

patients suffering from CIU than in healthy men. Decreased DHEA-S concentration has been recognized in different chronic diseases (2). In particular, it has been suggested that DHEA-S deficiency is a permanent feature of some autoimmune diseases and may contribute to their aetiology and/or pathophysiology (4, 5). However, no direct evidence is available to indicate whether reduced circulating concentration of the hormone contributes to the diseases (2, 5).

We do not know whether lower serum concentration of DHEA-S observed in CIU patients is the cause or rather the effect of urticarial processes. It has been suggested that, during inflammatory response, the adrenal steroid production is changed in the direction of cortisol, relative to DHEA and DHEA-S, such hormonal changes being probably necessary to achieve adequate cortisol levels at the expense of adrenal androgens (6). It is interesting to speculate that similar abnormalities in steroidogenesis might occur during chronic urticarial inflammation.

How does lower circulating DHEA-S actually contribute to CIU pathophysiology? The question proves both, difficult and complex as the specific molecular mechanism of action for DHEA-S, including mechanisms of DHEA-S effect upon the immunological function and inflammation, is unclear (2).

In conclusion, on the basis of the present study as well as our earlier investigations, it appears probable that circulating DHEA-S concentration may be lower in CIU patients, regardless of their gender. It seems that declining circulating concentration of DHEA-S is a phenomenon accompanying CIU, yet its significance and underlying mechanisms remain unknown. As adrenal androgens have been reported to exert immunoregulatory effects, it is interesting to speculate on DHEA-S deficiency role in urticarial inflammation irrespective of its primary or just secondary character.

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Novel pharmacotherapy of acute hereditary angioedema with bradykinin B₂-receptor antagonist icatibant

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Key words: angiotensin-converting enzyme inhibitor; angioedema; bradykinin B₂-receptor antagonist; C₁-esterase inhibitor deficiency; icatibant.

Several forms of angioedema seem to be induced by elevated bradykinin (BK) concentrations (1). These elevations are

caused either by an increased BK production as in hereditary angioedema (HAE) with altered C₁-esterase inhibitor (C₁-INH) (2), or by reduced BK inactivation, e.g. during angiotensin-converting enzyme (ACE) inhibitor treatment. Two types of HAE have been described. These comprise: HAE type 1 with decreased C₁-INH levels and a functional enzyme deficiency (85% of cases) or HAE type 2 with normal protein concentration but a functional C₁-INH deficiency (15% of cases) (3). BK-induced angioedema attacks do not respond to the 'standard treatment' for allergic angioedema such as corticosteroids and antihistamines. Currently, acute attacks of HAE are treated with oral tranexamic acid and/or intravenously administered C₁-INH concentrate derived from human plasma, generally leading to a decrease in oedema within 12–24 h (3). Tranexamic acid has an inhibitory effect on the activation of plasmin, which is involved in the pathogenesis of HAE (3).

In an ongoing, multicentre, double-blind, randomized phase III study (FAST 2: subcutaneous treatment of angioedema), we are currently treating HAE patients with icatibant (Jerini, Berlin), a select BK B₂-receptor antagonist. In the double-blind phase, icatibant is administered subcutaneously (s.c.) and tested against oral tranexamic acid until symptom relief has been achieved. In the open-label part of the study, patients experiencing angioedema attacks receive icatibant as required.

We described a 59-year-old patient with HAE type 1 who experienced 38 recurrent angioedema attacks in 13 months and was treated with icatibant in the open-label part of the study (4). The patient's characteristics and laboratory values are listed in Table 1. Notably, the frequency of acute angioedema attacks decreased after treatment of a chronic gastritis, which may have served as an additional trigger. Furthermore, 8 months after first icatibant application the patient received danazol (attenuated androgen) which can increase hepatic production of the C₁ inhibitor (3).

Icatibant, a selective bradykinin B₂-receptor antagonist, is effective in the treatment of hereditary angioedema.

