

report of Sanders and Fritz,³ our patient has demonstrated a good tolerance to the ingestion of foods rich in folic acid, suggesting that the antigenic determinants responsible for the hypersensitivity reactions are not present or are occult in natural folates but appear in the unconjugated synthetic form of the vitamin (pteroylglutamic acid).

According to our results, it seems unlikely that we are dealing with a type I immunologic mechanism. Alternative pathways, such as the direct release of mast cell mediators and complement activation, could be relevant but were not determined. Given that people in North America and other countries are receiving this vitamin in the form of mandatory folic acid–fortified food, we recommend a high degree of suspicion in every patient with chronic urticaria and a history of folic acid intake.

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ALLERGIC REACTION TO MECASERMIN

Mecasermin (Increlex; Beaufour Ipsen Inc, Paris, France), a recombinant human insulin–like growth factor I (IGF-1), was approved by the Food and Drug Administration in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency. In studies of children with short stature treated with mecasermin, no serious allergic reactions have been reported.^{1–5} However, a recent case report described the first occurrence of anaphylaxis to mecasermin.⁶

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We report a second case of cutaneous and systemic reactions to mecasermin.

An 11-year-old boy with short stature (height, –3.9 SDs; weight, –1.7 SDs [20.3 kg]) was treated with mecasermin after failing to respond to 3 years of growth hormone treatment. Three weeks after reaching the full mecasermin dose (120 μ g/kg subcutaneously twice daily), he developed urticarial lesions around the injection site (with each injection), progressing once to generalized urticaria. Mecasermin treatment was discontinued until the drug was administered under physician observation. Within minutes, the patient developed an urticarial lesion over the injection site, which was treated with oral diphenhydramine. During the following several hours, he developed urticarial lesions 10 cm in diameter (Fig 1) in several sites of previous injections, mild facial swelling, and cough. The patient remained afebrile and normotensive without tachycardia or tachypnea. The results of the physical examination were otherwise unremarkable. He was treated with oral diphenhydramine until the symptoms resolved. Mecasermin treatment was discontinued pending further evaluation.

Two months later, skin testing was performed with the diluent and mecasermin from the vial used at home, a different vial of the same lot, and a vial of a different lot. Skin prick testing was performed with dilutions of 1:100, 1:10, and full strength (10 mg/1 mL). Intradermal testing was performed with 0.02 mL of 1:100 and 1:10 dilutions. The histamine control was positive, with wheal-and-flare reactions of 3 mm and 10 mm, respectively. The results of tests with saline control, diluent, and dilutions of mecasermin were negative. Serum specific IgE antibody to mecasermin was not measured because no assay is available. Given the negative skin test results, lack of an adequate treatment response with growth hormone, and ongoing growth failure, a protocol that accomplished a rapid desensitization or a gradual dosing challenge to mecasermin was devised.

Mecasermin is injected subcutaneously starting at a range of 40 to 80 μ g/kg titrated over time to 120 μ g/kg twice daily. To reach an initial target dose of 80 μ g/kg, four 20- μ g/kg doses were administered subcutaneously every 30 minutes. Injections were rotated among the lateral aspect of the thighs and the posterior part of the upper arms and tolerated without reaction. Vital signs were monitored every 15 minutes, and rescue medications (epinephrine, ranitidine, diphenhydramine, methylprednisolone, albuterol, and isotonic sodium chloride solution) were administered at the bedside. Twelve hours after the start of administration, an 80- μ g/kg dose was tolerated, except for a small bruise with mild erythema that appeared over the injection site after several hours. In another 12 hours, a second 80- μ g/kg dose was given. Within 2 hours, an area of induration with warmth and erythema, but without pruritus, developed over the injection site.

To reevaluate for an IgE-mediated reaction, skin prick testing with full-strength mecasermin was performed. The histamine control was positive with wheal-and-flare reactions of 3 mm and 5 mm, respectively. The isotonic sodium chloride solution control and mecasermin tests produced negative results. Because no systemic symptoms occurred, twice daily injections were continued at home. The patient continued to have small erythematous wheals without pruritus over the injection sites. However, 3 weeks later, the patient developed angioedema of the lips 3 hours after an injection. The angioedema resolved over several hours. Mecasermin treatment was permanently discontinued.

This case is the second report of local and systemic cutaneous adverse effects of mecasermin clinically consistent with an allergic



Figure 1. Urticarial lesions over areas of previous injection on buttocks after mecasermin injection.

reaction. The structure and activity of mecasermin are identical to endogenous IGF-1,⁷ which is homologous to insulin.⁸ IgE-mediated reactions to insulin have been well documented,⁹ making it likely that the reaction in this case is also IgE mediated. Although skin tests to mecasermin produced negative results, in the absence of a larger experience in skin testing with novel compounds, their validity in determining the mechanism of a reaction cannot be established. Local reactions to insulin may be due to an IgG-mediated event,¹⁰ which is also a plausible explanation in this case.

An IGF-1 deficiency registry shows that an additional 307 patients treated with mecasermin reported no skin or allergic reactions.¹¹ However, only approximately half of children currently treated with mecasermin are enrolled in this registry. Mecasermin is increasingly used for short stature patients with unclear forms of IGF-1 deficiency. Physicians must be aware of the potential for allergic reaction to mecasermin and caution patients appropriately.

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USE OF ANGIOTENSIN RECEPTOR BLOCKERS AFTER ANGIOEDEMA WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

We recently published a meta-analysis¹ on the risk of angioedema associated with angiotensin receptor blocker (ARB) use in patients with previous angioedema from angiotensin-converting enzyme inhibitors (ACE-I). However, this study was limited by the few available trials. The recently published TRASCEND trial (Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease)² would have qualified for our meta-analysis. Given these new data, we elected to update our meta-analysis to better define the risk.

We used the same search strategy as described previously¹ using the dates June 2007 to December 2008. The statistical analysis was the same, except that we added an additional step of calculating the odds ratio (OR) of ARB vs placebo using the Peto method because we now had 2 randomized controlled trials.

Of the 31 additional unique articles identified in this updated meta-analysis, only the TRASCEND trial,² which evaluated ACE-I-intolerant patients, met the inclusion criteria. In this study of nearly 3,000 individuals, 75 patients with a history of angioedema or anaphylaxis had a history of angioedema due to ACE-I use. Of these patients, none in the telmisartan group and 1 in the placebo group developed angioedema. Of all the study patients, 2 in telmisartan group and 3 in the placebo group developed angioedema.

Combining the data in the TRASCEND trial with those used in the previous meta-analysis (Table 1),³⁻⁵ the risk of angioedema secondary to ARB use is 2.5% (95% confidence interval [CI], 0%-6.6%), and for confirmed cases secondary to ARB use it is 1.5% (95% CI, 0%-5.1%). There was no statistical heterogeneity between trials ($P > .30$).

In addition, the Peto method was used for the 2 randomized controlled trials^{2,4} to compare the risk of angioedema between ARB and placebo. There is no statistically significant difference in the odds of angioedema between ARB and placebo, although the CI is broad (OR, 1.1; 95% CI, 0.07-17).

This information further narrows and refines the estimate of risk of recurrent angioedema with an ARB after having experienced this with an ACE-I. The risk of this event is low, with the top end of the 95% CI being 6.6%, but it seems to occur. There is also a risk of angioedema due to ARB use with no previous use of ACE-I, although this incidence also seems to be low. Physicians can use this

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