



Letter

Desensitization to mecasermin in an insulin-like growth factor 1-deficient patient

In recent years, new technologies have enabled many advances in the so-called growth hormone (GH) axis. Insulin-like growth factor 1 (IGF-1) is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults because it is a primary mediator of the effects of GH.^{1–3} IGF-1 consists of 70 amino acids in a single chain with 3 intramolecular disulfide bridges, and it has a molecular weight of 7,649 Da.² IGF deficiency is characterized by the total or partial absence of detectable IGF-1 in serum or plasma. Patients with low IGF-1 levels and normal or high GH secretion were classified as having primary IGF deficiency.^{3,4} After single subcutaneous administration of 0.12 mg/kg of mecasermin in pediatric patients with severe IGF-I deficiency, the mean terminal half-life was estimated to be 5.8 hours.

Mecasermin (Increlex; Beaufour Ipsen Inc, Paris, France), a recombinant human 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.⁴ In studies of children with short stature treated with mecasermin, no serious allergic reactions have been reported.⁵ Non-IgE-mediated injection site reactions may be avoided or minimized by alternation of injection site among the upper arm, thigh, buttock, and abdomen and by the following techniques: avoiding the use of ultrashort needles, removing mecasermin from the refrigerator at least 20 minutes before injecting, and cleaning the site using soap and water instead of alcohol.⁴

A 3-year-old girl with short stature (height, -4.31 SDs) was diagnosed as having primary IGF deficiency. Primary IGF-1 deficit is characterized by basal IGF-1 less than -2 SDs, height less than -3 SDs, normal GH stimulation test results, no response in IGF-1 generation test and normal liver and kidney function; and normal electrolyte, hemoglobin A_{1c}, cortisol, and prolactin levels, celiac disease screen result, and thyroid function. The patient started the treatment with mecasermin (0.04 mg/kg/d) subcutaneously twice daily. The first 3 doses were administered at the hospital, without adverse effects. After 10 days of treatment, she developed urticarial lesions around the injection area, which progressed to a generalized urticaria in successive doses. Mecasermin treatment was discontinued, and an allergy evaluation was started.

The patient had a history of atopic dermatitis and food allergy (egg, peanuts, and lentils). The total IgE level was 850 U/mL. Skin prick testing and intradermal testing with mecasermin were performed with concentrations of 0.1, 1, and 10 mg/mL (full strength). Thus, no local reaction was noted with a systemic exposure to 0.02 mL of 10 mg/mL or 0.2 mg of mecasermin during intradermal testing. The results of all of the skin tests were negative. The

histamine control was positive, with a wheal-and-flare reaction of 7-mm wheal with 9-mm flare in prick testing and 10-mm wheal with 13-mm flare in intradermal testing. The results of skin testing with saline control were negative. The prick and intradermal skin test results using the preservative benzyl alcohol at a maximum concentration of 9 mg/mL were all negative.

Given the negative skin test results, a gradual dosing challenge to mecasermin was conceived. Mecasermin was again administered subcutaneously under physician observation. Challenge doses of 0.05, 0.10, 0.15, and 0.2 mg were administered every 20 minutes. The patient developed generalized urticarial lesions 10 minutes after the last dose of 0.2 mg. There were no respiratory symptoms or blood pressure changes. Serum tryptase levels did not change. Symptoms disappeared within 60 minutes after the oral administration of 0.5 mg of dexchlorpheniramine. A dose of 15 mg of deflazacort, which achieves peak plasma concentrations in 1.5 to 2 hours, was administered to prevent reactivation of urticarial symptoms.

Considering that mecasermin was the only available treatment for this patient, a desensitization protocol with the drug was proposed. The procedure and its risks were explained, and informed parental consent was obtained.

The patient was premedicated 30 minutes before the procedure with 0.5 mg of dexchlorpheniramine, 4 mg of montelukast, and 15 mg of deflazacort. The desensitization protocol was scheduled in 8 steps, starting with a subcutaneous dose of 0.0033 mg (Table 1). Doses were increasing every 20 minutes up to 0.4 mg (cumulative dose was 0.8 mg). The starting dose was selected according our own safety criteria, approximately 1/1,000 of the target dose. The patient continued with a daily administration of 0.4 mg of mecasermin twice daily without reporting new allergic reactions. Six months later, the patient had a growth rate of 6.83 cm/y (94.8th percentile; $+1.63$ SD).

There are 2 other cases of local and systemic cutaneous adverse effects of mecasermin clinically consistent with an allergic reaction.^{6,7} As in the case described by Metz et al,⁷ the results of skin testing in our patient were negative, and the reaction was confirmed after the drug provocation test. We did not find that our patient's reaction was IgE mediated; it could occur independently of IgE, with alternative mechanisms, including complement anaphylatoxin activation, neuropeptide release, immune complex generation, cytotoxicity, T-cell activation, or another pathway involving IgG and the release of PAF as the major mediator.

We present a case of successful desensitization lasting up to 6 months of follow-up with apparent clinical growth effect. A previous attempt of desensitization failed after 3 weeks of daily therapy, and mecasermin treatment was discontinued.⁷ However, our protocol for mecasermin desensitization stands out as a valuable option because our patient has been asymptomatic since then and her growth rate is now correct.

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Table 1
Mecasermin desensitization procedure^a

Step	Dose of preparation, mL	Mecasermin dose, mg	Cumulative dose, mg	Cumulative time, min
1	Dilution C: 0.165	0.0033	0.0033	
2	Dilution B: 0.063	0.0063	0.0096	+20
3	Dilution B: 0.125	0.0125	0.0221	+40
4	Dilution B: 0.250	0.025	0.0471	+60
5	Dilution A: 0.05	0.05	0.0971	+80
6	Dilution A: 0.1	0.10	0.197	+100
7	Dilution A: 0.2	0.20	0.397	+120
8	Vial: 0.04	0.40	0.8	+140

^aIn this protocol, the interval between doses was 20 minutes. Dilution A: 0.1 mL of pure vial (10 mg/mL) and 0.9 mL of physiologic saline solution (final concentration, 1 mg/mL). Dilution B: 0.1 mL of dilution A and 0.9 mL of physiologic saline solution (final concentration, 0.1 mg/mL). Dilution C: 0.1 mL of dilution B and 0.4 mL of physiologic saline solution (final concentration, 0.02 mg/mL).

Mecasermin is increasingly used for patients with forms of IGF-1 deficiency. Physicians must be aware of the potential for allergic reaction to this drug, but a desensitization procedure could be a good therapeutic option in some cases.

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