Use of Antihistamines After Serious Allergic Reaction to Methimazole in Pediatric Graves' Disease

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Graves' disease, adverse drug reactions, methimazole, pediatric, disease management

ABBREVIATIONS
^{131}I—radioactive iodine
ATD—antithyroid drug
fT3—free triiodothyronine
fT4—free thyroxine
GO—Graves' ophthalmopathy
MMI—methimazole
PTU—propylthiouracil

Ms Toderian carried out the chart review and summarized the case, completed the literature review, and drafted the initial manuscript; Dr Lawson managed the patient, conceptualized the unique aspects of the case and clinical lessons, and reviewed and revised the manuscript; both authors approved the final manuscript as submitted.

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abstract

Antithyroid drugs are usually considered first-line therapy for management of pediatric Graves' disease because they avoid permanent hypothyroidism, provide a chance for remission, and are less invasive than the alternatives of thyroidectomy or radioactive iodine. Methimazole (MMI) is the only antithyroid drug recommended in pediatrics due to the risk of propylthiouracil-induced liver toxicity. Allergic reactions with MMI occur in up to 10% of patients and, when mild, can be managed with concurrent antihistamine therapy. Guidelines recommend discontinuation of MMI with serious allergic reactions. We present the case of an adolescent girl with Graves' disease and a serious allergic reaction after starting MMI whose family refused radioactive iodine and was reluctant to proceed to surgery. Antihistamine therapy was successfully used to allow continued treatment with MMI. This case demonstrates extension of management guidelines for minor cutaneous allergic reactions to MMI, through the use of antihistamines for a serious allergic reaction, allowing us to continue MMI and provide treatment consistent with the family's preferences and values. *Pediatrics* 2014;133:e1401–e1404

Graves' disease is the most common cause of hyperthyroidism among children.[1] Treatment options include antithyroid drugs (ATDs), radioactive iodine (^{131}I), or surgery, with ATDs recommended as initial therapy in the pediatric population.[2] Historically, ATD options included methimazole (MMI) or propylthiouracil (PTU). In 2008, however, an expert National Institute of Child Health and Human Development panel evaluated PTU drug safety in children and recommended that PTU should never be used as first-line therapy for pediatric Graves' disease because of the risk for PTU-induced liver failure.[2] MMI's safety profile is better than PTU's, but up to 19% of children experience adverse events, most of which are minor allergic reactions.[3] When pediatric patients have significant adverse reactions to MMI, including serious allergy, ^{131}I or thyroidectomy is recommended.[2]

We present the case of an adolescent girl with Graves' disease and a serious allergic reaction to MMI whose family refused ^{131}I and was reluctant to proceed to surgery. We describe how antihistamine therapy was successfully used to allow continued treatment with MMI, consistent with the family's preferences and values.

CASE PRESENTATION

A 15-year-old girl of Chinese descent was referred to our endocrinology clinic for hyperthyroidism (thyrotropin 0.01 mIU/L [normal 0.5–5.5]; free thyroxine [fT4] 63.5 pmol/L [4.93 ng/dL] [normal 8.7–13.6 pmol/L]; free triiodothyronine [fT3] 41.7 pmol/L [2708 pg/dL] [normal 3.1–6.0 pmol/L]). Symptoms included fatigue, increased appetite, neck swelling, and intermittent, self-resolving episodes of chest pressure lasting 30 seconds. Heart rate was 120 beats per minute; blood pressure 119/76 mm Hg. She had a visible tremor, left proptosis, bilateral chemosis, double vision, and lid lag. The thyroid gland was diffusely enlarged and rubbery on palpation, with no nodules or bruits. Thyroid microsomal antibodies were negative. The diagnosis of Graves' disease with concomitant Graves' ophthalmopathy (GO) was established.

Because of the chance of hyperthyroidism remission with ATDs and the family's desire to avoid ^{131}I, MMI was started at 15 mg twice daily (0.6 mg/kg/d). Three weeks later, the patient returned with a 2-day history of rash and pruritus, describing an urticarial rash on the arms, legs, and trunk occurring after MMI was taken, and disappearing within a few hours of taking the medication. MMI was discontinued and the patient experienced no further episodes of urticaria. MMI was restarted a week later at a reduced dosage of 10 mg twice daily. Ten days after restarting MMI, she returned to clinic with worsening urticaria and reported swelling of the tongue and throat, consistent with an immunoglobulin E–mediated Gell-Coombs type I hypersensitivity reaction, with potential for anaphylaxis.[4] Past medical history was negative for asthma, allergic rhinitis, and eczema. Thyroid function showed improved but persistent hyperthyroidism (thyrotropin $<$ 0.05 mIU/L; fT4 43 pmol/L [3.34 ng/dL]; fT3 33 pmol/L [2143 pg/dL]). The diagnosis of an adverse drug reaction to MMI was based on physical findings, the temporal relationship between symptomatology and MMI administration, and the documented adverse event with previous exposure to MMI. No laboratory investigations or immediate hypersensitivity skin testing was performed, because the positive and negative predictive values for drug-specific tests have not been determined for most agents, including MMI.[4] Because of the escalating nature of the patient's reactions and the possibility of anaphylaxis, MMI was discontinued. The urticaria and angioedema resolved after 4 days. Consultations with colleagues considered experts in pediatric thyroid disease recommended temporary use of PTU followed by ^{131}I.

