

Hydroxyethyl starch (HES) compounds are synthetic polymers derived from amylopectin, and are classified by *in vitro* molecular weight (MW) into high, medium, and low MW preparations. However, HES is metabolized, and both the pharmacodynamic properties and adverse events of HES compounds depend on the *in vivo* MW. A low etherification index (0.4–0.5) and a low C2/C6 ratio (<8) lead to a rapid degradation, resulting in a small *in vivo* MW. In pentastarch, more than 90% of the amylopectin is etherified, and an average of four or five of the hydroxy groups in each 10-D-glucopyranose unit of the starch polymer is converted to OCH₂CH₂OH groups. Haes-Steril contains 6–10% pentastarch. To our knowledge, IgE-mediated hypersensitivity to a pentastarch solution has not been reported in the literature (1, 2). Generally, the diagnosis of IgE-mediated drug allergy is based upon history and the quantification of specific IgE and/or a positive skin test. In case of refusal/impossibility of skin testing and in the absence of the opportunity for a specific IgE determination, however, other methods are needed. IgE-sensitized basophils, on encounter with specific allergen, not only secrete and generate bioactive mediators (e.g., histamine), but also upregulate the expression of membrane markers (e.g., CD63). CD63 is anchored in the basophilic granule membrane and is weakly expressed on resting basophils. In contrast, as a result

of fusion between the granule and plasma membrane, CD63 is expressed with a high density on activated basophils, reflecting cell degranulation (3). This upregulation can be detected by flow cytometry, and calculation of the percentage of anti-IgE positive cells that coexpress CD63 allows assessment of basophil activation (4). CD63 upregulation can also be assessed with donor basophils that are incubated with serum of the patient.

Taken together, the results suggested the presence of pentastarch-specific IgE antibodies in the serum of this patient, sufficient to bind and activate the donor basophils. Given the temporal relationship, the clinical manifestations, and the positive activation test with basophils of the patient and passively sensitized basophils, an IgE-mediated reaction to Haes-Steril in this patient was established.

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Are IVIG for chronic unremitting urticaria effective?

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Key words: autoimmunity; intravenous immunoglobulins; urticaria.

● SOME patients with severe chronic idiopathic urticaria (CIU) do not respond to antihistamines alone and need high-dose, long-term corticosteroids for adequate control of the disease. For these patients, some alternative therapeutic approaches have been suggested, one of them being high-dose intravenous immunoglobulins (IVIG) (1). IVIG are extensively used to treat several autoimmune diseases. The rationale for their use in CIU stems from the observation that many patients show a wheal and flare reaction upon intradermal injection of autologous serum, and that

Table 1. Basophil activation tests

	Patient basophils	Donor basophils	Passively sensitized donor basophils
Negative control (without drug)	3	1	1
Positive control (fMLP)	58	38	n.d.
Haes-Steril [®] (30 g/500 ml)	77	0	18
Propofol (Diprivan [®]) 10 µg/ml	2	n.d.	n.d.
Cisatracurium (Nimbex [®]) 10 µg/ml	3	n.d.	n.d.
Sufenta (Sufentanyl [®]) 5 µg/ml	4	n.d.	n.d.

Results are expressed as percent CD63-positive basophils after activation. n.d.: not done.

histamine release may be induced by autoantibodies against the high-affinity IgE receptor (FcεRI) or against IgE (2–5). In the only study dealing with IVIG in CIU, 9/10 patients responded well: three were still in remission 3 years after the treatment, two had temporary complete remissions, and four had improved (1). This study reports on three patients with unremitting CIU treated with IVIG.

Patient 1 was a man aged 59 with a 7-month history of urticaria not controlled by hydroxyzine 25 mg twice daily. Deflazacort 30 mg daily gained partial control of the disease; however, symptoms returned as soon as doses were reduced. During the last 3 months, the patient experienced four severe angioedema episodes while on steroid therapy.

Patient 2 was a woman aged 49 with a 2-year history of unremitting urticaria. When first seen, she had been taking both cetirizine 10 mg and prednisone 25 mg daily for 4 months.

Patient 3 was a man with a 2-month history of severe urticaria only partially controlled by fexofenadine 180 mg and prednisone 12.5 mg daily.

All three patients were negative on SPT with food allergens and strongly positive on autologous serum test (4). All three had circulating thyroid autoantibodies with normal thyroid function. Serum from patient 2 induced significant histamine release (9.5%; cutoff at 5%) from normal basophils; the histamine release assay (HRA) was negative in patient 1 (3%).

IVIG (Ig Vena, Sclavo, Italy) were given at a dose of 0.4 g/kg/day for 5 days (1) while the patients continued their other therapies. No adverse effects were reported. Patients were followed-up weekly after IVIG administration. The effect was monitored by visual analog scale and activity scores.

- Patient 1 showed no change in disease activity; recurrent angioedema episodes

appeared during the 6 weeks after IVIG treatment.

- Patient 2 showed total remission for 3 weeks; effects were already appreciable on day 2. During the remission period, the patient was totally symptom-free and both steroids and antihistamines could be withdrawn. Subsequently, symptoms gradually relapsed; 5 weeks after IVIG treatment, disease activity had returned to pre-IVIG levels.
- Patient 3 showed better control of the disease with steroid plus antihistamines. By 1 month after IVIG treatment, such slight beneficial effect was no longer appreciable.

These results do not confirm previous encouraging reports of IVIG therapy in severe CIU (1). In the only responder, urticaria began to relapse after 3 weeks, a time interval corresponding to the half-life of IgG. This suggests that most of the clinical effect was associated with the anti-idiotypic effect of IVIG rather than with other reported immunomodulatory activities, such as induction of a functional blockade of Fc receptors, modulation of the secretion of cytokines, interference with T- and B-cell proliferation, or long-term selection of immune repertoires (6–10). The fact that also another patient showed a 3-week partial response seems to strengthen this hypothesis. The different outcome of IVIG administration in patients 1 and 2 was particularly interesting in the light of the HRA results. The responder was the HRA-positive, a condition associated with circulating anti-FcεRI or anti-IgE antibodies (2–5). The nonresponder was positive on autologous serum test but HRA-negative; such a condition has been associated with a hitherto uncharacterized 30-kDa protein causing histamine release from mast cells, but not from basophils (3, 4). IVIG seem to exert some effect in autoimmune CIU only. In view of the poor or only temporary clinical effects and of

their high cost, IVIG cannot be presently regarded as a treatment of choice in patients with severe CIU.

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