Table 1. Hereditary angioedema patient characteristics during acute laryngeal oedema

	Patient's values and characteristics	Reference values
Blood pressure (mmHg)		
Systolic	140	< 130
Diastolic	85	< 85
Heart rate (/min)	80	60–100
Temperature (ear) (°C)	35.9	35.5–37.9
Diseases	Hypertension, chronic gastritis, reflux oesophagitis	
Concomitant drugs	Danazol 600 mg/day Hydrochlorothiazide 25 mg/day Verapamil 160 mg/day	
Laboratory		
C1 INH function (%)	< 10	70–130
C1 INH antigen (mg/dl)	8	15–35
CRP (mg/dl)	< 0.3	< 0.5
Leukocytes (×1000/μl)	7.4	4–11.0
Urea nitrogen (mg/dl)	53	13–60
Urea acid (mg/dl)	6.7	3.4–7.0
Blood sugar (mg/dl)	120	60–110
Creatinine (mg/dl)	1.3	< 1.1
Haemoglobin (g/dl)	14.0	14–18.0
Haematocrit (%)	41.3	42–50
GOT (U/l)	36	< 35
GPT (U/l)	44	< 45
GGT (U/l)	21	< 55

A total of nine attacks were located in the head and neck region, four episodes were laryngeal, 19 affected the abdomen, two were associated with cutaneous swelling of the limbs and the remaining four involved the genital region. Treatment with icatibant led to rapid symptom relief. The episodes of the laryngeal edema were clinically most conspicuous, with dysphonia, dysphagia, and dyspnoea developing progressively within 2 h after onset of the attack. Transnasal flexible endoscopy revealed a laryngeal oedema of the upper airway (Fig. 1). Subcutaneous administration of 30 mg icatibant led to significant symptom relief within the following 1–2 h and a complete recovery after another 2 h allowing for discharge from hospital 6 h after admission. The other angioedema attacks were also successfully treated with icatibant. According to the patient, similar laryngeal and cutaneous angioedema attacks had been treated with C1-INH concentrate in the past and symptom relief generally occurred after approximately 12 h.

Icatibant administration was well tolerated, although brief local irritation at the injection site was experienced. Cutaneous burning lasted 10–20 s and erythema was completely resolved within 4 h.

Icatibant was effective in treating acute HAE attacks in the case presented, resulting in a rapid onset of symptom relief. The s.c. administration has the potential to improve the quality of life for HAE patients, particular those presenting with short-term recurrences, allowing them to perform self injections at home. In the future, icatibant might also be a new option for treatment of patients with angioedema induced by ACE inhibitors or other kinins.

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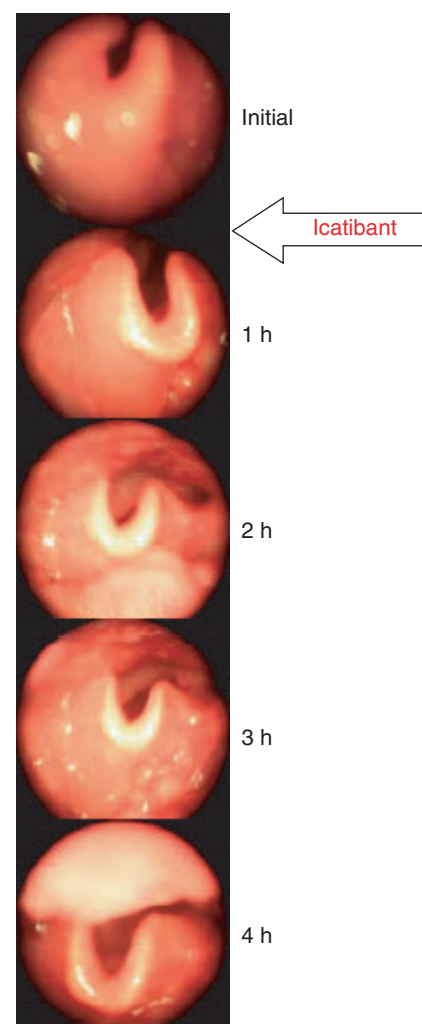


Figure 1. Endoscopic findings of a hereditary angioedema patient with acute laryngeal oedema before and after treatment with icatibant. Initially, the vocal cords are not visible due to a severe supraglottic oedema, leading to dysphonia, dyspnoea as well as dysphagia. After subcutaneous injection significant relief of symptoms was attained within 1–2 h and a complete recovery after another 2 h.

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Cutaneous adverse drug reaction induced by a generic substitute of Zyloric® with a residual sensitization to allopurinol

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Key words: allopurinol; cutaneous adverse drug reaction; generic substitute; Zyloric®.

