly being used both as first line treatment and in patients who relapse after medical therapy in Graves' disease, some studies have attempted to identify factors that may predict the response to RAI therapy [27-31]. Our data showed that goiter size, 24h RAIU, and serum T_3 levels at baseline were significantly associated with radioiodine therapy failure, although only serum T_3 levels were an independent predictor factor after multiple logistic regression analysis. These results contrast with those of some studies [28,31], but agree with the results of most others [27,29,30]. Indeed, the strong influence of these three measurements, all part of the initial evaluation of Graves' hyperthyroidism, to predict treatment outcome is an important finding of our study. The presence of large goiters (>50ml) and 24h RAIU values exceeding 90% were associated with therapy failure in all the cases observed, while the rate of therapy success in patients presenting 24h RAIU values above 90% and very high serum T3 levels (>7.68 nmol/L) was only 33%. These findings indicate that goiter size, 24h RAIU and serum T3 levels should be taken into account when making treatment decisions.

In agreement with most studies, age, sex, basal serum TRAb levels or smoking habit did not differ significantly between patients who responded or not to one single radioactive iodine dose [27-30]. A large retrospective study has recently identified male gender as an independent predictor of therapy failure [31]. In our study, all male patients were cured after receiving a single dose of radioiodine. Similarly to others [32], we observed that males presented with a more severe clinical and biochemical hyperthyroidism than women, but the proportional increase in calculated radioiodine dose was enough to overcome the severity of the disease.

Another interesting observation is related to the RAI dose given to patients who did not respond to treatment, since it has been suggested that an empirical increase in the

delivered dose of radioiodine could bring the treatment failure rate down to an acceptable level [33]. The dose received by patients who were not cured was about 30% higher than that received by cured patients, suggesting that dose correction based only on thyroid volume and 24 RAIU is not enough to overcome the more severe disease in these cases [27]. Indeed, we observed that, in contrast with successfully treated patients, patients who fail to respond to RAI treatment do not present a significant correlation between thyroid volume, 24h RAIU and serum T3 levels. However, it is important to call attention the distinction between the administered ^{131}I dose and the radiation delivered to thyroid. Although we used here "dose" as the millicuries of given ^{131}I, in radiation biology "dose" refers to the radiation dose to tissue, and one of the variables that determines radiation dose is the effective half-life of the ^{131}I in the thyroid gland, which was not determined in the present study. The presence of autonomous tissue with functional differences in uptake and iodine organification [28] may be an additional explanation for the fact that some cases of Graves' disease are less sensitive to RAI therapy, similarly to what is observed for multinodular goiters.

A possible limitation of this study is the number of patients in the sample. We observed a difference of approximately 2% between the groups. To determine the equivalence of both regimens in terms of efficacy (α=0,05 and β=0,20), 3,841patients would have to be included in each group. In our view this possible difference is not clinically significant to justify such a large study.

In conclusion, we demonstrated that methimazole pretreatment does not interfere with either the efficacy of RAI therapy or the period required to achieve control of hyperthyroidism in Graves' disease. Furthermore, about 90% of successfully treated patients from both groups were cured within 3 months of RAI dosing, suggesting that Graves' hyperthyroidism was cured faster in patients who did not receive pretreatment. Since we have previously demonstrated that radioiodine therapy without pretreatment is safe, we believe that most patients with Graves' hyperthyroidism could receive RAI therapy alone, avoiding the risk and costs associated with antithyroid drugs. Therapy failure was strongly associated with large goiters (>50g), very high 24h RAIU (>90%), and serum T_3 levels above 500 ng/ml at baseline; patients with these characteristics should be closely followed, and if hyperthyroidism persists 4 months after radioiodine administration, a second radioiodine dose should be prescribed. Another approach could be to give such patients empirical higher doses of radioiodine at the time of first treatment.

References

82. Vanderpump MPJ, Tunbridge WMC. The epidemiology of autoimmune thyroid disease. In: Volpé R, ed. Autoimmune endocrinopathies. Vol 15 of Contemporary endocrinology, Totowa, NJ: Humana Press, 1999:141-62.
83. Jacobson D.L, Gange S.J, Rose N.R., Graham N.M. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997; 84:223-43.
84. Weetman AP, Holt M, Campbell AK, Hall R, McGregor AM. Methimazole and generation of oxygen radicals by monocytes: potential role in immunosuppression. Br Med J 1984; 288:518-20.
85. Weetman A P, McGregor AM, Hall R. Evidence for an effect of antithyroid drugs on the natural history of Graves' disease. Clin Endocrinol 1984;21:162-72.
86. Volpé R. Evidence that the immunosuppressive effects of antithyroid drugs are mediated through actions on the thyroid cell, modulating thyrocyte-immunocyte signaling: a Review. Thyroid 1994,4:217-23.
87. Cooper DS. Antithyroid drugs and radioiodine therapy: a grain of (iodized) salt. Ann Intern Med 1994; 121:612-4.
88. Burch HB, Solomon B.L, Wartofsky L, Burman KD. Discontinuing antithyroid drug therapy before ablation with radioiodine in Graves' disease. Ann Intern Med 1994; 121:553-9.
89. Andrade V.A, Gross JL, Maia AL. Effect of methimazole pretreatment on serum thyroid hormone levels after radioactive treatment in Graves' hyperthyroidism. J Clin Endocrinol Metab 1999; 84:4012-16.
90. Crooks J, Buchanan W, Wayne EJ, Macdonald E. Effect of pretreatment with methylthiouracil on results of ^{131}I therapy. Br Med J 1960; 151-54.
91. Reynolds LR, Kotchen TA. Antithyroid drugs and radioactive iodine. Fifteen years' experience with Graves' disease. Arch Intern Med 1979; 139:651-653.
92. Holm LE, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. J Nucl Med 1982; 23:103-7.
93. Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot JL. Long-term follow-up study of compensated low-dose ^{131}I therapy for Graves' disease. N Engl J Med 1984; 311:426-32.

94. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995; 5:243-47.
95. Hancock LD, Tuttle M, LeMar H, Bauman J, Patience T. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves' disease. Clin Endocrinol 1997; 47:425-30.
96. Goolden AWG, Fraser TR. Effect of pretreatment with carbimazole in-patients with thyrotoxicosis subsequently treated with radioactive radioiodine. 1969. Br Med J 3:443-44.
97. Cunnien AJ, Hay ID, Gorman CA, Offord KP, Scanion PW. Radioiodine-induced hypothyroidism in Graves' disease: factors associated with the increasing incidence. J Nucl Med 1982,23:978-83.
98. Maracocci C, Gianchecchi D, Masini I, Golia F, Ceccarelli C. Bracci E, Fenzi GF, Pinchera A. A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. J Endocrinol Invest 1990; 13:513-20.
99. Imseis RE, Vanmiddlesworth L., Massie JD, Bush AJ, and Vanmiddlesworth N.R. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab 1998; 83:685-87.
100. Wayne EJ. Clinical and metabolic studies in thyroid disease. Br Med J 1960; 2:5165-172
101. Perros P. Anti-thyroid drugs treatment before radioiodine in patients with Graves 'disease: soother or menace? Clinical Endocrinology 2000,53:1-2.
102. Einhorn J, Saterborg NE. Antithyroid drugs in iodine ^{131}I therapy of hyperthyroidism. Acta Radiol 1962,58:161-67.
103. Goolden AWG, Fraser TR. Effect of pretreatment with carbimazole in patients with thyrotoxicosis subsequently treated with radioactive iodine. Br Med J 1969; 3:443-44.
104. Clerc J, Izembart M. Dagousset F, Heshmati JH, Heshmati M, Chevalier A, Léger AF, Barritault L. Influence of dose selection on absorbed dose profiles in radioiodine treatment of diffuse toxic goiters in patients receiving or not receiving carbimazole. J Nucl Med 1993; 34:387-93.
105. Kung AW, Yau CC, Cheng AC. The action of methimazole and L-thyroxine in radioiodine therapy: a prospective study on the incidence of hypothyroidism. Thyroid 1995, 5:7-12

106.Berg GEB, Michanek AMK, Holmberg ECV. Iodine-131 treatment of hyperthyroidism: Significance of effective half-life measurements. J Nucl Med 1996,37:228-32.

