

Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant)

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Background: In hereditary angioedema, bradykinin is assumed to be the most important mediator of edema formation.

Objective: To assess whether the selective bradykinin receptor-2 antagonist Icatibant is effective in acute edema attacks of hereditary angioedema.

Methods: In this uncontrolled pilot study, 15 patients with 20 attacks were treated with Icatibant. The attacks were analyzed by using a standardized and validated visual analog scale measurement and compared with historical data of untreated attacks. Plasma bradykinin concentration was measured before and 4 hours after intravenous Icatibant treatment.

Results: Symptom intensity decreased within 4 hours after administration of Icatibant; the median time to onset of symptom relief was 1.50, 1.42, and 1.13 hours in the intravenous groups and 0.58 and 0.45 hours in the subcutaneous groups, respectively. The median difference in the 10-cm visual analog scale 4 hours after start of treatment was 4.11 cm (95% CI, 1.72-6.07). Compared with untreated attacks, Icatibant treatment reduced the mean (SD) time to onset of symptom relief by 97% from 42 ± 14 to 1.16 ± 0.95 hours (all groups combined). Median bradykinin concentration was 7-fold above the norm during acute attacks at 48.5 pmol/L and decreased to 18.0 pmol/L 4 hours after Icatibant infusion or injection.

Conclusion: Icatibant was effective in treating acute attacks of hereditary angioedema.

Clinical implications: This is the first report demonstrating the clinical usefulness of antagonizing bradykinin binding to bradykinin receptor-2 in hereditary angioedema.

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Key words: Angioedema, hereditary angioedema, C1 inhibitor deficiency, bradykinin, bradykinin receptor-2 antagonist, Icatibant

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Abbreviations used

BR: Bradykinin receptor
C1-INH: C1 esterase inhibitor
HAE: Hereditary angioedema
VAS: Visual analog scale

Angioedema is clinically characterized by self-limiting episodes of marked edema involving the skin, gastrointestinal tract, and other organs. Various forms of acquired and hereditary angioedema (HAE) share this clinical presentation. HAE was first described by Quincke¹ and Osler.² “Classic” HAE is associated with a quantitative (type I) or qualitative (type II) deficiency of C1 esterase inhibitor (C1-INH) resulting from mutations of the *C1-INH* gene. To date, more than 180 mutations have been reported.^{3,4} Recently, a third type of HAE has been described that is not associated with a C1-INH deficiency and occurs mainly in women.⁵⁻⁷ In some of these families, mutations in the coagulation *factor XII* gene have been found in the affected women.⁸

Clinically, HAE caused by C1-INH deficiency is characterized by recurrent bouts of edema. Skin swelling is located mostly on the extremities, the face, or the genitals.⁹ Abdominal attacks are often associated with severe pain, vomiting, diarrhea, and symptoms of hypovolemia.¹⁰ Laryngeal edema is potentially life-threatening, and many cases of asphyxiation have been reported.¹¹⁻¹³

The pathogenesis of the acute edema attacks of HAE is not completely known. The low plasma concentration of functionally active C1-INH permits the activation of the kallikrein-kinin system, the early steps of the classical complement pathway, and even the fibrinolytic system, causing the release of vasoactive peptides. Recent data suggest that bradykinin is the most important mediator of HAE attacks: (1) bradykinin was found increased in plasma during acute attacks of HAE,^{14,15} (2) bradykinin levels were higher in blood drawn from an angioedema site compared with the levels in systemic circulation,¹⁶ and (3) a mouse deficient in both the *C1-INH* and the bradykinin receptor-2 (*BR-2*) gene revealed diminished

vascular permeability, suggesting that the bradykinin/BR-2 pathway mediates angioedema formation.¹⁷

Bradykinin circulates with a plasma half-life of 15 to 30 seconds because of its rapid degradation by angiotensin-converting enzyme and neutral endopeptidase, and by carboxypeptidases and aminopeptidases. Bradykinin causes vasodilation via its B2 receptor through increases in nitric oxide, epoprostenol (previously known as prostacyclin), and endothelium-derived hyperpolarizing factor. Two types of kinin receptors are currently known: the bradykinin B1 receptor and bradykinin B2 receptor. B1 receptors are highly inducible on inflammatory stimulation or tissue injury, suggesting that they are involved in inflammation, whereas B2 receptors are constitutively expressed and mediate most physiological actions of kinins, including vasodilation. Icatibant, previously designated as HOE140, is a highly specific antagonist for BR-2.^{18,19} It was shown to inhibit bradykinin-induced vasodilation in human beings.²⁰ Furthermore, increased vascular permeability in C1-INH knockout mice was reversed by using Icatibant.¹⁷