The options of ^{131}I and thyroidectomy were presented to the family. They refused ^{131}I, expressing concerns about long-term safety. Medical staff were apprehensive about ^{131}I given her severe ophthalmopathy (which later required bilateral orbital decompression and lateral canthoplasties). In addition, the patient had booked travel to China 3 weeks later where she planned to spend 6 weeks visiting family, creating logistic challenges in arranging ^{131}I or thyroidectomy before she left, and thyroid monitoring while there.

The patient was referred to a pediatric allergist who advised that MMI could be safely restarted with a concurrent course of diphenhydramine, an ^{1}H histamine-receptor antagonist, at 20 mg once daily 1 hour before MMI administered as a single 15-mg bedtime dose, with the goal of blocking the vasodilation initiated by an ^{1}H mechanism in acute allergic reactions.[5] After 10 days, during which no allergic symptoms occurred, she was advised to increase MMI to 15 mg twice daily. The diphenhydramine was reduced to 10 mg daily after 2 months, and then a week later, stopped completely. Total duration of diphenhydramine was 10 weeks. Two weeks after stopping diphenhydramine, she had no thyroid or allergic symptoms and was biochemically euthyroid (fT4 11.5 pmol/L [0.89 ng/dL]; fT3 3.8 pmol/L [247 pg/dL]) with a persistently suppressed thyrotropin ($<$0.05 mIU/L). She continued with MMI for the next 2 years with no further allergic symptoms, remaining biochemically euthyroid with a gradual normalization of her thyrotropin.

DISCUSSION

In the event of a serious allergic reaction to MMI in children, PTU should

not be used, except as preparation for ^{131}I or surgery.[2] The Management Guidelines of the American Thyroid Association and the American Association of Clinical Endocrinologists recommend that persistent minor cutaneous reactions to MMI can be managed with concurrent antihistamines. In our case, we successfully implemented and extended this recommendation to a serious allergic reaction, with the patient followed closely by an allergist, enabling the treatment to be consistent with the family's preference for ATDs and avoidance of surgery and ^{131}I.

After starting MMI, our patient developed urticaria and concurrent angioedema of the tongue and throat, suggestive of potential anaphylaxis.[6] The cause of the allergic symptoms, although directly linked with timing of MMI initiation, cessation, and reintroduction, cannot be definitely attributed to MMI, particularly given the known association between chronic idiopathic urticaria and autoimmune thyroid disease.[7] The Naranjo algorithm is a validated questionnaire for establishing adverse drug reaction causality, with a score of 10 indicating definite causality and a score of 5 to 8 suggesting probable causality. Application of the Naranjo algorithm to our case provided a score of 6, suggesting probable adverse drug reaction to MMI.[8]

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death, so the Hyperthyroidism Management Guidelines recommending MMI discontinuation were followed. ^{131}I was refused by the family because of concerns about its long-term safety. The medical staff were also reluctant to use ^{131}I because of her severe GO. ^{131}I is associated with a small but increased risk of development or worsening of GO compared with ATDs and, therefore, steroid prophylaxis is required for patients with preexisting GO.[9] Thyroidectomy was also not consistent with the family's treatment preferences and is associated with a higher complication rate.[10] Additionally, there were logistical concerns regarding the patient's upcoming travel plans, which factored heavily in the patient's and health professional's decision-making. As a result, there was a strong desire by both family and medical staff to keep the patient on ATDs.

ATDs avoid permanent hypothyroidism, which usually occurs after ^{131}I and surgery.[1] Furthermore, ATDs offer a chance of remission. Studies suggest that 25% to 29% of children achieve remission with every 2 years of ATDs,[11,12] with a recent study reporting long-term remission rates up to 49% after 8 to 10 years of ATDs.[13] As a result, many practitioners will keep patients on ATDs for 2 to 3 years, and only if remission is not achieved, or there is an adverse reaction to ATDs or nonadherence, will they recommend ^{131}I or surgery. Older age at diagnosis, lower initial thyroid hormone concentrations, and a more rapid initial response to ATDs have been shown to be predictors of early remission.[11] Our patient falls within these criteria except for her high initial fT4 and fT3 levels, and so had she not had an adverse reaction, she would have been encouraged to continue MMI therapy for 2 to 3 years. The use of PTU, the only other ATD available, was highly discouraged, even in the short-term, because of the concerns of PTU-induced hepatotoxicity and because the patient would not have access to adequate safety medical monitoring (ie, liver transaminase levels) while traveling in China. Additionally, PTU could never be a long-term solution given current guidelines and the risk of PTU-induced hepatoxicity. As the allergic reaction was driving the clinical decision-making, an allergist's opinion was sought, leading to the recommendation that MMI could be safely continued with concurrent antihistamine therapy.

Management guidelines for pediatric Graves' disease recommend MMI, ^{131}I, or surgery, encouraging dialogue between practitioners and patients to choose the treatment that best suits the patient and the patient's values. This case illustrates the highly individualized, and often complex nature of the treatment of pediatric Graves' disease. To our knowledge, this is the first report of pediatric Graves' disease in which a patient was able to continue on MMI after a serious allergic reaction. The approach presented here may provide an option for practitioners and families who are reluctant to use ^{131}I or thyroidectomy after a serious allergic reaction to MMI. This case also provides support for, and draws attention to, the recommendation for continuing MMI with concurrent antihistamine therapy after a minor cutaneous adverse event.

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