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Children with hyperthyroidism younger than age 7 require higher mg/kg doses of methimazole to normalize free T4 compared to older children

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Abstract

Background: Hyperthyroidism is much less common in children <7 years vs. older children and less well studied. It was our impression that the youngest patients needed a higher weight-based dose of methimazole (MMI) to achieve euthyroidism.

Objectives: To compare the mean MMI dose needed to normalize free T4 in younger (<7 years) vs. older children and the time taken to normalize free T4.

Methods: Based on chart review (2004–2012), patients were divided into groups based on age at diagnosis: <7 years (n=13), 7–12 years (n=30) and >12 years (n=40). Follow-up visits were reviewed until free T4 normalized.

Results: The mean dose of MMI (mg/kg/day) needed to normalize free T4 was 0.71 (±0.29) in the <7 group, significantly higher vs. the two older groups: 0.50 (±0.22) and 0.44 (±0.24). Months taken to achieve a euthyroid state was significantly longer in children <7 (6.23±3.91) vs. the older groups (3.10±2.12 and 3.18±2.86 months).

Conclusion: Hyperthyroid children diagnosed before age 7 required higher initial doses of MMI and took a longer time to become euthyroid than older patients. Clinicians should consider starting with higher weight-based MMI doses when treating younger patients to more rapidly normalize free T4.

Keywords: hyperthyroidism; methimazole; young children.

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Introduction

Hyperthyroidism due to Graves' disease in children has a peak incidence between 10 and 15 years of age (1). Although it is generally considered rare in the youngest children, we have seen at our institution a significant number of children being diagnosed under age 7 years. Available treatment options for hyperthyroidism in children and adolescents include antithyroid medications, radioactive iodine ablation and thyroidectomy. Antithyroid medication is often preferred as the initial treatment (2) with the hope of avoiding permanent hypothyroidism from radioactive iodine or surgery. Methimazole (MMI) is preferred over propylthiouracil (PTU) because its longer half-life allows for less frequent dosing, and PTU use is very low since the issuance of a black box warning due to a risk of severe liver injury (3). Other than urticaria, adverse effects of methimazole such as neutropenia and arthralgias are uncommon (4).

MMI is generally started at a dose of 0.2–0.5 mg/kg/day (range 0.1–1.0 mg/kg/day) and titrated to achieve euthyroidism and avoid hypothyroidism (5). Specific dosing guidelines for treatment in very young children are less well defined in the current literature. There are three studies in which prepubertal patients were compared with older patients in terms of clinical findings and response to therapy (6–8). To our knowledge, no study has looked specifically at the initial response to treatment in the very young prepubertal subjects. It has been our impression that the MMI doses required to achieve a euthyroid state after initiation of treatment in children who developed hyperthyroidism before age 7, when expressed as mg/kg/day, are significantly higher than those needed for older children.

The primary objectives of this study were to compare the mean MMI dose needed to normalize free T4 in younger (<7 years) vs. older children (7–12 years and >12 years) and to compare the time taken to normalize free T4 between the younger vs. older children.

Materials and methods

A retrospective chart review of patients with hyperthyroidism seen at Children's National Medical Center between 2004 and 2012 was conducted by searching billing records for visits with a diagnosis code of 242.00 or 242.90. Patients were divided into three groups based on age at diagnosis: <7 years, 7–12 years and >12 years. To be included, patients needed to have been treated with methimazole until initial achievement of a euthyroid state, defined here as a free T4 of <2.0 ng/dL. This was chosen because free T4 was measured in various laboratories using different methodologies including the direct non-dialysis method and equilibrium dialysis, and the upper limit of normal in these assays ranged between 20.6 and 26 pmol/L (1.6 and 2.0 ng/dL). Thyroid stimulating hormone (TSH) was not used to define euthyroidism, as there is often a delay in normalizing TSH after free T4 has normalized (9). Patient characteristics reviewed in the chart included medical history, family history of thyroid disorders and Trisomy 21 status.

Follow-up visits were reviewed for free T4 (largely done by the equilibrium dialysis method at our institution), and MMI dose was calculated as mg/kg/day. Time in months to achieve a euthyroid state was determined and compared across age groups. To encompass both the time and dose variables in one number, we calculated a "methimazole responsiveness index"=(dose when euthyroid in mg/kg/day)×(months to achieve a euthyroid state). Data were calculated using Microsoft Excel and differences between groups were analyzed using Student's t-test. We reviewed subsequent visits for evidence of remission and relapse. Remission was defined as a documented normal free T4 and TSH at least 3 months after discontinuing methimazole. Relapse was defined as a reappearance of hyperthyroidism, defined as suppressed TSH and free T4 >26 pmol/L (>2 ng/dL) after stopping methimazole within any time frame.

