Rescue pre-operative treatment with Lugol's solution in uncontrolled Graves' disease

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Abstract

Background: Graves' disease is a common cause of hyperthyroidism. Three therapies have been used for decades: pharmacologic therapy, surgery and radioiodine. In case of adverse events, especially agranulocytosis or hepatotoxicity, pre-treatment with Lugol's solution containing iodine/potassium iodide to induce euthyroidism before surgery could be advocated, but this has rarely been reported.
Methods: All patients hospitalised due to uncontrolled hyperthyroidism at the Karolinska University Hospital 2005–2015 and treated with Lugol's solution were included. All electronic files were carefully reviewed manually, with focus on the cause of treatment and admission, demographic data, and effects of iodine on thyroid hormone levels and pulse frequency.
Results: Twenty-seven patients were included. Lugol's solution had been chosen due to agranulocytosis in 9 (33%), hepatotoxicity in 2 (7%), other side effects in 11 (41%) and poor adherence to medication in 5 (19%). Levels of free T4, free T3 and heart rate decreased significantly after 5–9 days of iodine therapy (free T4 53–20 pmol/L, $P = 0.0002$; free T3 20–6.5 pmol/L, $P = 0.04$; heart rate 87–76 beats/min $P = 0.0007$), whereas TSH remained unchanged. Side effects were noted in 4 (15%) (rash $n = 2$, rash and vomiting $n = 1$, swelling of fingers $n = 1$). Thyroidectomy was performed in 26 patients (96%) and one was treated with radioiodine; all treatments were without serious complications.
Conclusion: Treatment of uncontrolled hyperthyroidism with Lugol's solution before definitive treatment is safe and it decreases thyroid hormone levels and heart rate. Side effects were limited. Lugol's solution could be recommended pre-operatively in Graves' disease with failed medical treatment, especially if side effects to anti-thyroid drugs have occurred.

Key Words
- Lugol's solution
- iodine
- potassium iodide
- hyperthyroidism
- Graves' disease

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Introduction

Graves' disease (GD) is common and can be treated by medication blocking thyroid hormone synthesis with drugs such as methimazole, carbimazole or propylthiouracil. With medication for 12–18 months, cure can be achieved, which is sustained in around 50–55% (1). Another option is surgery, which is often considered in recurrence of GD after medical therapy, in patients with large goitres, and when pregnancy is planned in the near future. The third possibility is treatment with radioactive iodine, where thyrocytes are exposed to local radiation, with a subsequent decline of hormone secretion. In these two latter alternatives hypothyroidism is a deliberate goal, treated by life-long levothyroxine.

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Pharmacologic therapy is often chosen in Europe as it is mostly well-tolerated. However, there are well-known side effects. Most feared is agranulocytosis, but other potential side effects include hepatotoxicity, loss of taste, arthralgia and most commonly rash, which can be severe. As medical treatment is planned for a considerable time, even mild side effects can make it necessary to change therapy. Surgery is much safer if the patient is euthyroid, as the thyroid gland is highly vascularised, and anaesthetic as well as bleeding complications are more frequent in untreated thyrotoxicosis (2).

Lugol's solution (LS) was invented in 1829 by the French physician Jean Guillaume August Lugol as a cure for tuberculosis. It is a solution of elemental iodine (5%), potassium iodide (10%) and distilled water. It has been used as a disinfectant, as a reagent for starch detection in organic compounds, in histologic preparations, in dental procedures and in diagnosis of cervical cell alterations, also known as the Schiller's test. Already in the 1920s LS was given as a pre-treatment to thyroid surgery (3). It became the standard pre-operative treatment to control hyperthyroidism. However, with the development of pharmacologic agents blocking the thyroid hormone synthesis and radioactive iodine, the need for pre-treatment with LS diminished.