107.Sabri O, Zimny M, Schulz G, Schreckenberger M, Reinartz P, Willmes K, Buell U. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab 1999,84:1229-33.

108.Tsurata M, Nagayama Y, Yokoyama N, Izumi M, Nagataki S. Long-term follow-up studies on iodine-131 treatment of hyperthyroid Graves' disease based on the measurement of thyroid volume by ultrasonography. Ann Intern Med 1993, 7:193-97.

109.Flower M, Saadi A, Harmer C, McCready R, Ott R. Dose-response study on thyrotoxic patients undergoing positron emission tomography and radioiodine therapy. J Nucl Med 1994, 21:531-36.

110.Bruin TWA, Croon CDL, De Klerk JMH, Isselt JWV. Standardized radioiodine therapy in Graves' disease: the persistent effect of thyroid weight and radioiodine uptake on outcome. J Inter Med 1994,236:507-13.

111.Peters H, Fischer C, Bogner U, Reiners C, and Schleusener H. Treatment of Graves' hyperthyroidism with radioiodine: results of a prospective randomized study. Thyroid 1997,7:247-50.

112.Allahabadia A, Daykin J. Holder RL, Sheppard MC, Gough SCL, Franklin JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. J Clin Endocrinol Metab 2000,85:1038-42.

113.Larsen PR, Davies TF, Hay ID.1998 The thyroid gland. In: Wilson JD, Foster DW, Kronenberg HM, Reed Larsen P, Eds. Williams textbook of endocrinology. Philadelphia: Saunders; 389-516.

114.Cooper DS: Treatment of thyrotoxicosis. In: Braveman LE, Utiger RD (eds): Werner and Ingbar' s The Thyroid: A Fundamental and Clinical Text, 7th Ed, Philadelphia, Lippincott -Raven, 1996, pp 713-34.

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Current mailing address of all authors:

Serviço de Endocrinologia

Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos 2350

90035 –003 Porto Alegre, RS, Brazil

Table 1. Baseline characteristics of patients with Graves' hyperthyroidism*

	Radioiodine group (N = 32)	Methimazole-radioiodine group (N=29)
Age (years)	35.1 ± 7.6	37.4 ± 7.8
Sex (M/F)	4 / 28	2 / 27
Smokers (n)	15 (46.9%)	12 (41.4%)
Body mass index (kg/m^2)	22.4± 3.1	23.1 ± 4.0
Range of disease duration (months)	7 (1 – 72)	12 (1-156)
Wayne's clinical index=	23.6± 9.2	21.8 ± 6.7
Thyroid volume (mL) ==	38.4± 19.8	31.3 ± 15.2
24 h radioiodine uptake (%)§	73.3 ± 17.5	70.0 ± 22.9
Dose ^{131}I (mCi)	10.6± 5.7	8.9± 4.6
Thyroxine - nmol/L	294.6 ± 98	293.4 ± 82,4
Free Thyroxine - - pmol/L	57,9 ± 21,9	59,2 ± 27,0
Triiodothyronine - - nmol/L	7,3 ± 3,1	7,1 ± 2,9
Thyrotropin concentration (µUI/mL)	< 0.03	< 0.03
TRAb (U/L)	62.2 (10,6 -407)	77,5 (11,5- 311,4)

*Values represent mean ± SD or median (range). The reference ranges for laboratory values are: thyroxine, 56.3-160.9 nmol/L (4.5-12.5 µg/dL); free thyroxine, 8.4-23.2 pmol/L (0.6-1.8 ng/dL); triiodothyronine, 1.19-2.8 nmol/L (78-182 ng/dL); and thyrotropin, 0.4-4.5 mU/L. Normal values for thyrotropin–receptor antibody are < 11 U/L. To convert thyroxine values to µg/dL and free thyroxine values to ng/dL, divided by 12.87. To convert triiodothyronine values to ng/dL, divided by 0.01536. All *P* values for the comparisons between groups were ≥ 0.05. =Euthyroidism index < 10; suspicion of hyperthyroidism =11-19; hyperthyroidism > 20. ==Thyroid volume was measured by ultrasonography. §Iodine uptake was measured 24 hours after the oral administration of 5 µCi (185 kBq) of ^{131}I and expressed as a percentage of the administered dose; reference values are 15-35%.

Table 2. Comparison between patients successfully treated with a single dose of RAI and those remaining thyrotoxic after 1 year

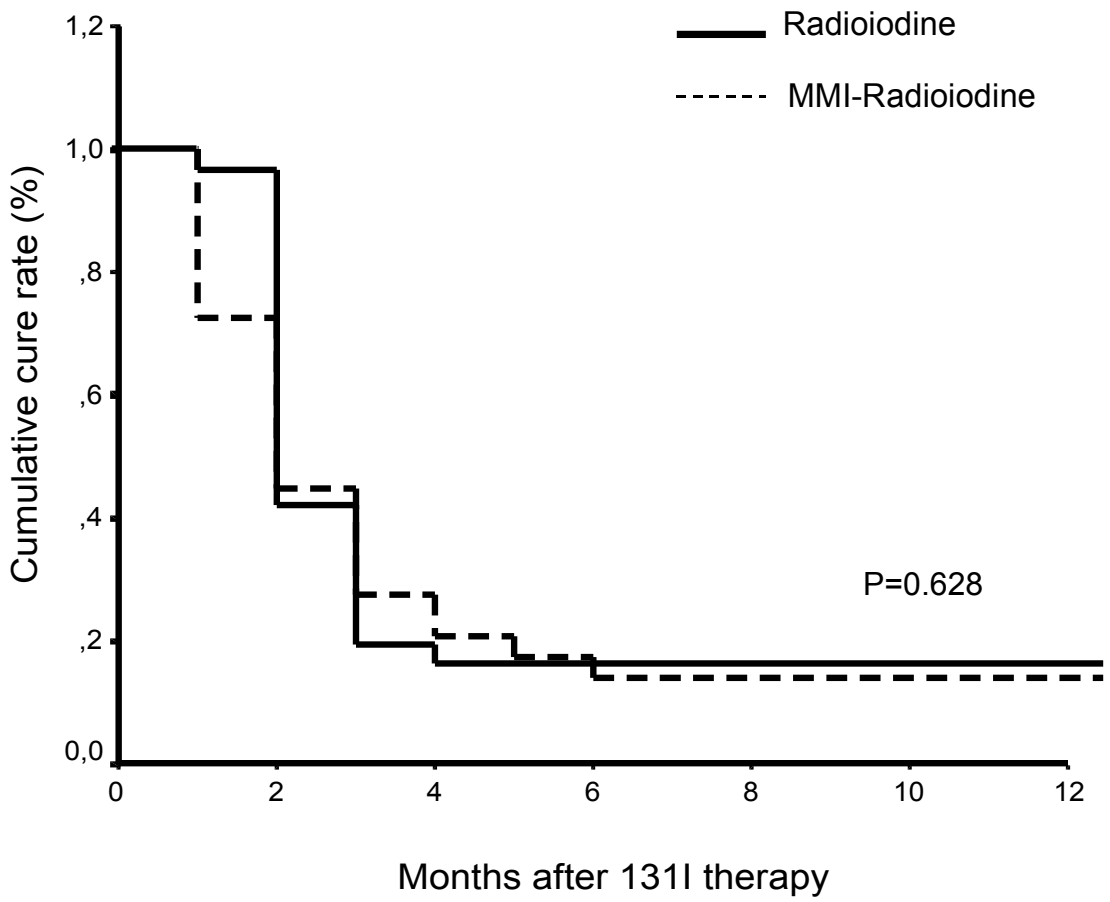
	Successfully Treated	Treatment failure
Nº of Patients	52	9
Age (yr)	36.2 ± 8.2	36.0 ± 4.3
Sex (male/female)	6 / 46	0 / 9
Wayne's clinical index	22.9±8.6	22.1±4.5
Body mass index (kg/m^2)	23.0±3.4	21.2±4.3
Duration of disease (months)	11 (1 - 156)	6 (3-60)
Thyroid volume (ml)	32.2 ± 16.4	51.7 ± 18.4*
24h RAI Uptake	69.3 ± 19.3	85.8 ± 19.9*
Dose ^{131}I (mCi)	9.1 ± 4.7	13.7 ± 6.9*
Thyroxine - nmol/L	289.6± 89	333.3 ± 100
Free Thyroxine - - pmol/L	59.2 ± 24	56.6 ± 21
Triiodothyronine - - nmol/L	6.7 ± 2.6	10 ± 4.0*
Thyrotropin concentration	< 0.03	< 0.03
TRAb (U/L)	71.8 (10.6- 407)	68.3 (23.6- 159)
Smokers (no.)	22 (42.3%)	5 (55.6%)

