

Assessment of hereditary angioedema treatment risks

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ABSTRACT

Therapies used for hereditary angioedema (HAE) have been associated with adverse events to include thrombosis, emboli, hepatocellular carcinoma (HCC), exacerbation of attacks, and anaphylaxis. It is difficult to determine incidence of these adverse events from the literature. For this reason we surveyed multiple HAE physicians to determine the risk associated with therapies used in HAE. This study was designed to determine by survey the risk of thrombosis associated with C1-inhibitor (C1-INH), worsening attacks with fresh frozen plasma (FFP), and carcinoma secondary to androgens (mainly danazol). An Internet-based survey was sent to physicians internationally who treat patients with HAE. The survey queried physicians about their observations while treating HAE. Of the 66 physicians who participated in the survey, 37 had patients (856 patients) who were on C1-INH but only 4 (total of 5 patients) had patients on C1-INH who experienced an thromboembolic episode. Of the 17 patients on C1 esterase inhibitor and an indwelling catheter, 3 experienced an embolic, thrombosis, or thromboembolic event. The likelihood of an abnormal event when a patient is on a C1-INH is 5/856 (0.6%), compared with 3/17 (18%) with a central catheter. The incidence of HCC is rare. The incidence of adverse effects to FFP is greater than the literature suggests. Patients with HAE should avoid indwelling catheters, use FFP only when other therapies are unavailable, and use androgens with caution. Most importantly, adverse events to drugs should be reported so that the true incidence of adverse events can be determined.

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Hereditary angioedema (HAE) is a serious inherited condition characterized by edema involving the skin, gastrointestinal tract, and upper airway. HAE is caused by a deficiency of C1-inhibitor (C1-INH), which is the major regulator of early steps of the complement and contact pathways and also has minor effects on the fibrinolytic and coagulation pathways.¹ With a deficiency of C1-INH, there is uncontrolled activation of the contact system either spontaneously or after a traumatic or stressful event leading to increased production of bradykinin causing the edema typical of HAE. Because of the development of new therapies, most experts feel there is no longer an indication for use of fresh frozen plasma (FFP).¹ Treatment indications for androgens have also decreased for this reason.²

Androgens and FFP are still used because of the lack of alternative treatment modalities in many countries. Presently, in the United States, Western Europe, and other nations there has been an increase in the use of C1-INH, icatibant, and ecallantide.^{3–7} C1-INH use appears to be very safe, but there is a concern that a risk of thrombosis and emboli exists because of historic

reporting of this side effect with off-label use of high doses in high-risk neonates and sporadic reports to government agencies. Our survey was meant to determine the experience of physicians, who focus on care of HAE patients, about the adverse events associated with FFP, androgens, and C1-INH. We focused on hepatocellular carcinoma (HCC) association with androgens, how often HAE patients receiving FFP exacerbate, and the association between thromboembolic events and the use of C1 esterase inhibitor. All three of these queries were difficult to ascertain from literature searches and the authors pursued the survey for this reason. The time since approval and use of ecallantide and icatibant has been limited making it unlikely that adverse effects, other than those documented in preapproval research, would be defined or discovered by a survey, and the authors did not feel that further discovery of the known adverse events was warranted.

METHODS

An Internet-based survey was sent to physicians both nationally and internationally who treat patients with HAE. The survey queried physicians about their observations while treating HAE patients. This met an Institutional Review Board exception. Physicians surveyed included those who participated in a recent HAE working consensus group and included physicians who are known to care for many patients with HAE. This consensus meeting had international participation.⁸ We also researched the literature for C1-INH adverse events by searching Google, PubMed, and Ovid for “thrombosis and C1-inhibitor,” “clots and

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C1-inhibitor," "emboli and C1-inhibitor," and the same terms using C1 esterase inhibitor. For androgen adverse events we used "carcinoma and androgens," "liver cancer and androgens," "hepatocellular carcinoma and androgens," and the same terms using danazol in place of androgens. Also searched was "hereditary angioedema and fresh frozen plasma," "hereditary angioedema and FFP," and "HAE and FFP."