Results

There were 13 patients in the <7 years group, with a mean age of 4.4 years (range, 3.1–6.6). The 30 patients in the 7–12 years group had a mean age of 10 years (7.4–12.3), and the 40 patients in the >12 years group had a mean age of 15.4 years (13.1–17.7) (Table 1). Over 75% of patients in all three groups were female. Family history was positive for thyroid disease for 77% of patients (n=10) <7 years old, 47% of patients (n=14) 7–12 years old and 35% of patients (n=14) 13–18 years old. Of patients <7 years old, 31% (n=4) also had a diagnosis of Trisomy 21, whereas 3% of patients who were 7–12 years old and 8% of patients 13–18 years old had Trisomy 21.

In Table 2, we present more detailed clinical, lab and treatment data on the 13 children diagnosed under 7 years of age. Initial thyroid tests show a range of severity at diagnosis from moderate to severe hyperthyroidism, which was similar to that seen in the older groups. We did not include TSH as it was fully suppressed in all cases. Because we did not have the same tests (total T4, free T4, T3) available for all patients, it was not possible to compare mean thyroid hormone levels at diagnosis for the different age groups. One patient (#9) developed urticaria, which resolved with dose reduction, but no cases of neutropenia or increased liver enzymes were noted.

The mean dose of MMI in mg/kg/day needed to normalize free T4 was 0.71 (±0.29) in the <7 years group vs. 0.50 (±0.22) in the 7–12 years group vs. 0.44 (±0.24) in the >12 years group (Table 1). Dose differences were significant between children diagnosed before age 7, and the two older groups (p=0.01, p<0.01). Time taken to achieve a euthyroid state was significantly longer in children diagnosed before age 7 vs. older children: 6.23±3.91 vs. 3.10±2.12 vs. 3.18±2.86 months (p=0.01, p=0.01). The mean MMI responsiveness index showed an even greater difference between the younger and the two older groups; it was 4.23 (<7 years old), 1.50 (7–12 years old) and 1.40

Table 1: Characteristics of the 3 age groups at diagnosis and during MMI treatment.

	Age <7	Age 7–12	Age >12
Number of patients	13	30	40
Mean age (range)	4.4 (3.1–6.6)	10 (7.4–12.3)	15.4 (13.1–17.7)
Mean weight at diagnosis (kg)	18.2 (13.6–24.9)	37.4 (19.7–64.5)	58.2 (21.3–86.6)
% Female	77	87	80
% Positive family history of thyroid disease	77	47	35
(%) with Trisomy 21[b]	4 (31%)	1 (3%)	3 (7.5%)
MMI mg/day when FT4 normal	13.85	18.06	25.13
MMI mg/kg/day when FT4 normal	0.71±0.29[a]	0.50±0.22	0.44±0.24
Time (months) from initial visit to first follow-up visit	2.8±2.01	2.1±1.34	2.0±1.44
Time (months) from initial visit to normal FT4	6.23±3.91[b]	3.10±2.12	3.18±2.86
Methimazole responsiveness index	4.23[c]	1.50	1.40
Percent attaining remission by the time of chart review	15% (n=2)	10% (n=3)	50% (n=20)

[a]p<0.01, p<0.00 vs. 7–12 and >12 year-old groups. [b]p<0.01 vs. 7–12 and >12 year-old groups. [c]p=0.004 vs. 7–12 group; 0.003 vs. >12 group.

Table 2: Clinical and initial lab data for patients diagnosed at younger than 7 years.

Case[b]	Age at Dx	Initial T4/FT4 nmol/L/ pmol/L (µg/dL/ng/dL)	Initial T3 nmol/L (ng/dL)	Wt (kg)	Months to euthyroid	MMI dose at euthyroid (mg)	MMI dose at euthyroid (mg/kg)
1	3.83	--/57 (--/4.42)	7.8 (505)	20.6	13	20	0.85
2[a]	5.25	179/27 (14/2.08)	4.0 (269)	15.1	5	7.5	0.43
3	3.67	--/103 (--/8.0)	10.5 (683)	16	12	12.5	0.63
4	4	417/99 (32.4/7.73)	10.5 (683)	15.2	2	20	1.2
5	4	205/41 (16/3.2)	5.9 (385)	N/A	12	10	0.49
6	3.83	--/60 (--/4.7)	ND	17.8	4	5	0.26
7[a]	5.58	--/39 (--/3.2)	ND	18.5	5	10	0.47
8	6.66	397/142 (31/>11)	ND	24.9	9	20	0.96
9[c]	5	270/121 (21/9.4)	ND	22.2	6	15	0.65
10[b]	4.92	315/-- (24.5/--)	ND	18.2	3	20	1.09
11[b]	3.08	--/71 (--/5.54)	ND	17.8	2	20	1.04
12[a]	4.75	--/--	FT3 14.3 pmol/L 9.4 pg/mL	17.9	4	10	0.49
13[a]	3.83	--/45 (--/3.48)	5.3 (342)	13.6	4	10	0.68

[a]Trisomy 21; [b]Patients 10 and 11 are siblings; [c]urticaria, which resolved with dose reduction.

