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Low doses of cholestyramine in the treatment of hyperthyroidism

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Abstract The enterohepatic circulation of thyroid hormones is increased in thyrotoxicosis. Bile-salt sequestrants bind thyroid hormones in the intestine and thereby increase their fecal excretion. Based on these observations, the use of cholestyramine has been tried. The present study evaluates the effect of low doses of cholestyramine as an adjunctive therapy in the management of hyperthyroidism. In a prospective, randomized, double-blind, placebo-controlled trial, 45 patients with newly diagnosed hyperthyroid Graves' disease were randomly assigned into the following treatment protocols: group I, cholestyramine 2 g BID, methimazole and propranolol; group II, cholestyramine 1 g BID, methimazole and propranolol; group III, placebo powder, methimazole and propranolol. The fixed dose of methimazole (30 mg/d) and propranolol (40 mg/d) was used. The study period was 4 weeks. Serum total triiodothyronine and free thyroxin were measured at baseline, and at the ends of the second and the fourth week of the study. The serum thyroid hormone levels decreased more rapidly and to a greater extent in the cholestyramine-treated groups. All of the patients in group I had achieved euthyroid state at the end of the study. We conclude that low dose of cholestyramine is an effective and well-tolerated adjunctive agent in the treatment of hyperthyroid Graves' disease. (ClinicalTrials.gov number, NCT00677469)

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Introduction

The gastrointestinal tract has a role in thyroid physiology. Thyroid hormone is metabolized mainly in the liver, where it is conjugated to glucurunides and sulfates. These conjugation products are then excreted in the bile. Free hormones are released in the intestine and finally reabsorbed, completing the enterohepatic circulation of thyroid hormone. A very small portion of the daily production of thyroxin (T_4) and triiodothyronine (T_3), less than 10%, is excreted in the stool [1–3]. In people with normal thyroid function, this pathway of T_4 and T_3 recirculation contributes so little to hormone availability that patients who have gastrointestinal disease or are receiving drugs that decrease T_4 absorption do not have abnormal thyroid function [4]. However, the thyrotoxic states are characterized by an increased enterohepatic circulation of thyroid hormones, as well as by an increased urinary and fecal excretion of both conjugated and free T_4 [5, 6].

Cholestyramine, an ionic exchange resin sequesters T_4 in the intestine and increases its fecal excretion. These phenomena were proven in hamsters in mid-1960 s [7]. Experimentally, it has been shown that 50 mg of cholestyramine can bind approximately 3000 μg of T_4 [8] and therefore can enhance the clearance of thyroid hormones. Because of the increased enterohepatic circulation of thyroid hormones during hyperthyroidism, attempts have been made to sequester these hormones in the intestine using ionic exchange resins [9–13]. Cholestyramine therapy has been studied in the treatment of thyrotoxicosis as an

adjunctive therapy to thionamides, and has been found to decrease thyroid hormone levels rapidly. In several trials, cholestyramine in combination with methimazole (MMI) or propylthiouracil, caused a more rapid decline in thyroid hormone levels than standard therapy with thionamides alone [9–11, 13]. In all of these trials, cholestyramine was dosed at 4 g orally two to four times a day.

This study was conducted to examine the efficacy of combination therapy of lower doses of cholestyramine with MMI and propranolol for treating patients with Graves' hyperthyroidism.

Results

Forty-five patients (30 women and 15 men, aged 20–54 years) with Graves' hyperthyroidism entered into the study. The mean age was 31.4 ± 5.2 years. The duration of symptoms of hyperthyroidism was 1–12 months. All the patients completed the study with good compliance and no loss of follow up. There were no significant differences in age, sex, body mass index, duration of symptoms, size of the thyroid gland, serum thyroid stimulating hormone (TSH), total T_3 (TT_3) and free T_4 (FT_4) levels between treatment groups at the baseline (Table 1).

As shown in Table 2, thyroid hormone levels decreased more rapidly and to a greater extent in the cholestyramine-treated groups (groups I and II). At the end of the second week of treatment, TT_3 and FT_4 levels had decreased more in groups I and II than those in placebo group (group III) (TT_3, group I: 45% and group II: 50% vs. group III: 29% reduction from baseline; FT_4, group I: 49% and group II: 54% vs. group III: 33% reduction from baseline). At the end of the fourth week, TT_3 and FT_4 levels had decreased more in the cholestyramine-treated groups (TT_3, about 60% reduction from baseline in groups I and II vs. 46% in group III; FT_4, 65% reduction from baseline in groups I and II vs. 53% in group III). Also there was no significant difference in the extent of reduction of thyroid hormone levels from baseline between both cholestyramine-treated groups at the ends of the second and the fourth week of treatment.

At the end of the second week of the study, 76% of the patients in group I and 60% in group II had achieved normal TT_3 and FT_4 levels, but only 26% of the patients in group III had normalized their thyroid hormone levels. At the end of the study, all of the patients in group I and 87% in group II had achieved euthyroid state, but only 60% of patients in group III had normal serum TT_3 and FT_4 levels. All of the patients in cholestyramine-treated groups tolerated the cholestyramine well. No significant bloating, flatulence, or constipation was reported.