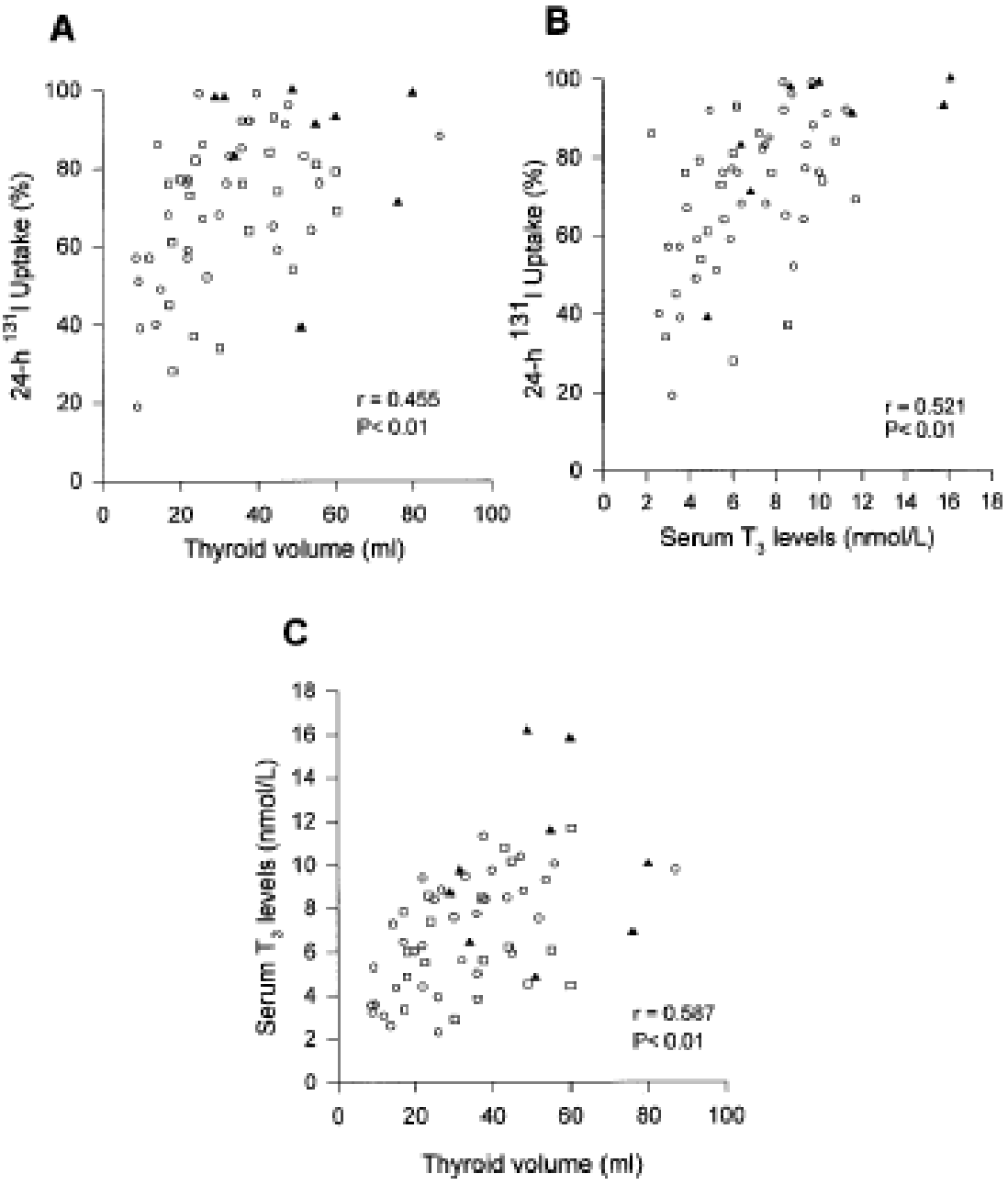
Values represent mean ± SD or median (range). The reference ranges for laboratory values are: thyroxine, 56.3-160.9 nmol/L (4.5-12.5 µg/dL); free thyroxine, 8.4-23.2 pmol/L (0.6-1.8 ng/dL); triiodothyronine, 1.19-2.8 nmol/L (78-182 ng/dL); and thyrotropin, 0.4-4.5 mU/L. Normal values for thyrotropin–receptor antibody are < 11 U/L. To convert thyroxine values to µg/dL and free thyroxine values to ng/dL, divided by 12.87. To convert triiodothyronine values to ng/dL, divided by 0.01536. All P values for the comparisons between groups were ≥ 0.05. =Euthyroidism index < 10; suspicion of hyperthyroidism =11-19; hyperthyroidism > 20. ==Thyroid volume was measured by ultrasonography. §Iodine uptake was measured 24 hours after the oral administration of 5 µCi (185 kBq) of ^{131}I and expressed as a percentage of the administered dose; reference values are 15-35%.

Legends to Figures

Figure 1. Kaplan-Meier estimates of the proportion of patients cured by a single dose of radioactive iodine. The velocity of cure (*i.e*. the prompt control of hyperthyroidism) was assessed by the Breslow test (P=0.628).