If bradykinin binding and activation of BR-2 are mainly responsible for angioedema formation in patients with HAE, a BR-2 antagonist should be efficacious in the treatment of acute swelling attacks of this disease. To assess whether this hypothesis proves true clinically, we treated patients with HAE with the BR-2 antagonist Icatibant to evaluate whether Icatibant is effective in treating acute cutaneous and abdominal attacks of HAE.

METHODS

Study design

We performed an uncontrolled pilot study to assess the efficacy of Icatibant. The design was composed of a 5 sequential group study in which the study drug Icatibant was administered either as a single i.v. infusion or a single s.c. injection. Each group consisted of 4 patients. Group I received 0.4 mg/kg body weight Icatibant administered i.v. over a period of 2 hours. Group II received the same dose infused over a period of 0.5 hours. Group III received 0.8 mg/kg over a period of 0.5 hours. Group IV and group V received 30 mg and 45 mg of Icatibant, respectively, administered s.c. in the lower abdominal region.

To be eligible for the study, patients must have had documented HAE and a recent attack frequency of at least 1 every 3 months. The current attack had to be moderate to severe at any location excluding laryngeal edema. Patients must have completed screening and arrived at the clinic within 10 hours after the start of an attack. Patients of both sexes from age 18 to 65 years were eligible. Women of child-bearing potential were included only after a negative urine pregnancy test. All patients were excluded who had a medical history of hematologic, hepatic, respiratory, cardiovascular, renal, or other medical conditions capable of altering the metabolism or elimination of drugs or interfering with the assessment of safety. When the patients came to the hospital for treatment, they were successively assigned to groups I to V.

Informed consent according to ICH/EU Good Clinical Practice and German guidelines was obtained from each eligible patient before entering the study. Local medical ethic committees approved the study protocol.

Patients

Patients were regularly followed at the outpatient clinic of the Department of Dermatology, University of Mainz, Germany, the

Center of Pediatrics in Frankfurt, and the Department of Dermatology and Allergy, University Hospital of the Rheinisch-Westfälische Technische Hochschule Aachen, Germany (this study was performed while Dr Frank still worked in the University Hospital of the RWTH Aachen). Diagnosis of HAE was based on personal history, family history, and plasma examination. Patients with acquired angioedema caused by C1-INH deficiency were excluded from the study.

Study drug

Icatibant (also called JE049 or HOE140) is a synthetic decapeptide that has a similar structure as bradykinin but contains 5 nonproteinogenic amino acids (D-Arg, L-Hyp, L-Thi, D-Tic, and L-Oic). It is stable and not degraded by bradykinin-cleaving enzymes like carboxypeptidase N (or kininase I) and angiotensin converting enzyme (or kininase II). The study drug was provided by the Jerini AG (Berlin, Germany).

In the past, extensive toxicologic studies have been performed with Icatibant in rats and dogs by various routes including i.v., intranasal, and inhalation application, all showing an excellent tolerability profile.

Before assessing Icatibant in patients with HAE, a phase I, placebo-controlled study was conducted to explore the optimal Icatibant dose and i.v. infusion regimen. For this study, an exogenous i.v. bradykinin challenge was selected as a pharmacologic tool to investigate the dose range and regimen required to ensure full bradykinin antagonism. Doses of Icatibant ranging from 0.025 to 0.8 mg/kg infused over a period of 4 hours produced a clear dose-dependent and time-dependent inhibition of all measured effects seen after bradykinin challenge.

Icatibant was infused i.v. as a 1-mg/mL solution or injected s.c. as a 10-mg/mL solution.