The questions included in the survey were the following:

1. "How many of your patients are on C1 esterase inhibitor (Cetor, Cinryze, or Berinert)?"
2. "How many of these patients on C1 esterase inhibitor have experienced a deep vein thrombosis (DVT)/pulmonary embolus (PE)/thrombus/emboli or other abnormal clotting disorder?"
3. "How many of your patients are on C1 esterase inhibitor and have an indwelling catheter placed?"
4. "How many of these patients on a C1 esterase inhibitor and an indwelling catheter have experienced a DVT/PE/thrombus while on treatment?"
5. "How many of the patients you have with DVT/PE/thrombus/emboli or other abnormal clotting are on prophylaxis therapy for HAE?"
6. "How many of the patients you have with DVT/PE/thrombus/emboli or other abnormal clotting are on demand therapy for HAE?"
7. "Do you have patients who had a DVT/PE or thrombus while on C1-inhibitor who do not have an indwelling central line? If so, how many?"
8. "How many of your patients are taking androgens?"
9. "How many of these patients on androgens have been diagnosed with hepatocellular carcinoma?"
10. "Have you had patients with HAE who have never been on androgens but developed hepatocellular carcinoma? If so, how many?"
11. "How many times do you estimate that you treated an HAE patient with fresh frozen plasma (FFP)?"
12. "How many times have you seen a patient get worse from the infusion of FFP?"
13. "How many times are you sure that FFP was the culprit and what the patient experienced was not the natural course of the HAE attack?"

RESULTS

Of the 66 physicians who participated in the survey, 37 responded that they cared for patients who were on C1-INH, but only 4 had patients on C1-INH who experienced an abnormal clotting episode. Seven of 66 physicians had patients on C1 esterase inhibitor and an indwelling catheter; 2 of these 7 had patients who experienced an abnormal clotting event. Of the 856 patients on C1 esterase inhibitor (Cetor [Sanquin, Am-

sterdam, The Netherlands], Cinryze [Viropharma, Exton, PA], or Berinert [CSL Behring, Marburg, Germany]), 5 experienced an abnormal clotting episode. Of the 17 patients on C1 esterase inhibitor and an indwelling catheter, 3 experienced an abnormal clotting event. Thus, the incidence of an abnormal clotting event for patients receiving C1 esterase inhibitor is 5/856 (0.6%), whereas the frequency of an abnormal clotting event for patients on C1 esterase inhibitor with an indwelling catheter is 3/17 (18%). Thrombotic episodes related to C1 esterase inhibitor use have been reported to the Food and Drug Administration (FDA) when C1-INH was used at suggested doses, but it was unclear whether the thrombosis was secondary to C1 esterase inhibitor or an indwelling catheter or both.⁹ Catheter-related thrombosis occurs in up to 50% of children and 66% of adults with a long-term indwelling catheter suggesting these catheters significantly predispose to thrombosis.¹⁰

In our survey, there were a total of 886 patients on androgens. Of the reported patients, only one developed HCC. Of the HAE patients not on androgens, none developed HCC. The literature search suggests an additional 4 cases being reported.¹¹⁻¹⁴ The total reported and surveyed cases include 5, making this a severe, but rare side effect (5.8 cases per 1000 users).

In the survey, a total of 337 HAE patients were treated with FFP and 41 of these 337 patients worsened (exacerbated the HAE attack) after the infusion of FFP. In 28 reports of these 41 patients, the physician was sure that FFP was the culprit and what the patient experienced was not the natural course of the HAE attack. The literature search failed to show many reports of worsening of HAE symptoms with the use of FFP for treatment; however, our survey suggests this is a definite possibility, with the risk being 83-122 per 1000 users. In the literature, one study of 13 patients with HAE reported worsening abdominal pain in 2 patients and new skin rash in 1 patient.¹⁵ Another search reported a failure to identify exacerbation of HAE symptoms with the use of FFP.¹

Data exist for the worsening of HAE symptoms after treatment with C1-INH, ecallantide (Kalbitor; Dyax, Cambridge, MA), and Icatibant (Firazyr; Shire, Boston, MA),⁴⁻⁷ but the percentages associated with these drugs is less than those reported with FFP. However, these reports suggest that assumed adverse events from treatment may in part be caused by the natural course of a HAE attack and not adverse effects to the therapeutic intervention.