LS causes an increased thyroidal iodide uptake, inhibits thyroid peroxidase which attenuates iodide oxidation and organification (4), as well as blocking the release of thyroid hormones (5). This acute Wolff–Chaikoff effect results in an increase in intrathyroid iodine concentration within 24–48 h and a decrease in thyroid hormone synthesis in normal rats (6). Escape from the acute Wolff–Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter activity, causing a decrease in intrathyroid iodide concentration (7). Thus, there is a therapeutic window between achieved euthyroidism and an escape phenomenon, illustrated by a patient treated with iodine for more than 30 days who developed serious hyperthyroidism (8).

In untreated hyperthyroidism 0.5 mL (375 mg) daily treatment with LS significantly reduces both free thyroxine (FT4) and free triiodothyronine (FT3) within 5–10 days, while TSH remains below the limit of detection (9). Aside from the effects on FT4 and FT3 levels, iodine also decreases the rate of blood flow, thyroid vascularity and intraoperative blood loss during thyroidectomy (10, 11). When medical therapy with anti-thyroid drugs fails due to side effects, such as agranulocytosis, rescue treatment is warranted to avoid atrial flutter and thyroid storm. One option is treatment with beta-blockers (12, 13), which could be used alone in high doses or preferably together with iodine (14, 15). With the advancement of therapeutic options LS before thyroidectomy is no longer a routine in many countries (16, 17), although it is still advocated in ATA guidelines with 5–7 drops thrice daily for 10 days (18). The use of LS currently in countries where it is not routinely recommended is unclear.

The aim of this study was to investigate which factors lead to iodine treatment in patients with GD, outcome effects of LS on thyroid hormone levels and clinical hyperthyroidism by measure of heart rate changes at a major centre where LS is not the mainstay of therapy before thyroidectomy.

Materials and methods

This retrospective study was conducted at the Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden. All patients with an International Classification of Diseases version 10 (ICD-10), with a code of E050 (Graves' thyrotoxicosis) and treated with iodine during 2005–2015 were included and all medical files were reviewed manually. All specialist out-patient visits and admissions in Sweden are coded with ICD-10 codes by the attending physician and are thereafter stored in both local and national databases (19). Treatment with oral drops using the dental solution (iodine and iodide potassium) with the same concentration as LS (APL Pharma Specials, Stockholm, Sweden) was used to control hyperthyroidism. Iodine concentration per drop was also measured.

The study was in accordance with the ethical standards of the institutional, national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective study formal consent is not required.

Assays

Dxl chemiluminescent assay (Access HYPERsensitive hTSH, Beckman Coulter Inc, USA) was used to measure TSH (reference range 0.4–3.5 mE/L). FT4 and FT3 were also measured with Dxl chemiluminescent immunoassay by the same manufacturer (reference ranges 8–14 pmol/L and 3.5–5.4 pmol/L, respectively). Iodine concentration in Lugol's solution was measured in duplicate by a modified Sandell–Kolthoff method (20) with spectrophotometric detection on microplates using the Pyrex test tube

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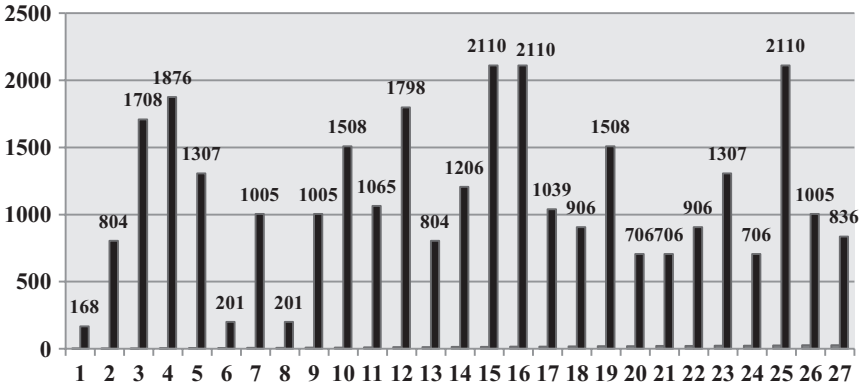

Figure 1
Accumulative doses of iodine solution in 27 patients with uncontrolled Graves' disease.