Procedures

Fifteen patients with 20 acute HAE attacks were treated with Icatibant (17 attacks in Mainz, 2 in Aachen, and 1 in Frankfurt). The locations of the edema attacks are shown in Table I. Venous blood samples for bradykinin measurements were collected from the unaffected arm before and 4 hours after ending the Icatibant administration. Patients were analyzed with respect to the period from initiation of treatment to onset of symptom relief as reported by patients and as documented by using a standardized and clinically validated visual analog scale (VAS), respectively.^{21,22} Patients marked the severity of skin swelling or abdominal pain on a 10-cm, nonhatched VAS. Concerning skin swelling, 10 cm was defined as the maximal skin swelling the patient had experienced at the affected site. Concerning abdominal pain attacks, a validated pain score was used in which 10 cm reflected unbearable pain. The VAS 4 hours after drug administration was compared with the VAS immediately before the injection or infusion. In addition, skin swelling scores were assessed according to Waytes et al.²³

The time to onset of relief of the treated attacks was also compared with a large number of untreated edema attacks that had occurred previously at similar locations in the same patient (intraindividual controls). This was possible because patients were regularly surveyed and data about the symptoms and course of their attacks were regularly collected, including the mean period to onset of symptom relief without treatment.

Adverse events were recorded from admission to the study center until 120 hours after the end of infusion or injection. Local tolerability at the infusion or injection site was evaluated. On discharge from the clinic after 4 to 20 hours, the patients were provided with diaries to record any symptoms of angioedema and adverse events they might experience before the next follow-up visit. C1-inhibitor concentrate (Berinert P; CSL Behring, Marburg, Germany) served as rescue medication. The study took place in the years 2003 and 2004.

TABLE I. Results of Icatibant treatment in 15 patients with 20 acute attacks of hereditary angioedema

Attack no.	Patient no.	Sex	Age (y)	HAE type	HAE manifestation	Icatibant dose	Treatment group, regimen	Time between onset of symptoms and start of treatment (h)	Onset of symptom relief after start of treatment (h)	End of attack after start of treatment (h)	Previous untreated attacks [†]	
											Number	Mean time to onset of symptom relief (h)
1	1	M	61	I	Arms	48 mg	Group I, 0.4 mg/kg, 2 hours, intravenous	8.0	1.0	1.5	130 [‡]	60
2	2	F	40	I	Left cheek, arms, legs	42 mg		8.8	2.0	7.5*	80 [‡]	48
3	3,	F	30	I	Abdominal	24 mg		9.8	5.0	7.0*	320 [‡]	48
4	4	M	45	I	Lids or Periorbital	30 mg	Group II, 0.4 mg/kg, 0.5 hours, intravenous	7.4	1.0	18.0*	10	34
5	3,	F	30	I	Abdominal	24 mg		8.7	2.9	25.0	320 [‡]	48
6	5	F	44	I	Legs	25 mg,		9.6	0.9	5.0*	210 [‡]	24
7	6	F	55	II	Abdominal	34 mg	Group III, 0.8 mg/kg, 0.5 hours, intravenous	4.6	1.3	1.5*	600 [‡]	24
8	7	F	20	I	Face, arms	34 mg		5.3	0.8	46.0	28	72
9	8	F	52	I	Legs	20 mg		9.5	1.5	10.0	22	24
10	9	F	40	I	Abdominal	43 mg	Group IV, 30 mg, subcutaneous	9.5	0.8	19.3	410 [‡]	48
11	10	F	53	I	Arms	52 mg		7.2	1.5	8.5*	58	24
12	11	F	43	I	Abdominal	60 mg		10.3	1.5	20.5*	73	36
13	12	F	36	I	Legs	56 mg	Group V, 45 mg; subcutaneous	9.8	0.6	8.5	370 [‡]	48
14	9,	F	40	I	Abdominal	0.34 mg/kg		1.9	4.5*	8.0*	800 [‡]	36
15	13	M	47	I	Legs	0.35 mg/kg		8.5	1.7	4.0*	800 [‡]	11
16	14	M	22	I	Arms, legs, gluteal	0.45 mg/kg	Group V, 45 mg; subcutaneous	7.6	1.0	20.5	225 [‡]	36
17	6,	F	56	II	Abdominal	0.37 mg/kg		8.5	0.2	5.7*	132 [‡]	62
18	15	M	31	I	Lid or periorbital, perioral, arms, legs	0.53 mg/kg		7.1	0.2	5.7*	59	24
19	4,	M	46	I	Abdominal	0.58 mg/kg	Group V, 45 mg; subcutaneous	5.0	0.1	0.9*	400 [‡]	60
20	11,	F	43	I	Arms, legs, abdominal	0.63 mg/kg		7.5	0.2	20.0*	100 [‡]	24
	Attack 2							3.8	0.1	20.0*	50 [‡]	24
	Attack 2						Group V, 45 mg; subcutaneous	7.5	0.2	20.0*	29	72
	Attack 2							5.2	0.8	4.0*	180 [‡]	48
	Attack 2							7.1	0.7	37.9	32	20
	Attack 2							5.2	0.8	4.0*	11	34
	Attack 2										800 [‡]	36
	Attack 2										800 [‡]	11

