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# Case report of an anaphylactoid reaction to arginine

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**Background:** Arginine is an agent commonly used to evaluate adequacy of growth hormone (GH) secretion. Because arginine is a simple amino acid, it is considered safe and rarely causes adverse reactions.

**Objective:** To report the second anaphylactoid reaction to arginine in a child undergoing stimulation testing with arginine for assessing GH secretion.

**Methods:** Allergy skin testing to arginine was performed with a protocol similar to penicillin testing 4 weeks after the anaphylactoid reaction.

**Results:** Testing revealed a positive response to the arginine.

**Conclusions:** The use of intravenous arginine as a test of GH reserve remains safe and effective, but it is prudent to have the equipment and medication available to treat an allergic reaction.

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## INTRODUCTION

Resting levels of growth hormone (GH) in children are too low to rule out GH deficiency. Testing for GH adequacy in short children involves using pharmacologic agents which cause the release of GH. A number of pharmacologic agents have been used to stimulate GH release.<sup>1–4</sup> Each of these agents has the potential for adverse reactions. Arginine is a commonly used agent and, being a simple amino acid, has been considered exceedingly safe. At our institution we have been using it as one of our standard agents for more than 10 years without any adverse reactions. Herein, we report an anaphylactoid reaction to arginine in a child undergoing stimulation testing with arginine for GH secretion.

## CASE REPORT

An 11-year-old boy was admitted to our short-stay testing unit for evalua-

tion of his short stature. He was scheduled to receive L-arginine and L-dopa stimulation tests according to the protocol of Penny et al.<sup>5</sup> He had not ingested any medications on the day of the procedure. After an overnight fast, R-Gen 10 (10% arginine hydrochloride) without preservatives (Pharmacia & Upjohn Co, Kalamazoo, MI) was infused intravenously at a rate of 5 mL/minute, which would have resulted in 12.5 g after 30 minutes. After 15 minutes of infusion he developed urticaria over his trunk, face, and extremities, as well as periorbital edema, perioral edema, and generalized pruritus. He began coughing but had no difficulty breathing. There was no feeling of impending doom. His blood pressure was 94/60 mm Hg; rate of respiration 20 breaths/minute, and heart rate 100 beats/minute. His lungs had bilateral expiratory wheezes throughout. The arginine infusion was immediately stopped and oral diphenhydramine 25 mg was given. Upon transfer to the emergency department, subcutaneous epinephrine, nebulized albuterol, and intravenous methylprednisolone were administered. Within 30 minutes he clinically improved and his lungs were clear. The urticaria persisted for 6 hours.

He was admitted to the hospital and received intravenous diphenhydramine, intravenous methylprednisolone, and nebulized albuterol every 6 hours and was discharged after 24 hours. There was minimal rise in GH levels during the brief infusion; his baseline GH level was <0.5 ng/mL and the level 30 minutes later was 1.7 ng/mL. Repeat testing has not been performed.

His past medical history was significant for an allergy to peanuts which consisted of swelling of his eyes and a red facial rash. There was a history of seasonal allergic rhinitis and mild asthma. There was no history of surgery, hospitalizations, or other possible recurrent exposure to latex which would predispose him to a latex allergy. The family history was significant for his mother having allergic rhinitis and a brother with GH deficiency.

## Methods and Results

The bottle of arginine from which the patient received the dose was sent to Pharmacia & Upjohn for evaluation. High performance liquid chromatography was performed. The testing found 10% arginine as indicated on the bottle.

Four weeks after this event, allergy skin testing to arginine was performed using a similar protocol to penicillin testing.<sup>6</sup> A fresh bottle of arginine was diluted with 2% albumin to a concentration of 1:10,000. Prick puncture testing on the forearm was performed with this concentration, along with 2% albumin as a negative control and histamine 1.0 mg/mL as a positive control. At 15 minutes the tests were read. The arginine and albumin gave a negative response whereas the histamine control gave a positive response of a 3-mm wheal and a 20-mm flare. Intradermal testing was performed on the lateral aspect of the arm with 1:10,000

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concentration of arginine, 2% albumin, and histamine 0.1 mg/mL. There was a 10-mm wheal and a 22-mm flare response to histamine and no response to arginine and albumin. An arginine concentration of 1:1,000 was then placed intradermally, and at 15 minutes, there was an 11-mm wheal and a 30-mm flare. Two physicians serving as controls received intradermal testing to 1:1,000 concentration of arginine, and the albumin and histamine controls. Both volunteers had negative tests to the arginine and albumin controls but positive tests to the histamine.

## DISCUSSION

Anaphylaxis is the clinical manifestation of immediate hypersensitivity that occurs after the interaction between a specific antigen and specific immunoglobulin (Ig)E antibodies. The interaction between IgE and antigen activates a complex series of events, resulting in histamine and other mediators of inflammation being released from mast cells.<sup>7</sup> These chemicals then produce the clinical symptoms of anaphylaxis. Anaphylactoid reactions are similar to anaphylactic reactions but do not involve IgE and antigen interactions. They are triggered by antigens acting directly on mast cells and basophils, causing mediator release and symptoms similar to anaphylaxis.

Antigens that cause anaphylaxis and anaphylactoid reactions include proteins, polysaccharides, and haptens.<sup>8</sup> Amino acids such as arginine should be too small to stimulate either type of reaction, as they are normally found in human plasma.

After performing a MEDLINE search, we were able to find one previously reported case of anaphylaxis to intravenous arginine in 1973.<sup>9</sup> At our institution we have performed approximately 1,500 arginine stimulation tests in the past 10 years with no allergic reactions.

The reason our patient had an anaphylactic or anaphylactoid reaction is unclear. One possibility is a contaminant or another antigen in the solution. The R-Gene is a synthetic preparation that is purified without preservatives and antibiotics, making this possibility

unlikely. Our patient had a positive response to a different bottle of arginine (different lot number) which mitigates against a contamination of the original solution. In the one case by Tiwary et al,<sup>9</sup> the authors theorized the possibility of polymerization of the arginine producing an antigenic unit. It is possible that our patient had an anaphylactoid reaction similar to that which occurs with radiocontrast material. It is theorized that the hyperosmolality of the radiocontrast material may play a role in this reaction. The arginine solution, having a high chloride content, is also hyperosmolar. Two separate groups reported hypotension when infusing intravenous arginine in human subjects.<sup>10,11</sup> They theorized that the hypotension was attributable to nitric acid release. In a letter to the editor, Paton<sup>12</sup> suggested that histamine release could have possibly played a role. Paton,<sup>12</sup> however, felt that the lack of reported pruritus, urticaria, and nasal congestion suggested that histamine release could not be the entire cause.

Allergy testing to penicillin has been well studied and can be relied upon.<sup>13</sup> Testing to medications that have not been validated can only suggest, but not diagnose, an IgE-mediated reaction. It is interesting that our patient had a positive skin test to a new bottle of arginine, whereas our two volunteers had no reaction at all at a similar concentration. Clearly, two negative controls alone is insufficient proof that arginine does not cause positive skin tests in healthy people.

## CONCLUSION

We have presented the second reported case of an anaphylactoid reaction to intravenous arginine. We can not fully explain why our patient had a hypersensitivity reaction to an amino acid that is found in human plasma. Although the risk of a hypersensitivity reaction is small with the use of intravenous arginine, it is prudent to have equipment, medication, and a protocol available to treat a severe reaction.

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