

Update on preventive therapy (prophylaxis) of hereditary angioedema

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ABSTRACT

The prophylaxis of patients with hereditary angioedema to prevent attacks has gone through major revision as new agents for prophylaxis have come on the market. Earlier treatments, developed empirically, included the fibrinolysis inhibitors epsilon aminocaproic acid and tranexamic acid and attenuated androgens such as danazol. With the development of these agents, many patients had relief of severe symptoms, and drugs in these classes have been the only treatments available in America. Their major disadvantage has been their side effects, which range from minor to severe. In Europe various products containing C1 inhibitor, the serum protein deficient in this disease, were prepared from pooled donor plasma. They were reported to be effective in ending attacks and in prophylaxis, but these products in general were not used in prophylaxis, in part because of the short half life of the plasma protein. One such product, C1 esterase inhibitor, has now been shown in a rigorous double-blind study to be effective in prevention of hereditary angioedema attacks and has been approved by the US Federal Drug Administration for prophylaxis of the disease. Its use has been attended by few side-effects, reflecting the fact that it is the purified naturally circulating product.

(Allergy Asthma Proc 32:17–21, 2011; doi: 10.2500/aap.2011.32.3412)

Treatment of hereditary angioedema (HAE) has been divided traditionally into long-term treatment, short-term therapy, and acute treatment. These designations were made before we had great insight into the pathophysiology of HAE and while we were attempting to develop therapy empirically. Nevertheless, the divisions were useful and have continued to the present. Long-term therapy was the designation given to prophylaxis or long-term preventive therapy. Given the enormous morbidity of this disease, the high costs of the disease in terms of physician and hospital costs, and the costs of missed work and being unable to work, prophylaxis to prevent attacks has always had high priority.¹ The designation of short-term therapy was for prophylaxis when patients were not having attacks, but might be expected to have an attack in the near future. Thus, a patient undergoing surgery, having extensive dental work done or in a traumatic accident might be treated to prevent a possible attack. The

need for this is clear. Many patients have attacks precipitated by trauma. If they see a dentist and the trauma of dental manipulation or gum injection leads to angioedema starting in the mouth, airway compromise may result. In the days before prophylaxis, these patients learned to dread going to the dentist. Short-term prophylaxis addresses this possibility. Acute therapy was therapy initiated after attacks had begun and was designed to terminate swelling.

DEVELOPMENT OF THE OLDER AGENTS

In this review we discuss both long-term and short-term preventive therapy. Long-term preventive therapy of HAE was the first area in which a therapeutic breakthrough was made. A Swedish group interested in defining diseases in which the newly described drug epsilon-aminocaproic acid (EACA), a fibrinolysis inhibitor, might be useful administered the drug to patients with a wide variety of diseases.² They reported their experience in treating many diseases over a 5-year period. It was noted that a single patient with HAE appeared to improve on EACA. The report was noted by another Swedish group who treated a second patient with EACA and confirmed the finding.³ The emphasis of the article they published was on the role of EACA on complement activation, thought at that time to be responsible for the angioedema, and on histamine metabolism. In fact, they were unable to identify the

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Presented at the Eastern Allergy Conference, Palm Beach, Florida, May 7, 2010

Supported by an educational grant from ViroPharma, CSL Behring, and Dyax Pharmaceuticals

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mechanism by which EACA controlled the development of angioedema. A year later Champion and Lachmann reported another family successfully treated with EACA.⁴ Frank *et al.* in 1972 conducted a double-blind study of the EACA prophylaxis, proving that it was far more effective than placebo in controlling attacks.⁵ In Europe a cyclical derivative of EACA, tranexamic acid, was developed and has become the standard fibrinolysis inhibitor used in the treatment of HAE, because it is more convenient to use and has a better toxicity profile.⁶ Tranexamic acid has not been available in capsule form in America and has not been used in this country. EACA is associated with a wide variety of long-term toxicities. Thrombosis has not been a problem but muscle aches and pains with weakness and markedly elevated creatine phosphokinase enzymes, as well as a feeling of severe fatigue to the point of disability, are noted with long-term EACA therapy. It is now believed that EACA functions by inhibiting plasmin activation of kallikrein and that by interrupting the kinin generating cycle, it tends to inhibit attacks, but this has not been studied carefully and is a supposition at this time. Because EACA use was clearly associated with great difficulty over time, more effective and safer prophylactic agents were needed.

