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Clinical Study

Adverse Events Associated with Methimazole Therapy of Graves' Disease in Children

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Objective. Graves' disease is the most common cause of hyperthyroidism in the pediatric population. Antithyroid medications used in children and adults include propylthiouracil (PTU) and methimazole (MMI). At our center we have routinely used MMI for Graves' disease therapy. Our goals are to provide insights into adverse events that can be associated with MMI use. *Methods*. We reviewed the adverse events associated with MMI use in our last one hundred consecutive pediatric patients treated with this medication. *Results*. The range in the patient age was 3.5 to 18 years. The patients were treated with an average daily dose of MMI of 0.3 ± 0.2 mg/kg/day. Adverse events attributed to the use of the medication were seen in 19 patients at 17 ± 7 weeks of therapy. The most common side effects included pruritus and hives, which were seen in 8 patients. Three patients developed diffuse arthralgia and joint pain. Two patients developed neutropenia. Three patients developed Stevens-Johnson syndrome, requiring hospitalization in 1 child. Cholestatic jaundice was observed in 1 patient. No specific risk-factors for the development of adverse events were identified. *Conclusions*. MMI use in children is associated with a low but real risk of minor and major side effects.

1. Introduction

Graves' disease is the most common cause of hyperthyroidism in the pediatric population [1, 2]. Treatment options for Graves' disease include antithyroid medications, radioactive iodine, and surgery [1, 2]. Antithyroid medications used in children and adults include propylthiouracil (PTU) and methimazole (MMI), and carbimazole, which is metabolized to MMI, and is available in Europe but not the United States [3].

Recently, a significant safety concern related to hepatotoxicity risk associated with PTU use in children was brought to attention [4, 5]. It is thus now recommended that PTU not be used in children, except in special circumstances [4, 5], and MMI should be used for antithyroid drug therapy in children.

To date, the majority of publications related to medical therapy for Graves' disease have focused on children treated with PTU [6–14]. The use of MMI in children has been described in far fewer reports [15]. The description of the nature of adverse events that are associated with methimazole use in the pediatric population is modest, as well.

At our center, we have routinely used MMI for Graves' disease therapy for many years. To provide insights into adverse events that can be associated with MMI use, we reviewed the adverse events associated with MMI use in our last one hundred consecutive pediatric patients treated with this medication.

2. Methods and Materials

This review of treatment practice outcomes was conducted with the approval of the Yale University Human Investigation Committee. All adverse events were reported to the United States Food and Drug Administration via the MedWatch program. Patients with the diagnosis of Graves' disease were identified from ICD-9 coding (242.0 or 242.9).

The diagnosis of Graves' disease was made if there were elevated total and/or free thyroxine [T4] and/or triiodothyronine [T3] concentrations, subnormal thyrotropin levels, and evidence of thyroid autoimmunity not thought to be consistent with Hashitoxicosis. The presence of goiter and ophthalmopathy supported the diagnosis of Graves' disease; however eye disease was present in only 60% of the patients.

Table 1: Adverse events associated with methimazole.

Age at diagnosis	Gender	MMI dose at time of AE (mg/day)	Duration of therapy at time of AE	Reaction
3 5/12	M	10	12 weeks	Mild liver injury
4	M	10	32 weeks	Myalgias/joint pain/facial urticaria
4 4/12	F	10	2 weeks	Pruritis and hives
4 3/4	F	30	2 weeks	Stevens-Johnson syndrome
5 1/12	F	7.5	3 weeks	Diffuse urticaria
7 10/12	F	15	4 weeks	Arthralgia
8 2/12	F	10	2 weeks	Rash and joint pain
8 4/12	F	10	3 weeks	Urticaria
8 5/12	M	20	9 weeks	Arthralgia
8 10/12*	M	10	18 months	Neutropenia (ANCA+)
8 10/12*	M	10	18 months	Neutropenia (ANCA−)
10 7/12	M	40	4 weeks	Myalgias
11 1/2	F	20	4 weeks	Lymphopenia and eosinophilia
12 5/12	F	20	12 weeks	Myalgias
12 6/12	F	30	12 weeks	Stevens-Johnson syndrome (hospitalization)
14 2/12	F	30	4 weeks	Stevens-Johnson, syndrome
15 4/12	F	30	2 weeks	Rash
16 11/12	F	20	4 weeks	Rash on arms and face
17 6/12	F	30	3 weeks	Pruritic rash

* identical twins

In situations where there was a question of the diagnosis, a ^{123}I uptake and scan was performed. Patients were diagnosed with Graves' disease in this setting only if the ^{123}I uptake was elevated.