F, Female; M, male.

*Because of difficulties in the determination of the complete end of an attack, the durations until only minimal residual swelling are presented.

[†]Only previous attacks that occurred in the same location as the current attack treated by Icatibant.[‡]Number of attacks estimated by patients.

TABLE II. Baseline demographic characteristics of the 15 patients*

HAE type I (no. [%])	14	(93)
HAE type II (no. [%])	1	(7)
Age (y), mean (SD)	41.1	(11.8)
Sex (male/female)	5/10	
C1-INH protein (g/L)	0.056	(0.019)
(HAE type I), mean (SD)		
C1-INH protein (g/L)	60.4	
(HAE type II)		
C1-INH activity (%), mean (SD)	18.94	(13.69)
C4 (g/L), mean (SD)	0.144	(0.078)
C1q (g/L), mean (SD)	0.148	(0.03)
Prophylactic treatment		
Danazol	2	(13%)
C1-INH concentrate	3	(20%)

*Normal range for C1-INH protein, 0.15 to 0.35 g/L. Normal range for C1-INH activity, 70% to 130%. Normal range for C4, 0.20 to 0.50 g/L. Normal range for C1q, 0.07 to 0.25 g/L.

Laboratory methods

Protein levels of C1-INH antigen, C4, and C1q were assayed by radial immunodiffusion, and C1-INH activity was determined using the chromogenic substrate C₂H₅CO-Lys(e-Cbo)-Gly-Arg-pNA (Immunochrom C1-INH; Technoclone, Vienna, Austria). Plasma bradykinin-(1-9)nonapeptide concentration (bradykinin) was specifically measured by liquid phase extraction, HPLC, and subsequent radioimmunoassay.¹⁴

Statistical analysis

Standard descriptive statistics were used to analyze the data. For efficacy analysis, a Wilcoxon for paired data was used for the VAS data combining all treatment groups. Likewise, a confidence for the median was computed on the basis of the binomial distribution. Of note, we evaluated 20 attacks in 15 patients. Because the patient is always the unit of analysis,²⁴ for patients with more than 1 attack, the individual mean was used for the VAS and average response (time to onset of symptom relief).

RESULTS

Patient characteristics are summarized in Table II. The median number of attacks was 20 per year. None of the patients received angiotensin-converting enzyme inhibitors, oral contraceptives, or estrogen replacement therapy. Five patients received prophylactic long-term treatment with danazol or treatment with C1-INH concentrate. Nevertheless, these individuals still had angioedema attacks and therefore could be included in this study.

Treatment with Icatibant (Table I) resulted in a median time to onset of symptom relief of 1.50, 1.42, and 1.13 hours in the i.v. groups (groups I, II, and III; 12 attacks) and 0.58 and 0.45 hours in the s.c. groups (groups IV and V; 8 attacks), respectively; treatment with Icatibant resulted in a mean (SD) time to onset of symptom relief of 1.16 hours (0.95 hours; all groups combined).