(12 × 100 mm) (Milton Roy Spectronic 301; Milton Roy Company, Rochester, NY, USA).

Statistics

Mean ± S.D. or median (range) was used when appropriate. Calculations were made using biochemical results at timepoint 0 compared with those at timepoint 1 and 2, and timepoint 0 vs 2. Differences were analysed with one-way ANOVA (Tukey's multiple comparisons test) using GraphPad Prism 7.01 (GraphPad Software). *P*-values <0.05 were considered significant.

Results

Twenty-seven patients (25 females) were treated with LS. Median age was 39 (23–64) years. All had GD with an elevation of FT4 and FT3, suppressed TSH, and measurable thyroid stimulating hormone receptor auto-antibodies (TRAb). They had all been treated with medical therapy previously, with the exception of one patient with primary neutropenia; eight (30%) had recurrent disease after finishing 18 months of previous medical therapy. One (4%) had also had a prior treatment with radioactive iodine. Four (15%) had thyroid associated ophthalmopathy with CAS ≥3. Two (7%) had moderate thyroid associated ophthalmopathy. Twelve subjects were smokers (44%), five (19%) were ex-smokers and 10 were (37%) non-smokers.

Twenty-six patients (96%) had a prior treatment with methimazole, and 16 (59%) had also tried to switch to propylthiouracil due to side effects. LS treatment was initiated in an out-patient setting in twelve patients (44%) with a dose of drops containing 6.7 mg/drop, most often 5 drops thrice, i.e., 100.5 mg iodine daily (timepoint 0). In all cases a set date for surgery was decided before iodine treatment was started, 7–10 days before thyroidectomy. Therapy was initiated at the ward for remaining fifteen patients (56%). In patients with unsufficient response, measured as elevated heart rate >80 and/or still evidence of biochemical hyperthyroidism, the dose was doubled after 2–5 days (n=15, 58%) (timepoint 1). A further re-evaluation was made at day 5 (5–9) (timepoint 2). All patients were admitted for the last part of the iodine treatment (6 days (0–12)), and recovery after surgery (1 day (1–3)). In all, patients received 1005 mg iodine (168–2110 mg) (Fig. 1). Initial dose in three patients was 1 drop thrice daily, and the one patient later treated with radioiodine was only taking LS for three days, explaining the wide range. Admission was planned in 22 patients (81%), while five patients (19%) were admitted acutely with a combination of atrial flutter and heart failure in one, rash in two and agranulocytosis and sepsis in two patients. A heart rate <80 was required before surgery. All but one patient (96%) were also treated with the beta-blocker propranolol as a part of the pre-operative treatment. The dose was initially 120 mg daily (40–240), and was increased during LS therapy to 130 mg (80–320) (P=0.005). Treatment with adjunctive therapy as cholestyramine or corticosteroids was not used.

Background information and side effects necessitating treatment with LS are shown in Table 1. The biochemical results at the commencement of LS and at follow-up are presented in Fig. 2. TSH levels did not change during treatment. FT4 levels were initially 53 pmol/L (20–100), after 2–3 days, 42 (18–100) (P=0.005) and after 6–9 days, 20 (8–52) (P=0.0002). During these time intervals FT3 levels were 20 pmol/L (6–50), 10 (5.7–36) (P=0.08) and 6.5 (4.3–8.3) (P=0.04), respectively. Heart rate changed from 87 beats/min (72–116) to 80 (54–120) (P=0.08) and 76 (60–96) (P=0.0007) following treatment (Fig. 2). Twenty-six (96%) subjects had total thyroidectomy and one (4%) was treated with radioactive treatment two months following LS (Table 1). The duration of treatment was 8.5 days (4–13).

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Table 1 Background data on 27 patients treated with Lugol's solution (LS).