Unrelated to the survey, we also researched literature for the risk of viral transmission associated with FFP. The Centers for Disease Control and Prevention suggests a 1 in 1.5 million chance of acquiring human immunodeficiency virus through blood transfusion, making the risk in the United States very unlikely;

Table 1 Adverse effects of FFP

Adverse Event	Frequency	Citation
Hepatitis B	0.97%	FDA
Hepatitis C	1.93%	FDA
HIV	0.19%	FDA
Anaphylaxis	0.58%	FDA
Worsening of HAE exacerbation	Unknown, but low frequency	

Source: Ref. 21.

Frequencies of adverse events as reported to the FDA for FFP from Q1 2004 to Q1 2012. Adverse events were counted if FFP was suspected as the drug causing the adverse event.

FFP = fresh frozen plasma; HAE = hereditary angioedema; HIV = human immunodeficiency virus; FDA = Food and Drug Administration.

however, the risk of viral transmission (hepatitis B virus, hepatitis C virus, and human immunodeficiency virus) may be higher in developing countries.^{16,17} Additionally, the estimated risk of anaphylaxis with blood transfusion in the United States is 1 in 500,000.¹⁸

DISCUSSION

The use of C1-INH as approved in the European Union and the United States for HAE poses a minimal risk of thrombosis. Risk has been reported in the literature, but most thrombotic events have occurred at doses far exceeding those used in HAE or with an indwelling catheter.⁹ The risk of a thrombotic event when administering C1-INH with an indwelling catheter is a concern and suggests that indwelling catheters should be avoided and used only when other alternatives are not available.

The consensus by multiple international groups is that the use of FFP is no longer advised when icatibant, ecalantide, or C1-INH (recombinant or human plasma derived) are available.^{8,19} The major reason for this is that the risk of viral transmission with FFP is greater than other HAE treatments.¹⁹ In addition, HAE attacks can be worsened by FFP use because not only C1-INH is present, but the substrates for the contact system are also present.¹ Our data indicate that physicians were often certain of the association between administration of FFP and worsening attacks. Although some literature may suggest that all medications used to treat HAE patients may be associated with a worsening of an HAE attack, our data show that physicians have observed significant worsening of HAE attacks after administration of FFP in far greater numbers than expected by chance alone. Another concern is that anaphylactic reactions are associated with FFP administration and thus further increases the risk associated with the use of FFP.

C1-INH concentrate, because of the many viral screening steps before and during the collection, and

Table 2 Adverse effects of androgens

Adverse Event	Comment
Weight gain	Common
Acne	Common
Flushing	Common
Sweating	Common
Voice changes	Common
Increased hair growth or hair loss	Common
Mood changes	Common
Hyperlipidemia	Less common
Hepatitis	Rare
HCC	Very rare

Source: Refs. 2 and 8.

HCC = hepatocellular carcinoma.

Table 3 Suggested monitoring for patients with HAE on androgens

Risk	Procedure	Frequency
Hyperlipidemia	Lipid panel	Every 6 mo
Liver toxicity	Liver function studies	Every 6 mo
Hematuria	UA	Every 6 mo
HCC	α -Feto-protein	Every 6 mo
Polycythemia	CBC	Every 6 mo
HCC	Liver ultrasound	Every year

Source: Refs. 2 and 8.

HAE = hereditary angioedema; HCC = hepatocellular carcinoma; CBC = complete blood count; UA = urinalysis.

preparation of the product to inactivate viruses, has less transmission concerns than FFP. If C1-INH concentrate is unavailable for on-demand therapy, FFP may be given during acute attacks but has a greater risk of viral transmission, worsening HAE exacerbation, and anaphylaxis and anaphylactoid reactions.

Similarly, if C1-INH is not available for prophylaxis, androgens, including danazol, can be used for prophylaxis. However, androgens carry risks of cholestatic jaundice, peliosis hepatitis, HCC, and multiple other side effects.²⁰ A summary of the adverse effects of FFP and androgens are listed in Tables 1 and 2.