Figure 2. A) Thyroid volume compared with 24-h radioiodine uptake values. B) Serum T_3 levels compared with 24-h radioiodine uptake values. C) Thyroid volume compared with serum T3 levels. The thyroid status resulting from one single dose of radioactive iodine therapy is indicated: hypothyroidism (O), euthyroidism ( ), and persistent hyperthyroidism (σ). To convert nmol/L to ng/dL divide by 0.01536.


Radioiodine
MMI-Radioiodine
Cumulative cure rate (%)
1,2
1,0
,8
,6
,4
,2
0,0
P=0.628
0
2
4
6
8
10
12
Months after 131I therapy


A
24-h 131I Uptake (%)
Thyroid volume (ml)
r = 0.455
P< 0.01
B
24-h 131I Uptake (%)
Serum T3 levels (nmol/L)
r = 0.521
P< 0.01
C
Serum T3 levels (nmol/L)
Thyroid volume (ml)
r = 0.587
P< 0.01

Hyperthyroidism Control Attenuates the Radioiodine Therapy-Induced Rise in Serum Thyrotropin-Receptor Autoantibodies in Graves' Patients

Vânia A. Andrade, M.D., Jorge L. Gross, M.D., Ph.D. ,
Ana Luiza Maia, M.D., Ph.D.

***Endocrine Division, Hospital de Clínicas de Porto Alegre,**
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

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Running title: ^{131}I therapy and serum TRAb levels.

Correspondence: Ana Luiza Maia, M.D., Ph.D.
Serviço de Endocrinologia
Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos 2350
90035 –003 Porto Alegre, RS, Brazil
Phone: 55-51-33168127 FAX: 55-51-33168777

Abstract

A controversial matter is whether antithyroid drugs have direct effect on the disordered immune system in Graves' disease, since these compounds also improve the hyperthyroid state, which itself perpetuate immune dysregulation. Sixty-one patients were randomly assigned to receive ^{131}I therapy while on hyperthyroid state (32 patients) or on biochemical euthyroidism achieved by methimazole treatment (30mg/day; 29 patients). Serum thyrotropin-receptors antibodies (TRAb) levels were measured on the day of ^{131}I dosing (D0), and on months 1, 3, 6 and 12 after ^{131}I administration. In hyperthyroid patients, TRAb levels increased significantly from D0 to month 1 (74.8 to 285.2 U/L; 281%) reaching its highest level on month 3 (399.4 U/L; 434%). After this, we observed a progressive decrease to the baseline levels on month 12 (78.9 U/L). In patients treated with methimazole, TRAb levels increased at month 3 (56.8 to 156.9; 176%), with significantly less intensity. TRAb levels were still elevated at month 6 compared to D0 values (153.3; 170%). Thereafter, TRAb levels decreased to baseline values (70.3 U/L) at month 12. The course of TRAb levels after ^{131}I treatment was significantly different between the 2 groups ($P<0.05$). Multiple regression analysis identified serum T_3 levels on D0 as a predictor of TRAb increment after ^{131}I therapy ($r^2=0.2$; $P=0.011$). In conclusion, the effect of ^{131}I therapy on TRAb levels is influenced by the thyroid status. We postulate that hyperthyroidism control rather than methimazole itself prevents ^{131}I treatment induced rise in serum TRAb levels on Graves' disease.

Introduction

Antithyroid drugs have been one of the standard modalities of therapy for Graves' hyperthyroidism either as first choice therapy or as pretreatment prior radioactive iodine in selected patients. Pretreatment with antithyroid drugs before radioactive iodine therapy is usually recommended in order to deplete preformed stores of thyroid hormones and to decrease the risk for hyperthyroidism exacerbation [1], although recent studies have shown that thyroid hormone levels do not increase after radioiodine dosing [2,3]. The pretreatment with methimazole does not interfere on the efficacy of radioactive iodine therapy [4,5].

A controversial matter about antithyroid drug effects is the possibility that these compounds may have direct effects on the disordered immune system that characterize Graves' disease. The most important effect of antithyroid drugs on hyperthyroidism control in Graves' disease is the inhibition of thyroid peroxidase, yet some studies also indicate a possible effect on modulation of the immunological process [6-9]. Some authors have suggested that antithyroid drugs have immunosuppressive actions which may contribute to the suppression of production of the thyrotropin-receptors antibodies (TRAb) [10-12], while other authors found evidences against these drugs effects [13]. Unquestionably, *in vitro* studies have shown antithyroid drugs modify lymphocyte transformation in response to a variety of stimuli [11,14]. However, even though effects on the immune system also have been observed *in vivo* [10,11,15-18], it has been difficult to prove that antithyroid drugs alters immune function, when, at the same time, the drugs are improving the hyperthyroid state, which itself perpetuate immune dysregulation [19].

Radioiodine treatment of patients with hyperthyroid Graves' disease is generally followed by a transitory increase in serum TRAb levels [20-22]. The explanation for this phenomenon is that radiation damage to thyroid cells release thyroid cells antigens, thus stimulating the production of autoantibodies [23]. The finding that methimazole blocks the rise in serum TRAb levels after radioiodine therapy has been suggested as an evidence of an organ-specific immunity effect [24].

We inferred that a previous study designed to evaluate the effect of methimazole pretreatment on the efficacy of ^{131}I therapy in Graves' hyperthyroidism [4] could be an interesting model to determine if hyperthyroidism control itself could blocks the ^{131}I induced rises in serum TRAb levels. Since the drug was discontinued before ^{131}I dosing, we could presuppose that it would have minimal or no effect on thorough 1-year TRAb course. Indeed, our results suggest that hyperthyroidism control, rather methimazole itself,

prevents the serum TRAb levels increment in response to ^{131}I administration in Graves' hyperthyroidism.

Material and Methods

Subjects

The study was carried out between February 1997 and March 2001. Consecutive patients with a recent diagnosis of Graves' disease attending the Endocrine Division at Hospital de Clínicas de Porto Alegre were eligible. Graves' hyperthyroidism was diagnosed on the basis of suppressed thyroid-stimulating hormone levels by sensitive assay, elevated serum thyroid hormone levels, 24-hour radioiodine uptake, and detectable levels of anti-TSH receptor antibody. Exclusion criteria were previous treatment with radioiodine or thyroidectomy, signs of moderate or severe ophthalmopathy (proptosis > 22 mm, ophthalmoplegia, chemosis or lagophthalmos), severe heart disease (symptomatic coronary heart disease, class III heart failure, New York Heart Association criteria), debilitating conditions, and large and compressive goiters (>150 g). Patients previously treated with antithyroid drugs whose treatment had been interrupted at least 3 months before the study were included.

Sixty-eight patients were enrolled. Five patients were lost before randomization. Two patients were withdrawn from the study shortly after randomization, 1 because of pregnancy and the other because of atrial fibrillation. Thus, this study includes 61 patients.

During the enrollment period the patients underwent a complete physical examination, including ocular examination and electrocardiogram. Data about duration of the disease, previous antithyroid drug therapy, and history of smoking were recorded, and thyroid volume was assessed by ultrasound, always by the same observer. The study protocol was approved by the Ethics Committee at the Hospital, and all patients gave their written, informed consent.

Treatment protocol and serial evaluation

Patients were randomly assigned to receive ^{131}I on hyperthyroidism (32 patients) or on biochemical euthyroidism after treatment with antithyroid drugs (29 patients). In the first group, patients received a single dose of radioiodine on the day of treatment (D0; 200 μCi/g of thyroid tissue as estimated by ultrasound, divided by the fractional 24-hour uptake

value). A clinical and laboratory assessment was performed on the day of treatment and monthly for 1 year after ^{131}I treatment.