Discussion

This study demonstrates that low doses of cholestyramine are effective in producing a rapid and complete decline of thyroid hormones in patients with hyperthyroid Graves' disease, when used in combination with methimazole and propranolol.

Experimental data has indicated that cholestyramine binds thyroxin thereby preventing its gastrointestinal reabsorption, and causing increased fecal T_4 excretion. In Syrian hamsters, 2.5 times more radiolabeled T_4 was found in the carcasses of control animals than in animals treated with cholestyramine for 14 days, with the difference accounted for by an increased fecal excretion of the T_4 [7]. In other experiments in rats, it was found that only 2.3% of labeled thyroxin crossed the intestinal wall during cholestyramine administration, while 73.9% was transported in the absence of cholestyramine [8]. Northcut et al. evaluated the absorption of radiolabelled thyroxin in two hyperthyroid patients and five healthy volunteers. In both patients and healthy volunteers, when cholestyramine was administered within 4–5 h after the use of levothyroxine, significant reduction (>50%) in levothyroxine absorption occurred [8]. Even though it is well established that anion exchange resins impair the absorption of exogenously administered T_4, in the euthyroid subject they do not cause a significant reduction in circulating thyroid hormone levels [14]. This could be due to the fact that the enterohepatic circulation is not increased in the euthyroid state (as it is in

Table 1 The baseline characteristics of the hyperthyroid Graves' patients before antithyroid drug therapy. Data are presented as means ± SD

Clinical parameters	Group I (n = 15)	Group II (n = 15)	Group III (n = 15)
Age (years)	32.1 ± 6.2	31.2 ± 5.7	32.4 ± 5.1
Female/male (cases)	10/5	9/6	11/4
Body mass index (kg/m^2)	22.7 ± 4.0	22.4 ± 3.5	21.7 ± 3.5
Duration of symptoms (months)	6.0 ± 2.8	5.23 ± 3.2	5.27 ± 3.4
Size of thyroid gland (g)	39.3 ± 5.3	41.1 ± 5.0	40.6 ± 4.8
TSH (μIU/ml)(0.2–5.1)	0.07 ± 0.02	0.05 ± 0.03	0.04 ± 0.03
Total T_3 (ng/dl)(70–205)	397.5 ± 169.0	412.2 ± 128.8	386.3 ± 182.4
Free T_4 (ng/dl)(0.8–2.0)	4.28 ± 1.91	4.16 ± 1.4	3.85 ± 1.4

Table 2 Thyroid hormone levels at the ends of the second and the fourth week of the study. Values represent means ± SD

Hormones	Group I	Group II	Group III	*P* value		
				I vs. II	I vs. III	II vs. III
Total T_3						
Baseline (ng/dl)	397.5 ± 169.0	412.2 ± 128.8	386.3 ± 182.4			
Week 2 (ng/dl)	188.1 ± 30.5	198.9 ± 63.8	259.6 ± 88.4			
Week 4 (ng/dl)	134.8 ± 29.3	139.6 ± 47.0	188.3 ± 62.3			
% reduction from baseline						
Week 2 (%)	45.3 ± 20.9	50.1 ± 14.9	28.5 ± 18.2	0.47	0.015	0.002
Week 4 (%)	60.5 ± 17.3	63.7 ± 14.6	46.3 ± 19.9	0.67	0.031	0.009
Free T_4						
Baseline (ng/dl)	4.28 ± 1.9	4.16 ± 1.4	3.85 ± 1.4			
Week 2 (ng/dl)	1.81 ± 0.4	1.87 ± 0.7	2.50 ± 0.8			
Week 4 (ng/dl)	1.21 ± 0.3	1.25 ± 0.6	1.73 ± 0.5			
% reduction from baseline						
Week 2 (%)	49.3 ± 23.3	54.4 ± 11.3	32.5 ± 16.2	0.43	0.013	0.001
Week 4 (%)	65.3 ± 18.4	69.7 ± 11.8	52.9 ± 12.7	0.42	0.025	0.003

the hyperthyroid patient), and perhaps because of a compensatory increase in thyrotropin secretion as the thyrotroph senses that the circulating thyroid hormone levels are declining slightly.

