

Hereditary angioedema: Short-term prophylaxis for surgery

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The change in our understanding over the past 30 years of both the cause and the treatment of hereditary angioedema (HAE) has been truly amazing. Until the 1970s, we did not have a description that tabulated disease manifestations in a large group of patients.¹ The clinical description along with important findings related to pathophysiology led to renewed interest in the treatment of this interesting life-threatening condition. Virginia Donaldson, in studying the blood level of a newly described plasma protein, C1 inhibitor, made the remarkable discovery that levels of the protein are low in patients with HAE.² The observation proved critical in ultimately allowing investigators to unravel its pathophysiology and to devise specific and effective therapy both for the treatment of acute attacks and for the prophylaxis. The observation was followed by the identification of types 1 and 2 HAE, type 1 being associated with a defective gene allele leading to no protein product of this allele circulating and type 2 HAE in which the allele makes a circulating nonfunctioning protein.³ Once we knew that patients had low levels of functioning protein, the idea of replacing the protein became paramount at a number of centers. In case reports it was noted that infusion of normal plasma in patients having attacks of angioedema would terminate the attacks by supplying plasma C1 inhibitor.⁴ Experience with this approach proved that, although most attacks were terminated, a few attacks became worse. The reason was clarified when we came to understand that attacks are precipitated by activation of the kinin generating system with release of bradykinin.⁵ In some patients, the activation of bradykinin precursors in fresh frozen plasma leads to more extensive angioedema formation before the infused C1 inhibitor down-regulates the system and turns off further bradykinin formation.

We reported some decades ago that it was safe to give fresh frozen plasma to patients to prevent attacks, when patients are attack free and there is concern that

attacks may be precipitated by surgical trauma, dental work, *etc.* We reported a series of patients in which this approach was successful for short-term prophylaxis.⁶ Fresh frozen plasma has its own set of issues including the possible transmission of viral illness and one would have to consider this suboptimal therapy. With the availability of purified C1 inhibitor prepared from plasma that is free of infectious agents and essentially free of contaminating proteins, it became possible to provide specific therapy, replacing only the protein that is missing.^{7,8} Similarly, because current preparations of C1 inhibitor protein are free of kinin precursors, they can be used safely in acute attacks. Double-blind studies have shown that C1 inhibitor effectively terminates attacks.

In addition, this agent has received Food and Drug Administration approval for the treatment of acute attacks. Studies of prophylaxis with this agent have also shown efficacy and the drug has been approved for prophylaxis of HAE.⁷ In the studies of treatment of acute attacks as well as studies of prophylaxis, this agent has not been 100% effective, which provides part of the background for this study.

The original studies that showed the effectiveness of treatment of acute attacks and prophylaxis by C1 inhibitor were followed up by extension studies in which patients continued to receive C1 inhibitor both prophylactically and for acute attacks. Some of these patients required potentially traumatic procedures including surgery and dental work and the outcomes of such treatments were collected in this article. Thus, as reported within the pages of this issue, Grant et al⁹ performed a retrospective analysis of data in the records of patient cohorts previously examined in double-blind studies in which the product Cinryze was administered. They determined the frequency of angioedema attacks after short-term prophylaxis for surgical and other procedures. They found that purified C1 inhibitor protein approved for long-term prophylaxis is effective at preventing swelling after surgical trauma of many types. Because these patients can develop life-threatening airway angioedema after trauma, it is not practical to do a double-blind study.

The retrospective nature of the study made it impossible to collect some data that would have made the study more valuable. So, *e.g.*, we know that a large

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number of patients had dental procedures, but we do not know what exactly those procedures were or how traumatic they were. In these individual patients we do not know what their incidence of angioedema attacks was before therapy and we do not know if they had similar procedures in the past that did or did not lead to attacks. This kind of data would be very useful but was not available in this retrospective analysis. Knowing that C1 inhibitor is effective as treatment of acute attacks and is also effective in prophylaxis, and knowing that fresh frozen plasma used prospectively has been reported to be effective, the results are not surprising. On the other hand, this study presents data on doses used for prophylaxis and we can now state that the incidence of angioedema after procedures is extremely low in this treated group. The finding will give many physicians and dentists comfort in knowing that they can treat patients with an established dose of purified C1 inhibitor, not expose them to infection, and feel confident that they will not have attacks. Thus, this article, although one might wish it had more extensive data, will be of help to treating physicians and to their patients. One might ask whether agents other than C1 inhibitor can serve the same purpose. Two drugs given subcutaneously, Kalbitor and Firazyr, have been shown in double-blind studies to terminate attacks of HAE.^{10,11} Both are peptides and presumably act for a period of hours. There is some reason to use the C1 inhibitor protein, which must be given i.v. because of its relatively long half-life of perhaps 40 hours in the circulation. The patient will be covered for possible angioedema attacks, not only during the procedure but after the procedure. It may be that these other agents will be useful as well but this is not proven.

After we described the use of fresh frozen plasma, others described the use of androgens in prophylaxis for procedures.¹² It was clear that the androgens would have to be administered for 5 days to a week before the procedure to be certain that they would be effective. We did not endorse that approach, because we had seen patients on androgens have occasional attacks of angioedema and, in the days when there was no treatment other than tracheostomy or intubation for acute attacks, it did not seem reasonable to us to put the

patient at that risk. On the other hand, with backup purified C1 inhibitor or other agents available to treat acute attacks, and androgens available that have very little toxicity over the course of a week, it may be reasonable to reconsider that approach.

We have gone, in a relatively brief period of time, from a clinical description of the disease to an understanding of pathophysiology, and that understanding of pathophysiology has led to highly effective therapy and altered the lives of this patient group.

REFERENCES

1. Frank MM, Gelfand JA, and Atkinson JP. Hereditary angioedema: The clinical syndrome and its management. *Ann Intern Med* 84:580–593, 1976.
2. Donaldson VH, and Evans RR. A biochemical abnormality in hereditary angioneurotic edema: Absence of serum inhibitor of C' 1-esterase. *Am J Med* 35:37–44, 1963.
3. Rosen FS, Pensky J, Donaldson V, and Charache P. Hereditary angioneurotic edema: Two genetic variants. *Science* 148:957–958, 1965.
4. Pickering RJ, Good RA, Kelly JR, and Gewurz H. Replacement therapy in hereditary angioedema. Successful treatment of two patients with fresh frozen plasma. *Lancet* 1:326–330, 1969.
5. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
6. Jaffe CJ, Atkinson JP, Gelfand JA, and Frank MM. Hereditary angioedema: The use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. *J Allergy Clin Immunol* 55: 386–393, 1975.
7. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 363:513–522, 2010.
8. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 124: 801–808, 2009.
9. Grant JA, White MV, Li HH, et al. Preprocedural administration of nanofiltered C1 esterase inhibitor for successive acute hereditary angioedema attacks. *Allergy Asthma Proc* 33:348–353, 2012.
10. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 363:532–541, 2010.
11. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 363:523–531, 2010.
12. Sheffer AL, Fearon DT, and Austen KF. Hereditary angioedema: A decade of management with stanazolol. *J Allergy Clin Immunol* 80:855–860, 1987. □

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