Age	39 years (23–64)
Sex	25 females (93%)
Smokers	12 (44%)
Ex-smokers	5 (19%)
Non-smokers	10 (37%)
Thyroidectomy	26 (96%)
Planned admission	22 (81%)
LS indication	
Agranulocytosis	9 (33%)
Hepatotoxicity	2 (7%)
Other side-effects	11 (41%)
Poor adherence	5 (19%)

Four patients (15%) had adverse effects of iodine treatment (rash $n=2$, rash and vomiting $n=1$ and swelling of fingers $n=1$). This was managed with dose reduction in two and stopping LS prematurely in two. These four women were aged 30, 35, 43 and 61 years, respectively, and the LS dose ranged from 225 to 1708 mg. Thyroidectomy was uneventful in all 26 patients who underwent operation. However, 7 patients (27%) developed temporary post-operative hypocalcaemia, treated with alfacalcidol and calcium carbonate in 5 (19%) and with only the latter in two (8%).

Discussion

Graves' disease is a common condition, however, it can have serious consequences if not treated promptly (21). If anti-thyroid drugs fail or cannot be used, surgery or radioiodine therapy are the treatment options. However, pre-treatment is often necessary, especially before surgery to improve outcome. LS has been used in this setting but very little has been published about its use. To the best of our knowledge, this is the largest study to report on LS in patients with Graves' disease who have failed medical therapy. The most common reason for failure was side effects, but all were successfully treated with LS pre-operatively or before radioiodine treatment.

LS significantly decreased plasma thyroid hormone levels and heart rate. FT4 decreased relatively more than FT3 levels. As the half time for T4 is considerably longer (6–7 days) than that for T3 (24 h) (22), and T4 is more tightly bound to thyroxin-binding globulin, a sharper decrease in FT3 than in FT4 could be expected. However, our findings may be explained by the observation in smaller studies indicating that thyroid hormone release is also affected by LS (5, 23).

Median length of stay at the Karolinska University Hospital for thyroidectomy is 25 h, compared to six days in the present study which includes only patients with more complicated disease. Thus, the cost for these patients is considerable. The final days of pre-operative optimization with LS was performed in the in-patient setting, which may not be necessary. However, in those with adherence issues, or agranulocytosis and sepsis, the in-patient optimization seems reasonable. In cases with contraindication to medical therapy radioiodine treatment could be an option. However, this is rarely performed in

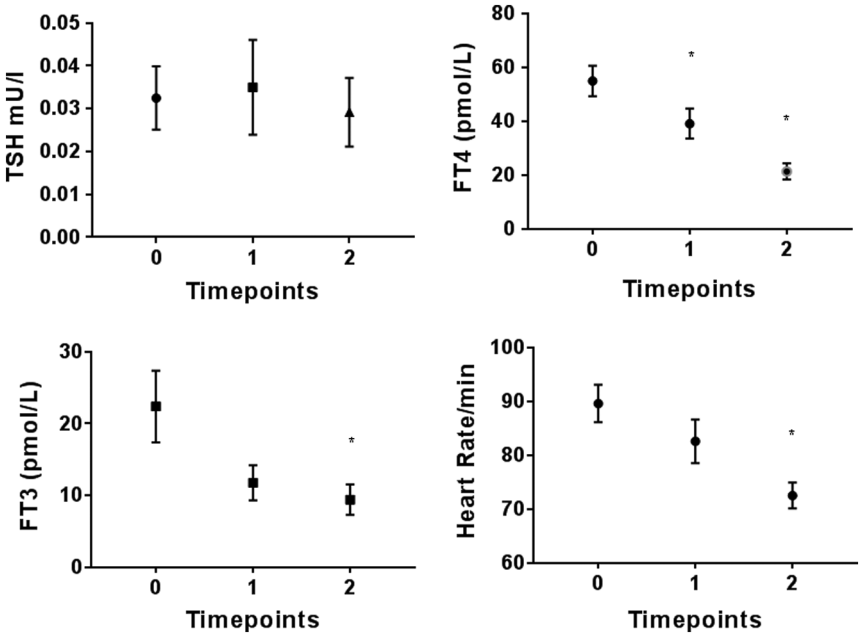

Figure 2
Initial TSH, free T4, free T3 and pulse, and changes during Lugol's solution. *Indicates $P<0.05$ compared to timepoint 0.