Our results are similar to the previous studies that found cholestyramine produces a more rapid decline in thyroid hormone levels than antithyroid medication used alone [10, 11]. Solomon's study had a double-blind, placebo-controlled, cross-over design but it only included a total of 15 patients. Statistical significance was noted in regard to the reduction of total and free T_4 but not TT_3 [10]. In that study, experimental group received cholestyramine powder 4 g four times per day and the patients were given varying doses of MMI, ranging from 15–60 mg/day, as determined by their clinical condition [10]. In our study, we included 45 patients with fixed doses of MMI (30 mg/day) and with too much lower doses of cholestyramine powder (group I: 4 g/day; group II: 2 g/day). Interestingly, Solomon et al. measured thyroid stimulating immunoglobulin and thyrotropin-binding inhibitory immunoglobulin and did not find any differences between the cholestyramine and the placebo treated patients in regards to these indexes of thyroid autoimmunity [10]. Mercado et al. included 30 patients with newly diagnosed Graves' disease, but the study was not placebo-controlled. The dosage of cholestyramine powder was 4 g TID for 1 month with fixed doses of MMI (30 mg/day). The levels of total and free T_4 as well as TT_3 all achieved a significant reduction at the end of the study [11]. In our study that included more patients, the levels of TT_3 and FT_4 all produced a significant reduction at the end of the second and the fourth week of the study with use of lower doses of cholestyramine. Tsai et al. used propylthiouracil (instead of MMI) and cholestyramine (4 g twice a day) in the treatment of 30 patients with Graves' hyperthyroidism in an uncontrolled study [13]. The results were similar to our study, but with use of higher doses of cholestyramine.

We designed two cholestyramine-treated groups with different doses of cholestyramine. Interestingly, the extent of reduction of serum TT_3 and FT_4 levels from the baseline at the ends of the second and the fourth week were similar in these two groups. Also, this study showed no significant difference between uses of 4 g (2 g BID) and 2 g (1 g BID) daily of cholestyramine powder in restoring euthyroid state to Graves' hyperthyroid patients after 4 weeks of therapy.

Constipation and abdominal discomfort are the primary side effects of cholestyramine treatment. In our study, in all the cholestyramine-treated patients, the treatment was well tolerated and no constipation was reported. Low doses of cholestyramine, high fiber diets in Iranian culture and the increased frequency of bowel movements in thyrotoxic state [15] could be the reasons why no constipation was found in our patients. Cholestyramine seems to decrease thyroid hormone levels at a slower rate than agents such as inorganic iodide and sodium ipodate. However, the use of iodide and ipodate is limited to the treatment of thyroid storm, given the development of escape phenomenon [16]. In contrast, cholestyramine's effect is maintained for at least 4 weeks, as other studies [10, 11, 13] and the present study have shown.

In conclusion, low dose of cholestyramine is an effective and well-tolerated adjunctive agent in the treatment of Graves' hyperthyroidism. It produced a more rapid and complete decline of thyroid hormone levels, and by 4 weeks of treatment, almost all the patients achieved the euthyroid state. Even though the use of antithyroid

medications alone will eventually achieve the same goal, it may have a role in extremely thyrotoxic patients in whom a rapid decline in thyroid hormone levels is desirable to avoid the risk of thyroid crisis.

Materials and methods

A prospective, randomized, double-blind (physician and patients), placebo-controlled design was used. Forty-five patients with newly diagnosed hyperthyroid Graves' disease were recruited from outpatient clinic at Namazi Hospital and randomly assigned (by research physician) to one of the following treatment protocols: group I (15 cases) taking cholestyramine 2 g BID, MMI 10 mg TID, and propranolol 20 mg BID; group II (15 cases) taking cholestyramine 1 g BID, MMI 10 mg TID, and propranolol 20 mg BID; group III (15 cases) taking placebo powder 1 g BID, MMI 10 mg TID, and propranolol 20 mg BID. The study period was 4 weeks in all the three groups.

The diagnosis of hyperthyroidism was established by the presence of signs and symptoms of thyrotoxicosis, accompanied by a diffuse goiter, an increased 24-h radioiodine uptake and biochemical evidence of hyperthyroidism [high circulating total and free T_4 and TT_3, as well as a suppressed TSH levels]. None of the patients had been treated previously. Patients with evidence of diabetes, kidney, or liver disease were not included in the study. All subjects gave their written informed consent after the investigator's explanation of the study, and the local Ethics Committee approved the study. Our research physician positively conducted a powder and pill count to ensure good compliance of patients over the 4-week study time. The treatment code was revealed at the termination of the study.

Patients were visited at the ends of the second and the fourth week of the study, and blood samples were taken for measurement of serum TT_3 and FT_4. The TSH level was measured only at baseline by immunoradiometric assay (IRMA) with inter- and intraassay coefficient of variation (CVs) of 5.2% and 3.8% respectively (Biosource TSH-IRMA kit, Biosource Europe S.A., Nivelles, Belgium). Serum TT_3 was determined by radioimmunoassay (RIA) with interassay CVs of 4.3% and intraassay CVs of 3.2% (Kavoshyar T_3 RIA, Kavoshyar Iran Co., Tehran, Iran). Serum FT_4 was measured by a solid phase competitive enzyme immunoassay with inter- and intra-assay CVs of 4.5% and 3.7% respectively (DRG Free T_4 ELISA, EIA–2386, DRG Instruments GmbH, Germany).

Statistical analysis

The analysis was performed using Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS Inc., 2001 Chicago, IL, USA). One-way ANOVA test was used for comparison of the percent reduction of serum TT_3 and FT_4 levels from baseline between treatment groups. P values <0.05 were considered as significant.

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