LETTER TO THE EDITOR
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Unsuccessful Desensitization in a Child with Hypersensitivity to Diazoxide

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Letter to The Editor:

Oral diazoxide therapy is used to treat hypoglycemia, and this treatment is usually well tolerated. Nonetheless, rashes and/or hematological reactions (i.e., thrombocytopenia) have been reported after intravenous or oral diazoxide treatment in literature.[1] In particular, the possibility of such adverse effects has most frequently been related to repeated exposure, as in continued oral therapy.

We herein describe the first case of both delayed and immediate skin reactions to diazoxide in a child affected by nesidioblastosis.

The patient: This is a case of a three-year-old girl affected by juvenile nesidioblastosis who started oral diazoxide in June 2015. She had a family history of atopy, and her personal history was positive for rhinitis and conjunctivitis during the grass pollen season. Within a few months, she progressively reached the dosage of 50 mg of diazoxide twice a day and 100 mg once a day.

Over a six-month period (from June 2015 until December 2015), she developed a generalized itchy eczema, with poor quality of life due to itching, especially during sleep time.

Keywords: Child, Desensitization; Diazoxide; Nesidioblastosis

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At nine months after beginning diazoxide treatment, she had a more severe immediate reaction characterized by cough (without a low oxygen rate or Bronchospasm), lips angioedema, and facial rash 30 minutes after intake of 50 mg of diazoxide (Figure 1).

The child was referred to the emergency room of the nearest hospital, and she received treatment with antihistamines. She quickly recovered but was advised to stop diazoxide. At 3 weeks after the acute reaction, she was referred to the Allergy Unit of Anna Meyer Children's Hospital, where she was investigated by skin prick tests (SPTs) for common inhalants and food allergens (i.e., pollen, mites, mold, cat and dog epithelia, milk, albumin, soy, wheat, cod fish, peanut and latex using commercial extracts at 0.1 mg/mL from Alk Abellò, Milan, Italy). Positive and negative controls for SPT included histamine (10 mg/mL, ALK-Abellò, Milan, Italy) and normal saline, respectively. She was positive for grass pollen SPT, in agreement with her reported allergy symptoms.

Although standardized tests have not been described in the literature, skin testing with diazoxide was performed to demonstrate a real state of hypersensitivity.

The child exhibited both an immediate and a delayed type of reaction. Consequently, we performed in vivo tests to detect the presence of diazoxide-specific IgE or -activated T lymphocytes according to the European Network for Drug Allergy[2] recommendations.

SPT was performed using a 1:10 dilution (2.5 mg/mL) of diazoxide capsules at a concentration of

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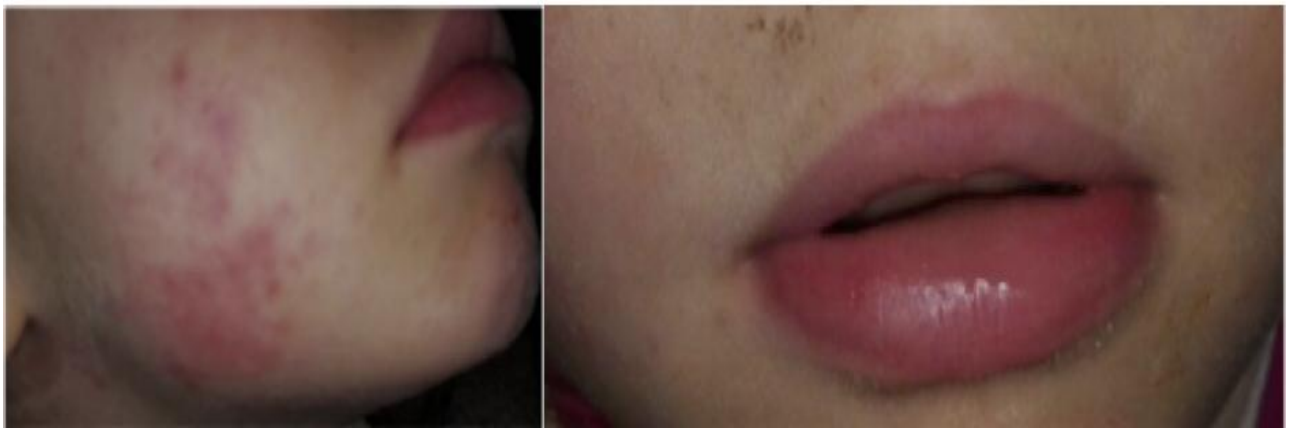