In the second group, patients were treated with methimazole (30 mg daily) until biochemical euthyroidism was achieved. Patients were considered to have reached euthyroidism when serum thyroid hormone levels were within the laboratory reference range. Patients received ^{131}I dosing 4 days after antithyroid drug discontinuation. ^{131}I dose was calculated in the same way as for the first group, based on a second 24-hour radioiodine uptake performed on the day of treatment. A clinical and laboratory assessment was carried out 4 days before radioiodine therapy; on D0 and then monthly for 1 year after ^{131}I therapy.

Serum levels of thyroxine (T_4), free thyroxine (FT_4), triiodothyronine (T_3) and TSH were measured in the morning on the days scheduled for clinical and laboratory assessment, as described above. Serum TRAb levels were measured on D0 and on month 1, 3, 6, and 12 after radioiodine therapy. None of the patients received antithyroid drug therapy after radioiodine therapy. The β-adrenergic blocking agent propranolol (80-120 mg/day) was given to patients if tachycardia > 120 beats/min.

Successful therapy was defined as euthyroidism or permanent hypothyroidism based on FT_4 measurements obtained at each monthly visit. To avoid misclassification of the thyroid status, we used two consecutive serum FT4 measurements in normal or low range, or, in cases of borderline upper range values, three serum FT4 values. The time of cure (month) was considered when the first serum FT4 measurement reached and persisted in the normal or low range. Therapy failure was defined as the need to repeat ^{131}I treatment or as persistent elevated serum thyroid hormone levels after 1 year of ^{131}I dosing.

Serum hormone measurements

Assays were performed on batched serum samples (duplicates) that had been stored at –20 ºC pending study completion. Serum T_4 and T_3 levels were measured using radioimmunoassay (Diagnostic Products, Los Angeles, CA; Immunotech, Marseille, France), and serum FT_4 levels were measured using Coat-a-Count (Immunotech, Marseille, France). Intra-assay coefficients of variation were as follows in euthyroid controls: T_4, 3-8%; T_3, 7-10%; and FT_4, 3-6%. For values in the hyperthyroid and hypothyroid ranges, intra-assay coefficients of variation were: T_4, 6-9%; T_3, 6-12%; and FT_4, 4-8% and T_4, 5-7 %; T_3, 6-10%; and FT_4, 4-6%, respectively. Interassay coefficients of variation were as follows (euthyroid controls): T_4, 10%; T_3, 12%; and FT_4, 7%. TSH level

was measured by a double-antibody sensitive assay (Immulite, Diagnostic Products). Serum TRAb levels were determined by radioreceptor assay (CIS-Bio International, Cardiff, France). The intra-assay and interassay coefficients of variation were 3.4-6.5% and 15.2, respectively. The reference ranges for each of these assays is shown in Table 1.

Statistical Analysis

Clinical and laboratorial characteristics between groups were compared using the χ^2 test or Fisher's exact test for qualitative variables, or by Student's t-test or Mann-Whitney's U-test / Kruskal-Wallis test for quantitative variables. The correlations between serum TRAb levels and clinical and laboratorial parameters were assessed using Spearman's rank. In each group, the variation of serum TRAb levels over time was assessed by analysis of variance by repeated measures (Friedman's test), followed by Dunett's test. Comparison of variation in serum TRAb levels between the two groups of patients was assessed by the general linear model for repeated measures followed by Mann-Whitney test. Multiple linear regression analysis was used to identify predictors of serum TRAb increment after ^{131}I administration. The variation in serum TRAb levels between the treatment day and month 3 were logarithmically transformed ($\log_{10}$TRAb) and forward selection was used. *P* values of less than 0.05 were considered as statistically significant. The Statistical Package for Social Science 10.0 professional software (SPSS, Chicago, IL) was used for the statistical analysis.

Results

Subjects

The characteristics of the 61 patients with Graves' disease that were randomly assigned to receive ^{131}I therapy on hyperthyroidism (32 patients) or to receive ^{131}I after treatment with antithyroid drugs (29 patients) are shown in Table 1. There were no significant differences between the two groups with respect to any of the characteristics listed, except for the thyroid hormone levels.

The median period of time required to achieve biochemical euthyroidism in the group of patients pretreated with antithyroid drugs was 12 weeks (2 to 48 weeks). At the time methimazole was stopped (4 days before radioactive administration) the mean serum T_3

and FT_4 levels were 2.2 ± 0.5 nmol/L and 17.7 ± 5.3 pmol/L respectively. The mean ^{131}I dose (10.6 ± 5.7 *vs*. 8.9 ± 4.6) and the number of patients using propranolol (3 *vs*. 2) and/or oral contraceptives (9 *vs*. 8) were similar in both groups. Methimazole was replaced with propylthiouracil (300 mg/day) in three patients who developed a cutaneous rash. All patients remained clinically stable throughout the study. No patients presented symptoms or signs of clinical ophtalmopathy. Hypothyroid patients received L-thyroxin replacement therapy .The acute changes in serum thyroid levels and the effect of methimazole pretreatment on the ^{131}I therapy have been previously reported [2,4].

Serum TSH receptor antibodies

At baseline all patients but 2 (3%), both randomized to the hyperthyroid group, tested positive for TRAb. In hyperthyroid patients, we observed a decrease in mean serum TRAb levels between baseline and D0 (114.6 *vs*. 74.8 U/L), but it was not statistically significant (figure 1). In the group pretreated with methimazole, mean serum TRAb levels decreased significantly from baseline to D0 (100.3 *vs.* 56.8 U/L; P<0.05). Accordingly, 25% of patients from this group tested negative for TRAb at ^{131}I dosing.

Serum TRAb levels at the day of ^{131}I administration presented a significant correlation with serum T_3 levels (r=0.590; P<0.001), duration of disease (r = -0. 325; P=0.028) and 24-hour radioiodine uptake (r = 0.351; P = 0.018). Age (P=0.708), sex (P = 0.117), thyroid volume (P = 0.135) and smoking habit (P = 0.807) were not associated with serum TRAb levels on the day of ^{131}I administration.

Serum TSH receptor antibodies after ^{131}I administration.

Radioactive iodine treatment induced a significant increase in serum TRAb levels in both groups of patients (Figure 1A). In the hyperthyroid group a significant increase (74.8 to 285.2 U/L; 281%) was observed as early as 1 month after ^{131}I administration. Serum TRAb levels peaked at month 3 (399.4 U/L; 434%), followed by a progressive decrease to the baseline levels at month 12 (78.9 U/L).

In the group of patients treated with methimazole serum TRAb levels did not change between the day of treatment and month 1 (56.8 *vs.* 64.1 U/L) whereas a significant increase from 56.8 *vs.* 156.9 U/L (176%) was observed on month 3. Six months after ^{131}I administration mean serum TRAb levels were still significantly elevated compared to baseline values (153.3; 170%); Thereafter, we observed a progressive decrease until month 12, when mean serum TRAb levels reached the baseline values (70.3 U/L).

As illustrated by the figure 1A, the course of mean serum TRAb levels after ^{131}I administration was significantly different between the two patient groups (P<0.05). Mean serum TRAb levels were significantly higher in the hyperthyroid group than in pretreated patients at months 1 and 3 (285.2 *vs.* 64.1 U/L; P=0.027 and 399.4 vs. 156.9 U/L; P=0.033, respectively). After 01 year of ^{131}I administration, there was no difference in the mean serum TRAb levels between the groups (78.9 *vs.* 70.3 U/L; P=0.801).