The improvement of symptoms from baseline to 4 hours after Icatibant treatment (Table III) was similar in

TABLE III. Symptom severity determined by VAS in 15 patients with 20 acute attacks of hereditary angioedema*

Patient no.	Attack no.	VAS at time of treatment with Icatibant (cm)	VAS at 4 h after Icatibant treatment (cm)	Reduction of VAS at 4 h after treatment (cm)
1	1	9.07	0	9.07
2	1	9.28	1.03	8.25
3	1	2.06	1.34	0.72
3	2	2.68	1.10	1.58
4	1	4.12	1.75	2.37
4	2	7.40	6.04	1.36
5	1	2.78	1.10	1.68
6	1	7.94	3.92	4.02
6	2	9.06	2.88	6.18
7	1	3.30	1.34	1.96
8	1	4.84	3.12	1.72
9	1	7.96	1.08	6.88
9	2	3.98	1.79	2.19
10	1	7.69	1.83	5.86
11	1	6.91	1.55	5.36
11	2	7.60	0.83	6.77
12	1	4.74	0.63	4.11
13	1	7.29	0	7.29
14	1	3.35	2.72	0.63
15	1	6.23	3.80	2.43

*In patients with 2 attacks, the mean of the attacks was used for statistics.

the s.c. and in the i.v. groups, with median difference in the VAS values of 5.31, 1.92, and 5.61 cm in the i.v. groups I, II, and III, and 3.15, and 4.31 cm in the s.c. groups IV and V, respectively.

The median difference (lower, upper 95% CI) in the VAS after 4 hours was 4.11 cm (1.72, 6.07) in all 15 patients (Fig 1). The *P* value is <.01.

Historical data of a large number of attacks manifesting at the same location as the current attacks were available from all patients. Ten of 15 patients had more than 100 HAE attacks before treatment (Table I). Unlike the short mean (SD) time to onset of symptom relief in all treated patients of 1.16 hours (0.95 hours), the untreated attacks in these patients (historical data) had a long mean (SD) time to onset of symptom relief of 42.01 hours (14.1 hours). Thus, treatment led to a 97% reduction concerning the time to relief. The mean (SD) period from start to end of an attack treated with Icatibant was 13.1 hours (11.8 hours). However, in 12 of the 20 treated attacks (in 11/15 patients), the end point of the respective attacks was recorded as minimal residual swelling (Table I). Time to end of attack is not listed.

Among the skin swellings treated with Icatibant, there were 6 facial swellings in 5 patients and 15 episodes of swellings of the extremities in 12 patients. After the onset of relief (Table I), there was no further increase or worsening of the skin swellings. Then the skin swelling continuously improved until it disappeared completely or until there was only a minimal residual swelling. The period between the maximum of skin swellings and the end of the swellings or the minimal residual swelling was 13.9 hours

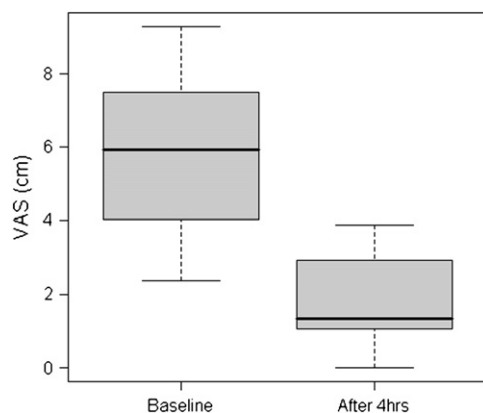


FIG 1. Symptom severity before and after 4 hours after onset of treatment with Icatibant.

(SD $\pm$ 12.3 hours; range, 0.5–45.2 hours) on average. All patients reported that all treated swellings were considerably shorter than usual. Nine abdominal attacks in 7 patients were treated with Icatibant. According to the patients' reports, Icatibant was markedly and rapidly effective in all attacks.

In 2 treated attacks in 1 patient, a recurrence of the abdominal pain attack occurred 14 and 17 hours after treatment with Icatibant, respectively (patient 11 in Table I). A male patient experienced a mild recurrence of a combined attack (skin swelling at several sites and abdominal pain attack) 20 hours after administration of Icatibant (patient 13). In a further male patient who was treated with Icatibant because of a skin swelling and a simultaneous abdominal attack, 20 hours after treatment, a new cutaneous swelling occurred (patient 15). A female patient experienced a swelling of the left foot. Twenty-seven hours after treatment with Icatibant, she experienced a relapse at the same site (patient 10). The 5 attacks were successfully treated with the rescue medication, 1000 U (3 attacks) or 500 U (2 attacks) Berinert P. Still, all patients initially responded to Icatibant and showed symptom relief.