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uncontrolled GD, since there is a risk of aggravation of the thyrotoxicosis (24), and treatment failure (25, 26) may be due to high I^{131} turnover (27). Alternative pre-operative treatment in this cohort could be treatment with beta-blockers alone (12, 13), or radioiodine therapy, which was avoided due to a combination of uncontrolled GD, thyroid size, high TRAb levels and thyroid associated ophthalmopathy. Further potential treatments could have been the addition of cholestyramine (28), and corticosteroids in cases of thyroid storm (29).

During surgery all patients were well, indicating a clinically satisfactory effect of LS. It is also worth noting the non-hormone positive effects of LS on risks of bleeding and thyroid vascularity (10, 11), however this was not evaluated in the current study. The mechanism has been suggested to be mediated by decreased angiogenesis and blood flow since the thyroid arterial blood flow, VEGF and IL-16 are all significantly reduced by LS (30). As surgery in our patients was uneventful, and peripheral thyroid hormones did not become completely normal, a contributing effect on the vasculature of iodine solution is plausible. In this cohort, temporary hypocalcaemia was seen in 27% post-operatively. This was lower than that previously reported in more stable patients with 44–65% experiencing transient hypocalcaemia (31, 32).

Doses of LS differ in the literature. Individualized iodine dose in euthyroid GD patients also treated with anti-thyroid drugs was 0.8 mg/kg iodine daily in the study by Yilmaz *et al.* (11). Erbil *et al.* used 10 drops thrice daily for ten days (10), a duplication of the dose we initially administered, whereas the ATA guidelines recommend 5–7 drops thrice daily (18). In another study 150 mg iodine daily was used (33). Thus, different doses have been applied which makes comparisons difficult. It can be argued that the dose in our cohort should be higher as our subjects generally had untreated disease due to side effects of anti-thyroid therapy. Optimal doses and duration of therapy to achieve the positive effects on vascularity and bleeding complications are also unclear. Hypersensitivity to LS is a known side effect and this was developed by 15% of our cohort. We could not find any relationship between LS dose and side effects. Other adverse effects of LS besides allergic reactions include sialadenitis and gastrointestinal disturbances, which none of our patients experienced.

An intriguing aspect is the risk of exacerbating hyperthyroidism by time with prolonged iodine treatment. The therapeutic window has been claimed to be 10–14 days after iodine administration before the blocking effect vanishes. It has been reported that T4 and T3 start to increase again after 21 days of iodine treatment in hyperthyroid patients (33). On the other hand, in Japan long-term treatment with iodine has been used, alone or together with anti-thyroid drugs, to achieve euthyroidism with good results (34). Whether this also works in patients with other ethnic backgrounds and iodine sufficiency is not known and should be explored in future trials.

The inherent limitations of all retrospective studies, particularly in that of ascertainment bias, are also present in this study. Moreover, the number of patients included was limited. However, we did not exclude any patients commenced on LS, we had comprehensive medical files and the study is the largest so far in this setting.