Prognostic factors of ^{131}I-induced rise in serum TRAb levels

In order to identify possible factors associated with ^{131}I-induced rise in serum TRAb levels, all patients were grouped for analysis. A multiple regression analysis was performed with the variation between the serum TRAb levels on the day of treatment and month 3 (log_{10}TRAb) as dependent variable. The following potential predictor factors were included as independent variables: Sex, age, duration of disease, thyroid volume, serum T_3 levels on the day of treatment, and smoking habit. Only baseline serum T_3 levels remained significantly associated with the peak increment of serum TRAb levels at month 3 (r^2=0,21; P=0.011). All other variables were eliminated from the model.

Relationship between thyroid function outcome and change in serum TRAb levels.

One year after ^{131}I administration, no statistical differences were observed between pretreated or not-pretreated patients with respect to permanent hypothyroidism (55.2% *vs.* 56.3%), euthyroidism (31.0% *vs.* 28.1%) or persistent hyperthyroidism (13.8% *vs*. 15.6%)[4]. In addition, there was no correlation between thyroid function course after ^{131}I dosing, as determined by the mean serum T_3 and free T_4 levels, and the course of mean serum TRAb levels (Figure 1A-C). However, patients who became hypothyroid presented higher serum TRAb levels increment [24 patients, median 191.0 interquartile range, 643.2 (17.9 to 661.1)] than those in euthyroidism [8 patients, median 0.94, interquartile range, 55.7(-11.5 to 44.2)] or hyperthyroidism [7 patients; median 38.8, interquartile range, 224.2 (-7.8 to 216.4)] after 1 year of ^{131}I therapy (Figure 2A; P=0.038). Nevertheless, at the end of 1-year there was no statistical difference in the serum TRAb levels among euthyroid, hyperthyroid, or hypothyroid patients (Figure 2B). Furthermore, despite of the treatment group or thyroid function outcome, 1 year after receiving ^{131}I therapy for Graves' hyperthyroidism, 80% of patients from the hyperthyroid group and 85% of pretreated patients remained positive for TRAb (Figure 2B).

Discussion

The analysis of serum TRAb levels after radioiodine dosing showed that the biochemical euthyroidism achieved by methimazole pretreatment before ^{131}I therapy is enough to lessen the radioiodine-induced increases in TRAb levels. These results suggest that methimazole effect on immune system response to ^{131}I administration in Graves' patients is due to its primary effects on thyroid follicular cells, though reduction in thyroid hormone production.

It is well recognized that the onset of Graves' disease and the recurrence of hyperthyroidism following therapy are associated with elevated levels of antibody receptors [15-18]. The anti-TSH receptor antibodies are produced due to alterations in immune homeostasis by an yet undefined mechanism [13]. There are controversial evidences that antithyroid drugs have immunosuppressive actions that may contribute to the suppression of TSH receptor antibodies [6-11]. The decrease in serum TRAb levels and the increased remission rate in Graves' disease after methimazole compared to propranolol treatment [12], as well as an *in vitro* effect of methimazole on immunocytes [14], are among the mentioned evidences favoring an immunosuppressive effect of antithyroid drugs. However, the decreased lymphocyte production and/or secretion of immunoglobulins shown *in vitro* occur at methimazole concentrations much higher than those found in crude thyroid homogenates of patients taking methimazole [11,14]. Other evidence against the immune effect of antithyroid drugs is the fact that long term remission of Graves' disease would be unlikely to result from an immunosuppressive agent with a relatively short duration of action [13]. Under any circumstances, it has been difficult to prove or reject the immune effects of antithyroid drugs *in vivo*, since these medications also improve the thyroid overactivity, a known cause of immune disorder [13].

The finding that methimazole blocks the transitory increase in serum TRAb levels observed after ^{131}I administration in hyperthyroid Graves' patients [24], has been suggested as an evidence of an organ-specific immunity effect. Nevertheless, our results indicate that the hyperthyroidism improvement achieved by methimazole treatment, rather than methimazole itself, is enough to lessen the immune system in response to ^{131}I therapy. In patients receiving ^{131}I with high thyroid hormone levels, we observed a significant increase in mean serum TRAb levels as earlier as 30 days after ^{131}I dosing, reaching the peak 3 months later. By contrast, in the group of patients pretreated with methimazole until biochemical euthyroidism, the ^{131}I administration was done at nearly normal thyroid hormone levels and the observed increase in mean serum TRAb levels occurred only after 3 months, with much less intensity. The observed TRAb response pattern in the hyperthyroid group was very similar to those reported by different studies [20,22,24] while the 1-year serum TRAb levels course in methimazole treated patients was virtually identical to those reported by others in patients using methimazole [26]. Since methimazole has been stopped 4 days before ^{131}I administration, it is very unlikely such prolonged effect on immune system, especially when we examine the prompt increase in thyroid hormone levels after its discontinuation [2,3]. In fact, the observed response pattern could be explained by primary effects of methimazole on thyroid hormone production, with secondary effects on the immune system via reduced thyrocyte-immunocyte signaling [13]. Moreover, a similar pattern of change in serum TRAb levels has been shown in patients treated with perchlorate before ^{131}I therapy [19], indicating that the thyroid status at the time of ^{131}I administration is the main determinant of the ^{131}I -induced rise in serum TRAb levels in Graves' patients.

Accordingly, serum T_3 levels on the treatment day was identified as the only independent predictor of the magnification of serum TRAb levels in response to ^{131}I in a multiple linear regression model. It is interesting to note, however, the lack of correlation between the thyroid hormone concentrations after ^{131}I and serum TRAb levels course, suggesting that once the release of thyroid cell antigens had occurred, with subsequent stimulation of antibody formation, the immune response pattern is independent of thyroid hormone status.

The clinical implications of the increase in serum TRAb levels after ^{131}I therapy is still a matter of speculation. Chiovato et al [26] has suggested that the increase in serum TRAb levels is caused by the release of TSH receptor molecules from disrupted follicular cells. Because the TSH receptor is a membrane protein, the post-radioiodine increase in serum levels of this antibody would be a marker of thyroid cell damage produced by ^{131}I, and a favorable prognostic for cure. In fact, we also observed that the patients who became hypothyroid presented larger increment in serum TRAb levels than patients who were in hyperthyroidism or euthyroidism at the end of the study. Assuming the serum TRAb levels as a marker of thyroid damage, it is interesting to note the similarity in serum TRAb increase between euthyroid patients and those who did not respond to ^{131}I therapy. This observation may reflect the clinical dilemma to calculate the ideal ^{131}I dose in order to preserve the thyroid function and, at the same time, avoid an unsuccessful therapy. Similar to what have been reported by others [27], 1 year after ^{131}I therapy most patients, regardless thyroid outcome, remained positive to TRAb, emphasizing that the underlying autoimmune dysfunction is still present.

Some studies have associated ^{131}I therapy with worsening of Graves' ophthalmopathy [28-31], and it has been hypothesized that the radiation damage would result in the release of thyroid antigens, which will promote an immune response against orbital components that share antigenic epitopes with the thyroid [32]. Based on this assumption the role of methimazole in the ophthalmopathy course after ^{131}I treatment has been addressed by some studies [33]. The authors concluded that although methimazole was able to suppress the surge of TRAb after ^{131}I, it was not of prognostic significance for development of Graves' ophthalmopathy. In addition, glucocorticoid therapy does not block the TRAb increase after ^{131}I [34] but it seems to have a therapeutic role in preventing ophthalmopathy development [30,35]. In this study, no patient from either group developed clinical ophtalmopathy during the 1-year follow up. Although we could not exclude a role of TRAb in the exacerbation of a preexisting ophthalmopathy because we have excluded patients with moderate or severe eye disease, it appears that the surge in serum TRAb levels does not have a major role in Graves' ophtalmopathy pathogenesis.