Figure 1. Itchy erythema and lower lip angioedema following unsuccessful dcesensitization in a child with hypersensitivity to Diazoxide

25 mg. The same dilution of diazoxide (2.5 mg/mL) was used to perform intradermal tests; saline solution was used as negative control. The results of both in vivo tests were negative also at 72 hours.[3]

To reach a confidant diagnosis, we performed a four-step drug provocation test with diazoxide at increasing doses (0.5-5-15-25 mg) every 30 minutes.[4] After the third dose, the patient developed angioedema of the lips. Consequently, the challenge was stopped, and she was diagnosed as hypersensitive.

After balancing the risks and benefits of such a therapy and after obtaining signed informed consent from her parents, we initiated a delayed desensitization protocol for diazoxide, such that it would be possible to control immediate reactions. Before starting the desensitization, laboratory analysis including a full blood count, hepatic and renal parameters, and markers for inflammation (e.g., C-reactive protein, CRP) were performed. To detect any incipient hypersensitivity reaction, skin and mucous membranes, body temperature, heart rate, and blood pressure were monitored before and at regular intervals during drug desensitization.

The desensitization started in April with a dose of 5 mg of diazoxide, and we increased the dose by 5 mg per week up to 50 mg, which was administered in June 2016.

After a month, while taking 50 mg of diazoxide, she developed facial ecchymosis (Figure 2), a mild increase in serum glutamic oxaloacetic transaminase (SGOT: 36 U/l normal values: 32 U/l) and a mild increase in creatine kinase (CK: 238 U/L normal values: 170 U/l). Blood exams were negative for infection, and she had no fever. Ultimately, the child's parents were advised to stop diazoxide treatment, and she completely recovered after 72 hours, with normalization of blood parameters.

Exanthematous drug eruptions are the most common delayed hypersensitivity reaction, and they have been reported to complicate 3 per 1000 courses of drug therapy.[5]

The usual practice is to permanently avoid the culprit drug and to use a structurally different, non-cross-reacting compound for future treatments. However, in this case, there was no alternative to the causative drug.

According to the literature, drug desensitization is safe and successful in uncomplicated and nonserious mild exanthems and fixed drug eruptions.[6]

In addition to the delayed diazoxide reaction, facial rash and lips angioedema occurring within 30 minutes is considered a mild type of immediate reaction.

Consequently, taking into account all factors, i.e., the need for therapy, the lack of a drug replacement, and the low grade of severity of the previous delayed reaction; we concluded that the potential benefit of desensitization outweighed the potential risks.

This case report showed that immediate and delayed reactions to the same drug could occur in the same patient. There are few studies to date about diazoxide hypersensitivity in children. Moreover, our case confirms that desensitization may be a possible procedure to apply in a patient for whom the treatment is mandatory. Regardless, the success of desensitization

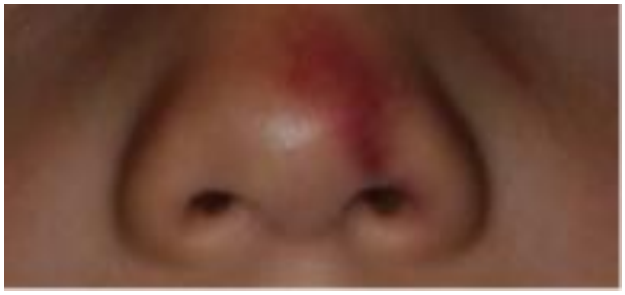

Figure 2. Ecchymosis following unsuccessful desensitization in a child with hypersensitivity to Diazoxide

in delayed reactions is not always predictable; in particular, this case showed the possible occurrence of even more severe reactions.

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