The medical records of the last 100 consecutively treated patients with the diagnosis of Graves' disease were reviewed. Data collected included the age, height, weight, ethnicity, and gender. Medication and dose information were also collected. Medical records were reviewed to determine if adverse events occurred, and the length of time from initiating therapy until when adverse events developed. For those patients receiving treatment with either surgery or radioactive iodine, this was noted. Initial thyroid function tests at diagnosis along with levels of thyroid stimulating immunoglobulin (TSI) or thyrotropin binding inhibitory immunoglobulin (TBII) were collected.

All data were recorded in an Excel data spread sheet. Data are presented as mean ± SEM. Statistical analysis among groups was performed by the Student's *t*-test.

3. Results

One hundred consecutively treated patients evaluated for Graves' disease were evaluated. The range in the patient age was from 3.5 years to 18 years. The mean age was 13.2 ± 3.5 years. 72% of the patients were female; 28% of the patients were male. 70% of patients were from the New Haven CT area; 30% of patients were from outside of the New Haven area. 62% of the individuals were Caucasian, 16% were Hispanic, 16% were Asian, and 6% were African American.

At diagnosis, TSH levels were 0.01 ± 0 mU/L. The initial total T4 levels were 18.3 ± 2.0 mcg/dL. The initial free T4 levels were 4.9 ± 2.4 ng/dL. Initial total T3 levels were 530 ± 175 ng/dL. TSI levels were available in 73% of the individuals and were 180 ± 70%. In all the patients in whom TSI was measured, levels were elevated.

The patients were treated with average daily dose of MMI of 0.3 ± 0.2 mg/kg/day. Medication was given once a day in 60% of patients and twice daily in 40% of patients.

Adverse events attributed to the use of MMI, were seen in 19 patients (Table 1). The most common side effects included pruritus and hives, which were seen in eight patients. Five patients developed diffuse arthralgia, muscle pain, and/or joint pain. One patient developed lymphopenia and esoinophilia. Two patients developed neutropenia with absolute neutrophil counts of 500 and 750 counts per cubic ml. This problem was detected upon evaluation of new onset fever. Three patients developed Stevens-Johnson syndrome with diffuse cutaneous eruption and mucous membrane involvement. One patient with Stevens-Johnson syndrome required hospitalization for three days. Mild liver injuryliver injury was observed in one patient. In this individual, the aspartate aminotransferase (AST; SGOT) was 184 u/L, the alanine aminotransferase (ALT; SGPT) was 379 u/L, the alkaline phosphatase was 355 u/L; the bilirubin was 0.18 mg/dL; and the gamma-glutamyl transpeptidase, (GGT) was 193 u/L. The age, methimazole dose, and length of time

from initiation of treatment until development of adverse events for each patient are shown in Table 1.

When clinical characteristics were compared in individuals who developed adverse events to methimazole with those who did not develop such reactions, no differences were detected as related to age, gender, dose, or ethnicity. There was no relationship to initial thyroid hormone levels, or circulating levels of immunoglobulins.

Of those individuals who developed adverse events to MMI, thyroidectomy was performed in three patients (ages 3–4 years). Radioactive iodine was administered to thirteen individuals (age range 8–18 years), and three patients were changed to PTU, as treatment with radioactive iodine or surgery was refused by the families.

Adverse events to MMI occurred within one month of therapy in 20% of the patients, within three months of therapy in 50% of patients, and within six months of therapy in 90% of patients. In three patients, adverse events occurred after one and a half years of treatment.

4. Discussion

Published reports related to the treatment of children with Graves' disease have generally involved cohorts of children treated with PTU [6–14]. These studies reveal an incidence of minor adverse events between 1% [13] and 15% [12]. Within reports in which the use of MMI has been described, there has been little description of adverse events associated with this medication. Our data suggest that methimazole can be associated with a risk of adverse events in up to 19% of individuals. If one excludes the eight patients with pruritus and hives, which are minor side effects, the more serious adverse events were found in 11% of patients.