In conclusion, our results demonstrated that in patients with Graves' disease, the mechanisms regulating autoantibody production after radioactive iodine administration are mainly influenced by the serum T_3 levels. Although the ^{131}I treatment-induced rise in serum TRAb levels was associated with the development of hypothyroidism, the increase in serum TRAb levels does not appear to have a major role in the natural course of the autoimmune disorder in Graves' disease.

References

115.Cooper D.S. Antithyroid drugs and radioiodine therapy: a grain of (iodized) salt. Ann Intern Med 1994; 121:612-14.

116.Andrade V. A, Gross J. L. and Maia A. L. Effect of methimazole pretreatment on serum thyroid hormone levels after radioactive treatment in Graves' hyperthyroidism. J Clin Endocrinol Metab 1999; 84:4012-16.

117.Burch H.B., Solomon B.L., Cooper D.S., Ferguson P., Waplert N., and Howard R. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after ^{131}I ablation for Graves' disease. J Clin Endocrinol Metab 2001; 86:3016-21.

118.Andrade V.A, Gross J.L. and Maia A.L. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 2001; 86:3488-93.

119.Braga M., Walpert N., Burch H.B., Solomon B.L., and Cooper D.S. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. Thyroid 2002; 12: 135-39.

120.Weetman A. P., Holt M. E., Campbell A. K., Hall R., McGregor A.M. Methimazole and generation of oxygen radicals by monocytes: potential role in immunosuppression. Br Med J 1984; 288:518-20.

121.Tötterman T. H., Karlsson F. A, Bengtsson M. and Mendel- Hartvig I. Induction of circulating activated supressor- like T cells by methimazole therapy for Graves' disease. N Engl J Med 1987; 316:15-22.

122.Komiya I., Yamada T., Sato A., Kouki T., Nishimori T., and Takasu N. Remission and recurrence of hyperthyroid Graves' disease during and after methimazole treatment when assessed by IgE and Interleukin 13. J Clin Endocrinol Metab 2001; 86 (8): 3540-44.

123.Zantut-Wittmann DE, Tambascia M.A, Silva Trevisan M.A., Pinto G.A., Vassalo J. Antithyroid drugs inhibit in vivo HLA-DR expression in thyroid follicular cells in Graves' disease. Thyroid 2001; 11(6): 575-80.

124.Fenzi G., Hashizume K., Roudebush C. P., and DeGroot L. J. Changes in thyroid-stimulating immunoglobulins during antithyroid therapy. J Clin Endocrinol Metab 1979; 48:572-76.

125.McGregor A. M., Petersen M. M., McLachlan S.M., Rooke P., Smith B. R., and Hall R. Carbimazole and the autoimmune response in Graves' disease. N Engl J Med 1980; 303:302-7.

126.Weetman A. P., McGregor A. M. and Hall R. Evidence for an effect of antithyroid drugs on the natural history of Graves' disease. Clin Endocrinol 1984; 21:163-72.

127.Volpé R. Evidence that the immunosuppressive effects of antithyroid drugs are mediated through actions on the thyroid cell, modulating thyrocyte-immunocyte signaling: a Review. Thyroid 1994,4:217-23.

128.Hallengren B., Forsgren A., and Melander A. Effects of antithyroid drugs on lymphocyte function *in vitro*. J Clin Endocrinol Metab 1980; 51:298-301.

129.Davies T.F. Thyroid-stimulating antibodies predict hyperthyroidism. J Clin Endocrinol Metab 1998; 83:3777-83.

130.Takasu N., Yamashiro K., Komiya I., Ochi Y., Sato Y., and Nagata A. Remission of Graves' hyperthyroidism predicted by smooth decreases of thyroid-stimulating antibody and thyrotropin-binding inhibitor immunoglobulin during antithyroid drug treatment. Thyroid 2000; 10:891-96.

131.Glinoer D., Nayer P., Bex M; Belgian Collaborative Study Group on Graves' Disease. Effects of l-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double- blind prospective randomized study. Eur J Endocrinol 2001; 144(5): 475-83.

132.Kim T. Y., Park Y. J., Park D. .J., Chung H., Kim W. B., Kohn L. D., and Cho B. Y. Epitope heterogeneity of thyroid-stimulating antibodies predicts long-term outcome in Graves' patients treated with antithyroid drugs. J Clin Endocrinol Metab 2003; 88(1):117-24.

133.Wenzel K. W. and Lente J. R. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. J Clin Endocrinol Metab 1984; 58:62-9.

134.Atkinson S., McGregor A.M., Kendall-Taylor P., Peterson M.M. and Smith B.R. Effect of radioiodine on stimulatory activity of Graves' immunoglobulins. Clin Endocrinol 1982; 16:537-43.

135.Teng W., Stark R., Munro A.J., Young S.M., Borysiewicz L.K. and Weetman A. P. Peripheral blood T cell activation after radioiodine treatment for Graves' disease. Acta Endocrinologica 1990; 122: 233-40.

136.Soliman M., Kaplan E., Abdel-Latif A., Scherberg N. and DeGroot L.J. Does thyroidectomy, radioactive iodine therapy, or antithyroid drug treatment alter reactivity of patients' T cells to epitopes of thyrotropin receptor in autoimmune thyroid diseases? J Clin Endocrinol Metabolism 1995; 80; 2312-21.

137.DeGroot L.J. Radioiodine and the immune system. Thyroid 1997; 7:259-64.

138.Nakazato N., Yoshida K., Mori K., Kiso Y., Sayama N., Tani J., Nakagawa Y., and Ito S. Antithyroid drugs inhibit radioiodine-induced increases in thyroid autoantibodies in hyperthyroid Graves' disease. Thyroid 1999; 9:775-79.

139.Weetman A.P., McGregor A.M. Autoimmune thyroid disease: Developments in our understanding. Endocr Rev 1984; 5: 309-55.

140.Chiovato L., Fiore E., Vitti P., Rocchi R., Rago T., Dokic D., Latrofa F., Mammoli C., Lippi F.; Ceccarelli C., and Pinchera A. Outcome of thyroid function in Graves' patients treated with radioiodine: role of thyroid- stimulating and thyrotropin- blocking antibodies and of radioiodine- induced thyroid damage. J Clin Endocrinol Metab 1998; 83:40-46.

141.Aizawa Y., Yoshida K., Kaise N., Kaise K., Fukazawa H., Kiso Y, Mori K., Sayama N., Kikuchi K., and Abe K. Long-term effects of radioiodine on thyrotrophin receptor antibodies in Graves' disease. Clin Endocrinol 1995; 42:517-22.

142.Tallstedt L., Lundell G., Torring O., Wallin G., Ljunggren J., Blomgren H., Taube A., and the Thyroid Study Group. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. N Eng J Med 1992; 326:1733-8.

143.Tallstedt L., Lundell G. Radiodine treatment, ablation, and ophthalmopathy: a balanced perspective. Thyroid 1997; 7:241-45.