Cutaneous adverse drug reactions (CADR) caused by generic drugs seem to be rare or have rarely been reported except in the case of antiepileptic drugs (1). Generic drugs have the same activity compound as the original drug but their excipients can be very different both from a qualitative and quantitative point of view. These excipients can be responsible for inducing CADR (2). We report on the first case of a CADR that occurred when a drug that had been well tolerated for 15 years was replaced by its generic substitute.

A 59-year-old man, who had taken Zyloric® (100 mg) pills (allopurinol, lactose, povidone, magnesium stearate, corn starch; Laboratoires Glaxo Wellcome, Marly-le-Roy, France) for 15 years developed a maculopapular rash (MPR) 3 days after the replacement of Zyloric® pills by its generic substitute, Allopurinol Ge® (Labora-

toires Eurogenerics, Boulogne Billancourt, France; allopurinol, yellow bee wax, hydrogenated soy, vegetable oils, peanut oil, soy lecithin, polysorbate 80, ethylparahydroxybenzoate, gelatine, glycerol, sorbitol, sorbitan, yellow iron oxide, titanium dioxide). Four days after stopping the intake of Allopurinol Ge®, the MPR spontaneously disappeared.

Histological examination of the skin biopsy sample revealed perivascular lymphohistiocytic infiltration with polymorphonuclear eosinophil cells. Biological findings remained normal without liver involvement.

Two months after the disappearance of the CADR, the patient took Zyloric® again and developed generalized itchy eczematous plaques, with a more severe involvement of the flexure areas, the 3 days following the re-intake of the drug. This second CADR caused by Zyloric® was less severe than the previous one caused by Allopurinol Ge®. Three months later, the intake of Zyloric® was disrupted and the CADR vanished in 3 days. There was no other modification in the usual treatment.

Dermato-allergological investigations were performed 3 months after the disappearance of the CADR and after stopping Zyloric® intake. Drug patch tests were performed according to the guidelines of the European Society of Contact Dermatitis (3) in performing drug skin tests. We performed the tests with the standard series of excipients and preservatives, allopurinol diluted at 10% in petrolatum (pet.), in water (aq.) and in alcohol (Chemotechnique Laboratory, Malmö, Sweden), Allopurinol Ge® (30% in pet., aq., alcohol), Zyloric® (30% in pet., aq. and in alcohol) and the excipients of the two commercialized forms of allopurinol (glycerol, sorbitol 10% aq., titanium dioxide 10% aq., hydrogenated soy, peanut oil, soy lecithin, gelatine, methylparahydroxybenzoate, ethylparahydroxybenzoate, propylparahydroxybenzoate). Pricks tests were also carried out with Zyloric®, Allopurinol Ge®, allopurinol and the excipients of Zyloric® and Allopurinol Ge®. The results were negative for both the tests as found either by immediate or delayed readings.

To our knowledge, we report on the first case of CADR caused by allopurinol, appearing after replacing the well-tolerated Zyloric® by one of its generic substitutes, Allopurinol Ge®. The generic substitute was responsible for inducing a sensitization to allopurinol, which unfortunately led to a relapse of the CADR when Zyloric® was reintroduced, even though the clinical features were less severe in the second CADR.

According to the firms that market the two drugs, there are no common excipients between Zyloric® and Allopurinol Ge®, and therefore the excipients do not seem to be the cause for the sensitization. Could allopurinol itself be responsible?

In the few reported cases in the literature of CADR occurring after the replacement of a drug by its generic substitute, the adverse effect does not relapse when the original drug is re-administered. A 38-year-old woman, who took carbamazepine (Tegretol®) for some years, developed an erythema multiformis like dermatosis, a week after the replacement of Tegretol® pills by its generic substitutes. The skin lesions spontaneously disappeared after the stopping of the generic formulation. When the patient took Tegretol® again, there was no relapse of the CADR (1).

The re-administration of the original drug initially taken usually permits an adequate bioavailability, a therapeutic efficiency with a good tolerance. Thus, to our knowledge, here is the first case in which the reintroduction of the original drug was associated with a relapse of the CADR. New mechanisms must be evoked for these types of therapeutic accidents, involving the role of excipients other than those listed on the pharmacological notice or a non-tolerated commercialized form of the drug that induces a sensitization to the active compound.

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