Adenocarcinoma of the liver appears to be associated with use of androgens. Obtaining a true incidence is difficult because most cases are not published. From our survey of physicians who treat high numbers of HAE patients, we have shown that HCC is a rare but potentially fatal side effect. These data suggest that the diligence in assessing for this adverse effect in patients using androgens is important and doses should be kept to the "minimal effective dose." Table 2 includes the common adverse effects of androgens. The suggested medical surveillance for adverse effects associated with androgens is included in Table 3.

Table 4 Adverse events of medications used for HAE

Medication	Significant Adverse Events	Risk
C1-INH	Viral transmission Anaphylaxis	Extremely rare Rare
Ecallantide	Anaphylaxis	Approximately 3%
Icatibant	Local irritation	Approaches 100%
Recombinant C1-INH	Anaphylaxis	Rare and only reported in rabbit allergic people
Androgens	HCC Cardiovascular adverse events Multiple other adverse events	Very rare Common Common
FFP	Anaphylaxis Viral transmission Worsening of attacks	Rare Rare Common
Fibrinolytic agents	Multiple adverse events	Common

Source: Refs. 1, 2, 8, 13, 16, and 19.

HAE = hereditary angioedema; C1-INH = C1-inhibitor; FFP = fresh frozen plasma; HCC = hepatocellular carcinoma.

Adverse effects are not limited to androgens and FFP. Adverse effects also occur with the newer and specific agents; however, serious adverse effects seem to be encountered less often. Table 4 summarizes the main adverse effects of agents commonly used in the treatment of HAE. All therapies have a potential for adverse events and monitoring patients on therapy and reporting potential adverse effects or events to the Food and Drug Administration is essential to ensure optimal care of patients with HAE.

REFERENCES

- Prematta M, Gibbs JG, Pratt EL, et al. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 98:383–388, 2007.
- Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proceedings* 29:225–231, 2008. (Epub ahead of print April 2, 2008.)
- Craig TJ, Wasserman RL, Levy RJ, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J Clin Immunol* 30:823–829, 2010.
- 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.
- 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.
- 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.
- 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.
- Cicardi M, Bork K, Caballero T, et al.; Hereditary Angioedema International Working Group (HAWK). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: Consensus report of an International Working Group. *Allergy* 67:147–1157, 2012.
- Lunn M, Santos C, and Craig T. Cinryze as the first approved C1 inhibitor in the USA for the treatment of hereditary angioedema: Approval, efficacy and safety. *J Blood Med* 1:163–170, 2010.
- Baskin JL, Pui C, Reiss U, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. *Lancet* 374:159–169, 2009.
- Gleeson D, Newbould MJ, Taylor P, et al. Androgen associated hepatocellular carcinoma with an aggressive course. *Gut* 32: 1084–1086, 1991.
- Goodman MA, and Laden AM. Hepatocellular carcinoma in association with androgen therapy. *Med J Aust* 1:220–221, 1977.
- Kew MC, Van Coller B, Prowse CM, et al. Occurrence of primary hepatocellular cancer and peliosis hepatis after treatment with androgenic steroids. *S Afr Med J* 50:1233–1237, 1976.
- Bork K, Hardt J, Staubach-Renz P, and Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: A retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 112:58–64, 2011.
- Tang R, Chen S, and Zhang HY. Fresh frozen plasma for the treatment of hereditary angioedema acute attacks. *Chin Med Sci J* 27:92–95, 2012.
- Shang G, Seed CR, Wang F, et al. Residual risk of transfusion-transmitted viral infections in Shenzhen, China, 2001 through 2004. *Transfusion* 47:529–539, 2007.
- Centers for Disease Control and Prevention (CDC). HIV transmission through transfusion – Missouri and Colorado, 2008. *MMWR Morb Mortal Wkly Rep* 59:1335–1339, 2010.
- Klein HG. Allogeneic transfusion risks in the surgical patient. *Am J Surg* 170:21S–26S, 1995.
- Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 6:24, 2010.
- Fay A, and Abinun M. Current management of hereditary angio-edema (C1 esterase inhibitor deficiency). *J Clin Pathol* 55:266–270, 2002.
- Food and Drug Administration (FDA). Fresh frozen plasma. 2012. Available online at DrugCite. www.drugcite.com/?q=FRESH+FROZEN+PLASMA&s=&a=3; accessed January 13, 2013.

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