144.Bartalena L., Marcocci C., Bogazzi F., Manetti L., Tanda M.L., Dell' Unto E., Bossio G. B., Nardi M., Bartolomei M. P., Lepri A. L., Rossi G., Martino E. and Pinchera A. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73-78.

145.Bartalena L., Pinchera A., and Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev 2000; 21:168-99.

146.Gorman CA. Pathogenesis of Graves' ophthalmopathy. Thyroid 1994; 4:379-83.

147.Kung A.W.C, Yau C.C., and Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. J Clin Endocrinol Metab 1994; 79:542-46.

148. Gamstedt A, Wadman B, Karlsson A. Methimazole, but not betamethasone, prevents ^{131}I treatment–induced rises in thyrotropin receptor autoantibodies in hyperthyroid Graves' disease. J Clin Endocrinol Metab 1986; 62:773-77.

149. Bartalena L., Maracocci C., Bogazzi F., Panicucci M., Lepri A. and Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med 1989;321:1349-52.

Legends to Figures

Figure 1. Changes in serum TRAb (A), FT_4 (B) and T_3 (C) levels in patients with Graves' disease who were treated with radioiodine alone (hyperthyroidism) or methimazole + radioiodine (MMI-treated). The dotted lines denote the reference range. * $P < 0.05$ for the comparison with the value on the day ^{131}I dosing (D0). # $P < 0.05$ for the comparison between groups.

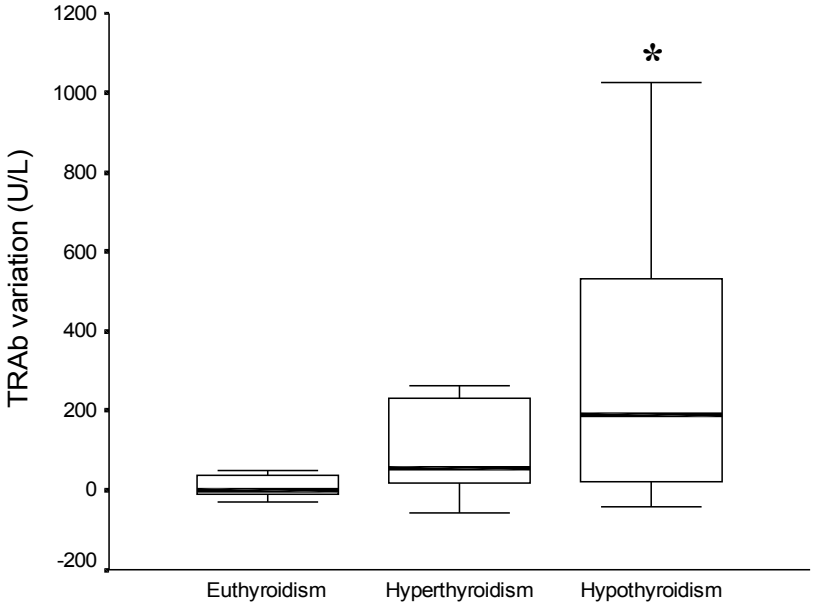
Figure 2. Serum TRAb increment (A) and serum TRAb levels at 1-year after ^{131}I treatment in patients with euthyroidism, persistent hyperthyroidism, or hypothyroidism. The dashed line denotes the upper normal values for TRAb (<11 U/L). *P<0.05.

Table 1. Characteristics of patients with Graves' disease on the day of ^{131}I administration.

	Hyperthyroid patients (N = 32)	**MMI -Treated patients** (N=29)
Age (years)	35.1 ± 7.6	37.4 ± 7.8
Sex (M/F)	4 / 28	2 / 27
Smokers (n)	15 (46.9%)	12 (41.4%)
Range of disease duration	7 (1 – 72)	12 (1-156)
Thyroid volume (mL) =	38.4± 19.8	31.3 ± 15.2
24 h radioiodine uptake (%)§	73.3 ± 17.5	70.0 ± 22.9
Dose ^{131}I (mCi)	10.6± 5.7	8.9± 4.6
Thyroxine - nmol/L	302.4 ± 95.2	155.7 ± 60.5*
Free Thyroxine - pmol/L	56.6 ± 19.7	21.6 ± 4.6*
Triiodothyronine - nmol/L	7.95 ± 3.8	3.78 ± 1.9*
Thyrotropin concentration	< 0.03	< 0.03
TRAb (U/L)	62.2 (10.6 -407)	77.5 (11.5- 311.4)

Values represent mean ± SD or median (range). **P* values for the comparisons between groups < 0.05. The reference ranges for laboratory values are: thyroxine, 56.3-160.9 nmol/L (4.5-12.5 µg/dL); free thyroxine, 8.4-23.2 pmol/L (0.6-1.8 ng/dL); triiodothyronine, 1.19-2.8 nmol/L (78-182 ng/dL); and thyrotropin, 0.4-4.5 mU/L. Normal values for thyrotropin–receptor antibody are < 11 U/L. To convert thyroxine values to µg/dL and free thyroxine values to ng/dL, divided by 12.87. To convert triiodothyronine values to ng/dL, divided by 0.01536. =Thyroid volume was measured by ultrasonography. §Iodine uptake was measured 24 hours after the oral administration of 5 µCi (185 kBq) of ^{131}I and expressed as a percentage of the administered dose; reference values are 15-35%.

A


1200
1000
800
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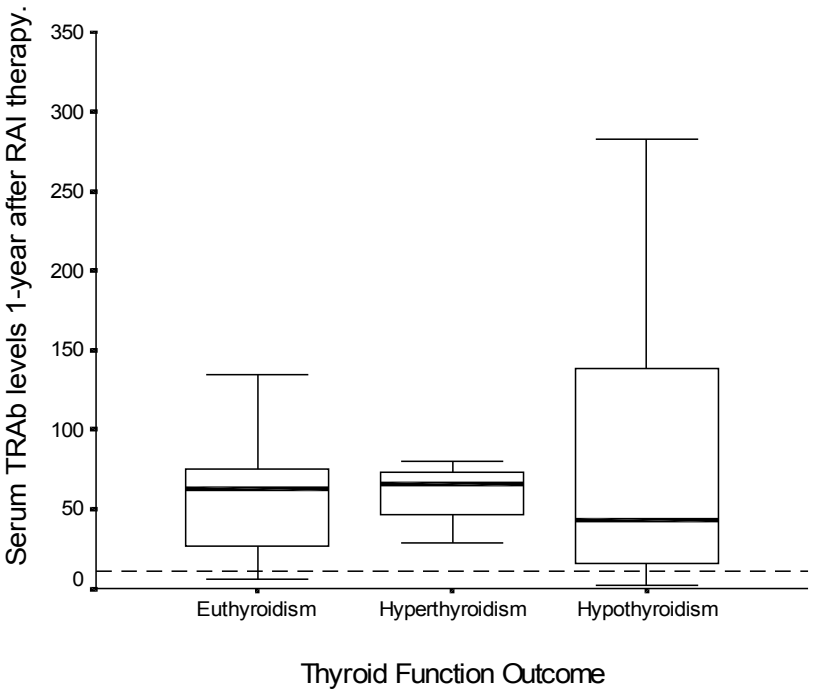
400
200
0
-200
TRAb variation (U/L)
*
Euthyroidism
Hyperthyroidism
Hypothyroidism

B


350
300
250
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Serum TRAb levels 1-year after RAI therapy.
Euthyroidism
Hyperthyroidism
Hypothyroidism
Thyroid Function Outcome