Frank and his colleagues were struck by the endocrinologic aspects of HAE.⁷ The disease is equal in incidence in male and female subjects and becomes worse at the time of puberty in both sexes. Nevertheless, they noted that it is made much more severe by estrogens, such as those in birth control tablets, and the majority of patients that come to a clinic are women. In their experience most women were much improved clinically during the latter part of pregnancy and many of the patients that they were following said that the last trimester of pregnancy was the best period that they had experience clinically in many years. They never had attacks precipitated by the trauma of delivery, although some of the patients often had attacks precipitated by other trauma. The findings were not uniformly true and a minority of the women seen in Frank's clinic became much more severely ill. The finding is of interest because German investigators have reported that German women generally become more severely ill during pregnancy and the Australians have reported that their experience is similar to that in America.⁸ A recent European report based on a questionnaire sent to a large number of European women came to the conclusion that $\sim 1/3$ of patients got better, $1/3$ became worse, and $\sim 1/3$ had no change.⁹ The reasons for these differences are unknown. Because progesterone rises progressively during pregnancy and falls precipitously on delivery, Frank's group first studied the effect of progesterone as prophylaxis in a small group of patients. The essentially negative study was never published. Although they noted that all of the treated

Table 1 Results of a double-blind study of the use of danazol vs. placebo in hereditary angioedema prophylaxis

	Total Courses	Attack-Free Courses	Attacks
Placebo	46	3	43
Danazol	42	41	1
Total	88	44	44

Patients received drug or placebo for about a month. At the end of each study period they went on to the next random drug or placebo course. If patients experienced an attack, the course they were on was deemed a failure and they continued immediately to the next random course. The marked effect of danazol in prophylaxis is evident.

women felt better, there was no decrease in the frequency of attacks when the drug was compared with placebo. Other more recent uncontrolled studies suggest that some women will respond well to this agent.

Our group set out to find a gonadotropin inhibitor that would decrease the synthesis of estrogens in both men and women. The drug chosen for study was Danazol, a gonadotropin inhibitor that was being developed as a female contraceptive and that was felt to be safely used in women. In a double-blind study it was shown that this drug is extremely effective in prophylaxis of HAE (Table 1) and in some patients, surprisingly, raises the blood level of C1 inhibitor to normal.¹⁰ The drug was so effective it was approved by the Food and Drug Administration (FDA) for HAE prophylaxis based on study of these nine patients. Because this is a heterozygous disease in which patients have one normal gene allele and one abnormal gene, the finding suggests that the functional output of the normal gene increases on danazol therapy. There is data to both support and refute this suggestion and the question is not settled. Over the years it has been quickly discovered that all of the 17 methylated and attenuated androgens are useful in the prophylaxis of HAE. Testosterone itself is not effective. A similar androgen, stanozolol, has also received FDA approval for HAE therapy but it is currently not easily obtained in the United States.¹¹ Interestingly, it also has been found that androgens increase the level of bradykinin degrading enzymes such as aminopeptidase P.¹² At present, it appears that androgens both decrease the formation of bradykinin and increase its degradation, thereby preventing these bradykinin-initiated attacks.

There are many side effects associated with danazol therapy and most of these side effects are associated with the other attenuated androgens as well.¹³ Almost all patients note weight gain and most patients have lipid abnormalities. Plasma LDL and cholesterol are

increased and HDL levels fall. Because the patients are on these agents for prolonged periods, these are not minor complications. Some patients develop liver function abnormalities with abnormal liver enzymes. In a handful of patients liver cysts or carcinomas have been reported. Some patients develop myopathies, hematuria, headaches, abnormal menses, increased or decreased libido, hair loss or gain, or have anxiety reactions. In general, all of these side effects are quite mild and it is unusual for patients to come off danazol therapy because of side effects. Nevertheless, the side effect list is long and of concern. When patients are treated the dose is progressively lowered until patients are having occasional attacks, because the severity of the side effects is dose related. Clinical signs and symptoms are followed and the levels of blood proteins are not used to determine clinical effectiveness. Impeded androgens are not of use in some patient groups. They can not be used in children because of the possibility of premature closure of the epiphyses and can not be used in pregnancy because of the danger of masculinization of the fetus. They are ineffective in some people. In addition, there are no i.m. or i.v. preparations. Testosterone itself is not effective. The drugs must be given orally and, if a patient is having an abdominal attack with edematous gastrointestinal mucosa, the drugs may not be absorbed. The androgens are useful in prophylaxis but they are not useful in acute therapy. They do not have an effect for a minimum of 48 hours. For all of these reasons it was important that other forms of therapy be developed that have fewer side effects and be useful in all patients. There was a long history of using plasma-purified C1 inhibitor to treat acute HAE attacks and attention has been turned back to this agent for both acute treatment and prophylaxis.