In conclusion, the treatment of uncontrolled hyperthyroidism with LS is safe and it decreases thyroid hormones and pulse frequency. Side effects were limited. LS could be recommended pre-operatively in GD with failed medical treatment, especially if side effects to anti-thyroid drugs have occurred.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1 Abraham P, Avenell A, McGeoch SC, Clark LF & Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database of Systematic Reviews* 2010 **1** CD003420. (doi:10.1002/14651858.CD003420.pub4)
2 Pearce EN. Diagnosis and management of thyrotoxicosis. *BMJ* 2006 **332** 1369–1373. (doi:10.1136/bmj.332.7554.1369)
3 Plummer HS. The value of iodine in exopthalmic goiter. *Journal of the Iowa Medical Society* 1924 **14** 66–73.
4 Leung AM & Braverman LE. Consequences of excess iodine. *Nature Reviews Endocrinology* 2014 **10** 136–142. (doi:10.1038/nrendo.2013.251)
5 Paul T, Meyers B, Witorsch RJ, Pino S, Chipkin S, Ingbar SH & Braverman LE. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. *Metabolism* 1988 **37** 121–124. (doi:10.1016/S0026-0495(98)90004-X)
6 Wolff J & Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. *Journal of Biological Chemistry* 1948 **174** 555–564.
7 Eng PH, Cardona GR, Fang SL, Previti M, Alex S, Carrasco N, Chin WW & Braverman LE. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter

http://www.endocrineconnections.org
DOI: 10.1530/EC-17-0025

messenger ribonucleic acid and protein. *Endocrinology* 1999 **140** 3404–3410. (doi:10.1210/endo.140.8.6893)
8 Leustean L, Preda C, Ungureanu MC, Danila R, Mogos V, Stefanescu C & Vulpoi C. Jod-Basedow effect due to prolonged use of Lugol solution-case report. *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi* 2014 **118** 1013–1017.
9 Tan TT, Morat P, Ng ML & Khalid BA. Effects of Lugol's solution on thyroid function in normals and patients with untreated thyrotoxicosis. *Clinical Endocrinology* 1989 **30** 645–649. (doi:10.1111/j.1365-2265.1989.tb00270.x)
10 Erbil Y, Ozluk Y, Giris M, Salmaslioglu A, Issever H, Barbaros U, Kapran Y, Ozarmagan S & Tezelman S. Effect of Lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 2182–2189. (doi:10.1210/jc.2007-0229)
11 Yilmaz Y, Kamer KE, Ureyen O, Sari E, Acar T & Karahalli O. The effect of preoperative Lugol's iodine on intraoperative bleeding in patients with hyperthyroidism. *Annals of Medicine and Surgery* 2016 **9** 53–57. (doi:10.1016/j.amsu.2016.06.002)
12 Turner P & Granville-Grossman KL. Effect of adrenergic receptor blockade of the tachycardia of thyrotoxicosis and anxiety state. *Lancet* 1965 **2** 1316–1318. (doi:10.1016/S0140-6736(65)92340-8)
13 Adlerberth A, Stenstrom G & Hasselgren PO. The selective beta 1-blocking agent metoprolol compared with antithyroid drug and thyroxine as preoperative treatment of patients with hyperthyroidism. Results from a prospective, randomized study. *Annals of Surgery* 1987 **205** 182–188. (doi:10.1097/00000658-198702000-00013)
14 Feek CM, Sawers JS, Irvine WJ, Beckett GJ, Ratcliffe WA & Toft AD. Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. *New England Journal of Medicine* 1980 **302** 883–885. (doi:10.1056/NEJM198004173021602)
15 Schwartz AE, Clark OH, Ituarte P & Lo Gerfo P. Therapeutic controversy: thyroid surgery – the choice. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 1097–1105. (doi:10.1210/jcem.83.4.4740-1)
16 Kaur S, Parr JH, Ramsay ID, Hennebry TM, Jarvis KJ & Lester E. Effect of preoperative iodine in patients with Graves' disease controlled with antithyroid drugs and thyroxine. *Annals of the Royal College of Surgeons of England* 1988 **70** 123–127.
17 Shinall MC Jr, Broome JT, Baker A & Solorzano CC. Is potassium iodide solution necessary before total thyroidectomy for Graves disease? *Annals of Surgical Oncology* 2013 **20** 2964–2967. (doi:10.1245/s10434-013-3126-z)
18 Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, *et al.* 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 2016 **26** 1343–1421. (doi:10.1089/thy.2016.0229)
19 Falhammar H, Frisen L, Hirschberg AL, Norrby C, Almqvist C, Nordenskjold A & Nordenstrom A. Increased cardiovascular and metabolic morbidity in patients with 21-hydroxylase deficiency: a swedish population-based national cohort study. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 3520–3528. (doi:10.1210/JC.2015-2093)
20 Pino S, Fang SL & Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. *Clinical Chemistry* 1996 **42** 239–243.
21 Falhammar H, Thoren M & Calissendorff J. Thyrotoxic periodic paralysis: clinical and molecular aspects. *Endocrine* 2013 **43** 274–284. (doi:10.1007/s12020-012-9777-x)
22 Rang HP, Dale MM, Ritter JM, Flower RJ & Henderson G. *Rang and Dale's Pharmacology*, 7th ed. London, UK: Churchill Livingstone, 2010.
23 Safran M & Braverman LE. Effect of chronic douching with polyvinylpyrrolidone-iodine on iodine absorption and thyroid function. *Obstetrics and Gynecology* 1982 **60** 35–40.
24 Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, Bucher HC, Muller-Brand J & Muller B. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007 **334** 514. (doi:10.1136/bmj.39114.670150.BE)
25 Alexander EK & Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1073–1077. (doi:10.1210/jcem.87.3.8333)
26 Erem C, Kandemir N, Hacihasanoglu A, Ersoz HO, Ukinc K & Kocak M. Radioiodine treatment of hyperthyroidism: prognostic factors affecting outcome. *Endocrine* 2004 **25** 55–60. (doi:10.1385/ENDO:25:1:55)
27 Berg GE, Michanek AM, Holmberg EC & Fink M. Iodine-131 treatment of hyperthyroidism: significance of effective half-life measurements. *Journal of Nuclear Medicine* 1996 **37** 228–232.
28 Yang Y, Hwang S, Kim M, Lim Y, Kim MH, Lee S, Lim DJ, Kang MI & Cha BY. Refractory Graves' disease successfully cured by adjunctive cholestyramine and subsequent total thyroidectomy. *Endocrinology and Metabolism* 2015 **30** 620–625. (doi:10.3803/EnM.2015.30.4.620)
29 Baeza A, Aguayo J, Barria M & Pineda G. Rapid preoperative preparation in hyperthyroidism. *Clinical Endocrinology* 1991 **35** 439–442. (doi:10.1111/j.1365-2265.1991.tb03562.x)
30 Huang SM, Liao WT, Lin CF, Sun HS & Chow NH. Effectiveness and mechanism of preoperative Lugol solution for reducing thyroid blood flow in patients with euthyroid Graves' disease. *World Journal of Surgery* 2016 **40** 505–509. (doi:10.1007/s00268-015-3298-8)
31 Hallgrimsson P, Nordenstrom E, Bergenfelz A & Almquist M. Hypocalcaemia after total thyroidectomy for Graves' disease and for benign atoxic multinodular goitre. *Langenbeck's Archives of Surgery/Deutsche Gesellschaft fur Chirurgie* 2012 **397** 1133–1137. (doi:10.1007/s00423-012-0981-1)
32 Pesce CE, Shiue Z, Tsai HL, Umbricht CB, Tufano RP, Dackiw AP, Kowalski J & Zeiger MA. Postoperative hypocalcemia after thyroidectomy for Graves' disease. *Thyroid* 2010 **20** 1279–1283. (doi:10.1089/thy.2010.0047)
33 Philippou G, Koutras DA, Piperingos G, Souvatzoglou A & Moulopoulos SD. The effect of iodide on serum thyroid hormone levels in normal persons, in hyperthyroid patients, and in hypothyroid patients on thyroxine replacement. *Clinical Endocrinology* 1992 **36** 573–578. (doi:10.1111/j.1365-2265.1992.tb02267.x)
34 Okamura K, Sato K, Fujikawa M, Bandai S, Ikenoue H & Kitazono T. Remission after potassium iodide therapy in patients with Graves' hyperthyroidism exhibiting thionamide-associated side effects. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3995–4002. (doi:10.1210/jc.2013-4466)

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