After s.c. injection, local reactions were noted in all patients, including itching, urticarial wheal, erythema, and mild burning pain. Pain lasted for some minutes, itching urticarial wheal for some hours, and residual erythema cleared within 24 hours. All symptoms resolved spontaneously and did not demand medical intervention. In none of the patients was the response severe enough that the patient would consider refusing therapy. One patient experienced moderate headache more than 4 hours after the infusion of Icatibant. There were no other adverse events assessed as related to the study drug. Local skin irritation at the i.v. infusion site was not reported. None of the patients had an increase of blood pressure.

Plasma bradykinin was consistently (in all attacks) increased as much as 30-fold above normal levels (median increase 7-fold). At 4 hours after Icatibant infusion, median bradykinin was decreased from initial 48.5 to

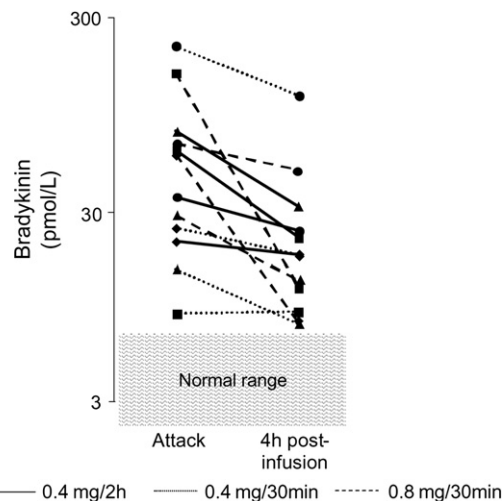


FIG 2. Plasma bradykinin during acute attacks of hereditary angioedema and after intravenous administration of Icatibant. Note the logarithmic scale. All initial bradykinin levels are well above normal, and all but 1 of 12 Icatibant administrations resulted in decreased bradykinin levels.

18.0 pmol/L (Fig 2; $n = 12$). Similarly, 4 hours after subcutaneous administration of Icatibant, bradykinin was decreased from 75.0 to 30.5 pmol/L, but this decrease did not reach significance ($n = 8$).

DISCUSSION

Current treatment of patients with HAE includes long-term prophylaxis and treatment of acute edema attacks.^{25,26} Long-term prophylaxis with attenuated androgens (mainly danazol and stanozolol) is effective in many patients. However, a number of side effects were reported, including virilization in females, weight gain, and even liver cell adenoma and carcinoma.^{27–29} Although attenuated androgens reduce the total number and the severity of attacks considerably in most patients, use in children, teenagers, and women in child-bearing age is problematic. Long-term administration of tranexamic acid is less effective but shows fewer adverse events. Acute attacks can be efficiently treated with C1-INH concentrate. The C1-INH concentrate is derived from human plasma and has to be injected intravenously. High plasma bradykinin levels are found in patients with acute attacks of HAE,^{14,15} and bradykinin is likely to mediate the clinical symptoms via its receptor BR-2.

In the current uncontrolled proof-of-concept study, we assessed a new mode of treatment in HAE, a BR-2 antagonist in acute attacks of the disease. The BR-2 antagonist Icatibant has a high specificity for the B2-receptor and inhibits a variety of B2-mediated effects.¹⁹ Its half life in plasma is 2 to 4 hours. It is degraded by peptidases, and the degradation products are excreted via the kidneys. Until now, the effectiveness has been assessed in seasonal allergic rhinitis^{30,31} and asthma.³² Furthermore,

its effects on the response to angiotensin-converting enzyme inhibitors and other drugs have been studied.^{33,34} In our study, we found a marked beneficial effect of Icatibant in patients with HAE. Icatibant improved skin swelling and abdominal pain attacks of the disease.

Treatment with Icatibant was beneficial in all attacks of all patients. Using a 10-cm VAS, administration of Icatibant led to a significant absolute reduction of symptoms of 4.11 cm after 4 hours. It has previously been shown that a reduction of 1.3 cm or 1.6 cm using VAS is the minimal clinically significant difference in acute abdominal pain.^{21,22} Thus, we strongly believe that the clinical benefit observed in our study is not attributable to a placebo effect. It is well known that corticosteroids and antihistaminics are not effective in HAE because of C1-INH deficiency—that is, they are not more effective than placebo. Consequently, if Icatibant had not been effective, the patients would have reported the lack of efficacy, similar to the lack of efficacy of corticosteroids and antihistaminics. Because all patients reported a clear beneficial effect of Icatibant, we conclude that this drug was effective in the severe and moderate acute attacks of HAE.