(13–18 years old), with highly significant differences between the youngest and the two older groups (p=0.004, p=0.003). The percentage of patients attaining remission during the period of the chart review were 15% (n=2) vs. 10% (n=3) vs. 50% (n=20), respectively.

Discussion

There have been few previous studies comparing the clinical findings and therapeutic responses of children with Graves' disease based on age. In one study, prepubertal children had higher thyroid hormone levels when they initially presented and required longer treatment duration to achieve remission than pubertal children (6). The other two studies reported that the time to achieve remission in prepubertal patients was longer than for pubertal patients (7, 8) but did not report the time taken to achieve initial control of hyperthyroidism. No study has looked specifically at the initial response to medical treatment in the youngest prepubertal subjects. Our retrospective chart review provided evidence that children diagnosed with Graves' disease before age 7 required a mean higher initial dose of methimazole/kg/day to achieve a euthyroid state and took a longer time in months to achieve a euthyroid state than older children.

Our patients diagnosed with Graves' disease at younger than 7 years of age were more likely to have a family history of a thyroid disorder. This is in contrast to data from Shulman et al., who found a similar percentage with positive family history across age groups (6). In addition, a higher percentage of patients (31%) diagnosed before age 7 also had a diagnosis of Trisomy 21, though the numbers involved are small. The association of thyroid disorders and Trisomy 21 is well established, with hypothyroidism being more common than hyperthyroidism (10).

The reason that more MMI and longer periods of treatment were required to achieve a euthyroid state for the youngest children compared to the older two groups of children is not clear. The fact that there was no difference between doses required for the older two groups, one consisting of mainly prepubertal 7–12 year-old patients and one of mainly pubertal 13–18 year-old patients, would argue against the possibility that hormonal changes seen during puberty affect the MMI responsiveness. It also seems unlikely that compliance with treatment was worse in the younger group as due to their young age, there was likely greater parental supervision of medication than in older patients, particularly in teenagers. We speculate that as remission rates are lower in the very young, there may be an intrinsic difference in the progression and course of the disease accounting for the need for larger methimazole doses needed to control the hyperthyroid state. A difference in T3 levels at presentation in the very young children could be a factor, as studies have shown that high T3 levels at diagnosis predict a poorer response to antithyroid therapy (11). However, we had T3 levels on only 7 of 13 of the children under age 7, and they were not consistently obtained in the older children, so we could not adequately assess this possibility. Another possible explanation is that younger children may metabolize MMI more quickly than older children, but there is no published data to support or refute this explanation.

The limitations of this study included a small sample size in the youngest group and a retrospective design. We did not have free T4 and T3 data for every visit, particularly the initial visit for which labs were done at outside laboratories, but for follow-up visits most patients had free T4 levels

done by our hospital's equilibrium dialysis assay. There was also not a standardized interval between visits in the first year of treatment, so that for some patients, a longer period of time to achieve a free T4 of <2.0 could have been due to a longer interval between visits or a missed visit. We did find that the time from the initial visit to the first follow-up visit was slightly longer (2.8 months) for the <7 group than for the 7–12 group (2.1 months) and the >12 group (2.0 months), but this difference was mainly due to one patient (#5) not being seen for 8 months (mean without this patient was 2.3 months), and 9 of 13 had their first visit within 2 months. A prospective study with the same outcome measures would be useful to look in detail at differences observed between younger and older children to further delineate reasons for the need for higher doses and longer treatment times to achieve the initial euthyroid state.

Conclusion

Treatment of very young children with Graves' disease is a challenge. They are often very symptomatic on presentation, and they also appear to have a lower rate of long term remission. We present evidence that they need to be treated with a higher mean initial mg/kg/day dose of methimazole to avoid a prolonged period of hyperthyroidism. The use of such higher doses did not result in significant side effects We therefore propose using a higher initial weight-based dose of methimazole for children younger than 7 years of age than is typically needed for children older than 7. Based on our data, a dose of at least 0.7 mg/kg/day or 10–20 mg/day is an appropriate starting dose for children younger than 7 years.

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