THE BACKGROUND OF C1-INHIBITOR USE IN PROPHYLAXIS

Three independent groups began the process of purifying C1 inhibitor from pooled plasma of thousands of donors in the mid-1970s. All three groups had extensive experience in purifying γ -globulin from plasma and had available facilities for processing plasma in large quantities. The Dutch Red Cross in Amsterdam, The Netherlands, Behring Pharmaceuticals in Marburg, Germany, and the American Red Cross in Washington, DC all successfully purified the protein. C1 inhibitor was reported effective in treating HAE attacks in studies of all three products. Gadek *et al.* reported on the biochemical effect of the American Red Cross C1 inhibitor on C1 inhibitor and C4 blood levels in eight patients with HAE in 1980 and showed that in the five patients who were having attacks at the time of infusion, it terminated the attacks.¹⁰ Agostoni and Cicardi studied the Dutch Red Cross product and re-

ported that it was effective in terminating an attack.¹⁴ It is this product that in a modern version has been approved for prophylaxis in the United States. Similarly, Bork studied the CSL Behring product and showed that it was effective in an anecdotal report.¹⁵ All of the early studies relied on historical experience to determine effectiveness of the agents, and it was important that a double-blind study to compare C1 inhibitor with placebo be performed in this highly variable disease. Such a study was reported by Waytes *et al.* in 1996.¹⁶ This study compared still another C1-inhibitor product prepared by Immuno of Austria with placebo. They reported both the effectiveness in terminating attacks and, in an inpatient portion of the study, in prophylaxis of disease. In the prophylaxis part of the study they showed in six patients with severe disease who had not responded to conventional treatment that receiving this agent, at 25 U/kg every 3 days for a total of 5 infusions, was highly effective in prophylaxis. They followed the blood level of C1 inhibitor and C4 over the entire period of treatment. Blood levels of C1 inhibitor rose to normal immediately after infusion and by 3 days after infusion were again markedly depressed, illustrating the short half-life of this plasma protein. As in earlier studies, the blood levels of C4 came back to normal more slowly, but then remained normal for the duration of the study. Placebo infusions did not affect either C1 inhibitor or C4 levels. Patient's attacks decreased by 60% compared with placebo but, interestingly, they did not decrease to zero.

The CSL Behring product, Berinert, was first licensed in Germany in 1985 and has been approved or licensed in Europe since that time. The Dutch Red Cross serum protein purification laboratory was merged into Sanquin in 2003. In 1989 heat treatment had been added and more recently nanofiltration was added to further ensure sterility. The aforementioned two products have been available in Europe for acute treatment of HAE attacks for several decades and many reports attest to their effectiveness, but they have not been available in the United States. With the onset of the acquired immunodeficiency syndrome epidemic in 1980, the American Red Cross turned its attention away from HAE and their C1-inhibitor product was no longer made.

TRIALS OF THE CURRENTLY APPROVED C1-INHIBITOR PREPARATION

Other reviewers will discuss therapy of acute disease, but it should be remembered that C1 inhibitor is a physiological protein that controls many mediator systems in blood. It is capable of down-regulating clotting factor XIIa and plasmin generation as well as kallikrein generation, and complement activation. Under normal circumstances the protein prevents unto-

Endpoints Results: Median of within Patient Percent Differences (95% CI)

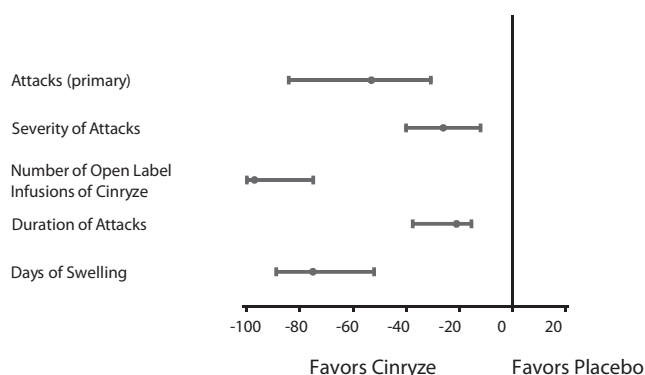


Figure 1. The effectiveness of Cinryze prophylaxis in preventing hereditary angioedema (HAE) attacks. Shown is the statistical analysis of the activity of Cinryze in decreasing attack frequency, severity, duration, days of swelling, and open-label rescue treatments in the prophylaxis study. The effect is marked but, as in other studies, attack frequency did not decrease to zero.