In our study, patients received treatment as long as 10 hours after the onset of symptoms. The mean period to onset of symptom relief recorded by patients (all groups combined) was 1.16 hours, whereas in untreated attacks from the same patients and at a similar location of disease manifestation, the mean period to onset was 42.01 hours, reflecting a reduction of 97%. Until now, only 1 randomized double-blind study in HAE has been conducted, assessing C1-INH replacement therapy for acute HAE attacks.^{23,35} Waytes et al²³ reported a mean time to the beginning of symptom improvements of 0.9 hours for 55 treated attacks in 11 patients, and 9.4 hours for the control group. Treatment started not later than 5 hours after the begin of an attack. In a later report about the same study, Kunschak et al³⁵ evaluated 11 patients with 70 treated attacks, in which attacks were also included that were treated later than 5 hours after symptom onset. The authors observed a mean period of 1.7 hours between drug administration and onset of symptom relief in patients receiving therapy compared with 15.4 hours in untreated controls. Hence, the reported time to relief was similar to that observed in our patients.

In 4 patients with 5 attacks, there occurred recurrences of the swelling or new angioedema episodes after an initially highly effective treatment. This occurred in 2 patients after i.v. treatment and in 2 other patients after s.c. treatment. In all other patients, however, there were no recurrences. The reasons for recurrences or new angioedema attacks after treatment with Icatibant can only be speculated about. The relatively short half life ranging from 2 to 4 hours might be one of the reasons. Further studies with the drug are necessary to evaluate this issue and the treatment of throat swellings.

The local injection reactions included itching, urticarial wheals, erythema, and mild burning pain. They were observed in all patients after s.c. administration but not in

patients who received the drug intravenously. The pathogenesis of this kind of side effect remains unclear. They might be explained by an agonistic activity of Icatibant at very high local concentrations. The initial urticarial wheal indicates a pathogenetic involvement of histamine. Although it is unknown why HAE symptoms recurred in some of the attacks treated with Icatibant, the reason might be the plasma half life of 2 to 4 hours.

The measurement of bradykinin levels by a very sensitive and specific method confirmed in all acute HAE attacks of our patients that plasma bradykinin is increased during angioedema attacks, and that the relief of symptoms after treatment is accompanied by a decrease in plasma bradykinin. However, the decrease of plasma bradykinin levels was not complete (Fig 2), and the treatment-induced change in plasma bradykinin was not directly related to the degree of relief of symptoms. This is not surprising, because unlike after C1-inhibitor treatment of HAE attacks,¹⁴ in which the generation of bradykinin is reduced, the Icatibant treatment does not interfere with generation or metabolism of bradykinin, but it blocks the BR-2 mediating the effect of bradykinin (edema). This blockade appears to remain intact even in the presence of increased bradykinin levels. Individual differences in enzyme activities may cause different metabolism (kininases, neutral endopeptidase, aminopeptidases, dipeptidylpeptidase) or generation of bradykinin (kallikreins, plasmin).

A major limitation of the study presented here is that it is not a controlled, double-blind, randomized study. Furthermore, the number of patients is relatively low, and 15 patients with 20 attacks were treated with various regimens concerning dose and route of administration. On the other hand, this is the first observation of a novel mode of treatment of acute HAE attacks, and our aim was to assess whether it is effective in HAE. Furthermore, the fact that treatment with a BR-2 antagonist is effective leads to further insight in the pathogenesis of acute attacks of HAE by confirming the importance of bradykinin in these attacks.

In conclusion, we believe that the BR-2 antagonist Icatibant is effective in skin swellings and abdominal pain attacks of HAE and, thus, may represent a new mode of treatment in this disease. Until now, there has been no therapy approved for use in the United States for HAE. Patients in the United States are treated symptomatically with mostly limited and, unfortunately, sometimes fatal outcomes. Ideally, our study will pave the way for larger randomized, placebo-controlled trials.

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