Based on published reports describing outcomes for children treated with antithyroid medications for Graves' disease, up to 10 years ago, PTU was more widely used than MMI [11–13]. More recent data however, suggest that two thirds of children in the United States treated with antithyroid medications are now being treated with MMI, and one-third are treated with PTU [4].

Recently, a concerning risk of hepatotoxicity resulting in liver failure in children and adults and in pregnant women treated with PTU has been brought to attention [4, 16]. Based on the incidence of reported cases of acute liver failure and liver transplantation associated with PTU, it is estimated that up to 1 in 2,000 children will sustain acute liver injury in response to PTU [4, 16]. As the result, it is recommended that PTU not be used in children except in special circumstances, such as when an individual has had a toxic reaction to methimazole, and antithyroid medication is needed until definitive treatment either in the form of surgery or radioactive iodine can be performed [4]. As such, MMI use in the pediatric population is expected to increase.

Our data show that MMI is associated with adverse events in children. The most common adverse events were related to cutaneous eruptions and arthralgia. We observed one child who had cholestatic liver injury associated with methimazole. In the adult population, cholestatic liver injury has been reported to be associated with MMI use [17]. MMI associated liver injury is most typically seen in individuals who are older rather than younger, and in those who are treated with higher rather than lower MMI doses [17]. There were no reported cases of severe liver injury in any of our patients. In the individual who developed modest transaminase and alkaline phosphatase elevations, this condition reversed fully within one month after discontinuation of the medication.

Of concern was the development of Stevens-Johnson syndrome in three of the children, one of which required hospitalization. In each child, the condition reversed without long-term sequelae. Of note, the three patients who developed Stevens-Johnson syndrome were receiving large doses of MMI (30 mg). At present we do not know, though, if the risk of Stevens-Johnson syndrome is dose-related. Whereas most of the adverse events associated with MMI occurred within the first half year of the treatment onset, we observed adverse events after one and a half years of therapy in three children. These observations show that children treated with MMI warrant close follow-up for the development of potential toxic events.

Our observations raise the question about the utility of routine monitoring of hematological profiles or liver function tests or transaminase levels in patients on antithyroid medications. At present there is little evidence to support the notion that routine monitoring of these parameters is effective in minimizing the risk of antithyroid drug related adverse events [3, 18, 19]. If PTU is used, it is recommended that PTU should be stopped immediately and liver function and hepatocellular integrity be assessed in children who experience anorexia, pruritis rash, jaundice, light colored stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea or fatigue [19, 20]. In addition, PTU and MMI should be stopped immediately and white blood counts be measured in children who develop fever, mouth sores, pharyngitis, or feel ill [3]. While routine monitoring of white blood counts may detect early agranulocytosis, it is not recommended because of the rarity of the condition and the lack of cost-effectiveness [3, 18]. Agranulocytosis has been reported in about 0.3% of adult patients taking MMI or PTU [3, 18, 19]. Data of the incidence of agranulocytosis in children is not available, but is estimated to be very low. In adults, agranulocytosis is dose-dependent with MMI, and rarely occurs at low doses [3, 18]. When it develops, agranulocytosis typically occurs within the first 100 days of therapy in 95% of individuals [3, 18].

We recognized that a potential limitation of our study is that our referral patterns may bias our outcomes, as some of the patients coming for second opinions may have been treated beforehand with MMI doses higher than we typically use. The demographics of self-referred patients may also differ from that seen in a typical cross-section of children with Graves' disease. Our patients are also not typically treated beyond two years with MMI, which influences our ability to observe long-term side effects.

At present, PTU and MMI are the only antithyroid drugs available for Graves' disease in the United States [3]. PTU was introduced for clinical use in 1948 and MMI in 1950 [20]. Although MMI is less hepatotoxic than PTU, our data show

that MMI use is indeed associated with potential adverse events, which can be serious. Considering the hepatotoxicity risk associated with PTU, and the other minor and major adverse events associated with both PTU and MMI, strong consideration should be given to the development of less toxic antithyroid medications for use in children and adults.

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