ward generation of bradykinin by down-regulating activation of the kinin-generating system. The only currently available agent that has been studied in a controlled prophylaxis trial is the Dutch Red Cross agent, now imported by Viropharma (Exton, PA) and sold under the brand name Cinryze.¹⁷ The prophylaxis portion of the trial followed a blinded trial of acute therapy. Patients had a preliminary screening visit to establish their diagnosis and then participated in an acute treatment trial. After this portion of the study and, while the patients were still blinded with respect to the drugs they had received, they entered the prophylaxis trial. The placebo-controlled trial that was conducted was a crossover study in which patients received either C1 inhibitor or placebo at 1000 U i.v. every 3–4 days for a 12-week period and then crossed over for an additional 12 weeks to receive the alternate agent. If patients on any agent continued to have attacks, they were eligible to receive in an unblinded fashion 1000 U of C1 inhibitor as rescue medication. The drug proved effective at decreasing attack frequency and duration as well as attack severity, and the number of open-label rescue therapy treatments was markedly reduced in patients receiving drug compared with placebo (Fig. 1). The study confirmed the fact that psychological factors have a major effect on attack frequency in HAE. An interesting patient in the prophylaxis study actually had more attacks during treatment with Cinryze than on prophylaxis because of life events, which increased the attack frequency. When the trial was over, the patient's life circumstances returned to normal and attack frequency decreased markedly. It is interesting that HAE patients in

all double-blind trials tend to have a higher attack frequency than those being treated with known open agents where the patient is perfectly confident that the agent will terminate attacks. These factors must be acknowledged in considering treatment regimens in patients with HAE. In October of 2008 Cinryze was approved by the FDA at 1000 U i.v. biweekly for prophylaxis.

THEORETICAL PROBLEMS AND ADVANTAGES

All plasma products have a risk of infection. The risk is minor with C1-inhibitor products because no infection has been observed for decades with the current products. Both start with the blood from healthy American donors and go through potent virus reduction purifications. These are drugs that have been used for decades in Europe without difficulty. At present, they are given i.v., which is a disadvantage. Because patients are all heterozygotes and synthesize normal C1 inhibitor, allergy to the administered product is unlikely. Because this is the normal physiological protein, presumably, it will provide normal physiological regulation.

SHORT-TERM THERAPY

As mentioned previously, there are circumstances where it is important to prevent attacks. Fresh frozen plasma (FFP) as a source of C1 inhibitor has been recommended for the treatment of acute attacks.¹⁸ We do not recommend FFP for treatment of acute attacks although it is clear that the vast majority of patients do note termination of attacks. FFP supplies high-molecular-weight kininogen and prekallikrein, two proteins that are consumed during kinin generation. The cleavage of high-molecular-weight kininogen in some patients generates additional bradykinin. The supply of fresh substrate for kinin generation may make attacks worse before the attack starts to resolve and we have seen patients develop more severe angioedema after FFP. Nevertheless, when the patient is not having an angioedema attack it is safe to give FFP and we have reported on its use in dental and other types of surgery.^{19,20} Two units of FFP in our hands has prevented all acute angioedema attacks. Others have advocated 1 week of attenuated androgen therapy. Androgens such as danazol, even when used at high dose, usually have minimal side effects in a week and those that occur disappear rapidly. They have been used successfully before dental and surgical procedures.²¹ Obviously, the new C1-inhibitor preparations can also be used to provide protection in these situations. In providing the deficient protein, while being free of kinin substrates, this agent is ideal for preventing attacks.

CONCLUSIONS

Thus, in the period of one professional lifetime we have gone from no complete clinical picture of the syndrome to a complete clinical picture, to an understanding of the gene defect and the pathophysiology of the disease, and to having drugs available for prophylaxis that bring this disease under control. As discussed in another review²² the acute therapy has progressed in a similar highly satisfactory way. The future of patients with HAE is markedly improved.

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