



Letter

Assessment of home infusion program for treating nonlaryngeal hereditary angioedema attacks

Ecaltantide is a plasma kallikrein inhibitor reported to be effective in treating attacks of hereditary angioedema (HAE).¹ Ecaltantide had an anaphylaxis rate of 2.7% after subcutaneous administration in clinical trials, and according to the label it must be administered by a health care professional.² Therefore, patients need to travel to an urgent care center, emergency department (ED), or physician office for treatment. To circumvent this requirement, which for many patients decreases access to care, a home infusion program was developed. No published data exist regarding the success or safety of such a program for HAE treatment, and a better understanding of the benefits and challenges of this program is essential to improving the care of HAE patients.

A retrospective review of data collected by the home infusion company from September 2011 to December 2012 was performed. All patients receiving ecaltantide as part of the infusion program had a previously documented HAE diagnosis and were referred to this program by the physician managing their HAE. A nurse or pharmacist screened all HAE patients before beginning services. The patient was assessed for comorbidities, previous experience with ecaltantide, and access to emergency medical services. The sponsoring pharmacy required the nursing service be located within 90 minutes of the HAE patient to respond within a maximum of 4 hours. Referrals were deemed ineligible for the program when a patient did not have access to emergency medical services and/or the patient resided outside the preapproved distance from the nursing services (4.5%). They were also ineligible if they had a history of only laryngeal attacks (0.65%) or were pediatric referrals (0.65%), but there were no referrals denied for medical reasons.

Patients would contact the nursing program at the onset of an HAE attack, and a nurse responded to the patient requests for treatment for nonlaryngeal HAE attacks within a maximum of 4 hours. Patients with laryngeal attacks were advised to go directly to the ED. The nurse performed a complete assessment of the patient on arrival to the patient's home and administered ecaltantide as

ordered by the patient's prescribing physician. The nurse was dispatched to the patient's home with an anaphylactic kit and intravenous start supplies. Nurses in the program were required to attend a yearly live training session and complete a posttest with a score of higher than 80% to qualify to treat HAE patients in the home care setting. During this training, they learned how to distinguish between clinical manifestations of HAE attacks, hypersensitivity reactions (HSRs), and other possible causes of the presenting symptoms. They learned that clinical manifestations shared by HSRs and HAE attacks included the following: peripheral angioedema, abdominal angioedema (eg, abdominal pain, nausea, vomiting, and diarrhea), laryngeal angioedema (eg, throat tightness, hoarse voice, dysphagia, dyspnea, stridor, and airway compromise), hemodynamic changes or compromise (eg, from anaphylaxis or from third-spacing or volume-depletion in bowel angioedema—more common in anaphylaxis than in HAE attacks), erythema (nonpruritic, serpiginous erythematous rash sometimes occurs in HAE attacks). They also learned that clinical manifestations observed in HSRs instead of HAE attacks included cutaneous symptoms (pruritus, urticaria, or flushing), respiratory symptoms (chest discomfort or wheezing), nasal symptoms (rhinorrhea, sneezing, or nasal congestion), and throat irritation. The training also reinforced the principle that the absence of all of these signs or symptoms did not exclude the possibility that a HSR could still be occurring.

The trained infusion nurses contacted the patient's prescriber as necessary based on physical assessment findings and/or whether the ecaltantide treatment did not result in resolution of the HAE attack. Nurses were instructed to closely monitor the patient for at least 1 hour after ecaltantide administration because all anaphylaxis cases in the clinical development program occurred within 1 hour after dosing. Patients classified as having anaphylaxis during a home infusion were discharged from the home infusion program. Finally, before administering a repeat dose of ecaltantide, nurses were instructed to reassess the patient to confirm that the symptoms experienced by the patient were reflective of an HAE attack and not a HSR.

Patient demographics, type of HAE attacks, time to nurse response, number of ecaltantide doses used, and time to onset of symptom relief, as well as HSRs to ecaltantide, were reviewed during the study period.

Between September 2011 and December 2012, 158 HAE patients had 1,177 nursing visits to treat HAE attacks. Most patients were female (71%), with a mean (SD) age of 38 (15) years. Most HAE attacks were combined abdominal and peripheral (36.2%), peripheral alone (32.9%), or abdominal alone (27.5%), with a small number of laryngeal attacks (3.1%). The mean (SD) time to nurse response was 64 (5) minutes (Fig 1), and the mean (SD) time to

Disclosures: The data used for this review were provided by Walgreens Infusion Services. Our group evaluated all the information for every patient enrolled in this home nursing program from September 2011 to December 2012. No patient data was withheld from us and all the information regarding adverse reactions was reported and the authors had full access to the data. There was no agreement to any limitations by the authors. The data were gathered by a nurse, specifically trained in managing HAE attacks, at the time of the visit using a standard form. Walgreen's is a separate entity from the company that makes ecaltantide. Walgreen's maintains these data and were the primary contact for us to obtain access to the data. This provides another level of protection on the integrity of the data. Other potential investigators can contact the Walgreen's home infusion company to gain access to these data. Dyax provided funding to support the statistician that completed the data analysis.

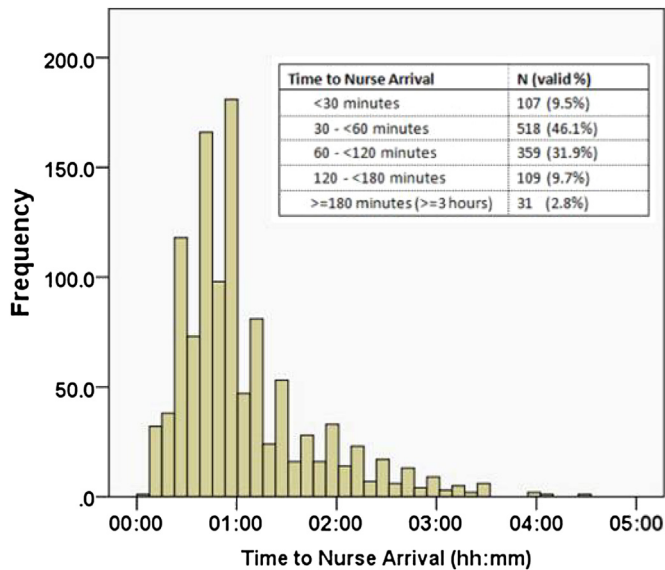


Figure 1. The mean time to nurse response was 64 minutes. Most nurse visits (87.5%) occurred within 120 minutes after the patient call. Almost all nurse visits occurred within 180 minutes.

patient-reported onset of symptom relief, after ecallantide administration, was 42 (5) minutes. Most patients (76.4%) only needed one dose of ecallantide for treatment of the HAE attack.

There were 9 HSRs, and 7 of these were categorized as anaphylaxis by the medical affairs department of the manufacturer of ecallantide. During these HSRs, patients experienced a combination of cutaneous (7 of 9 patients, with 1 or more of the following: hives, flushing, redness, itching, and/or throat swelling), respiratory (5 of 9 patients, with 1 or more of the following: chest tightness, cough, and/or difficulty breathing), cardiovascular (2 of 9 patients, with 1 or more of the following: dizziness and/or heart racing), or gastrointestinal (3 of 9 patients, with 1 or more of the following: stomach pain, nausea, and/or difficulty swallowing) symptoms. Eight of the 9 patients with HSRs were sent to the ED, although none of the patients required intubation, hospital admission, or medications to support their blood pressure. All HSRs resolved without sequelae. Six of 7 patients with anaphylaxis were given epinephrine. Some patients with HSRs also received diphenhydramine (3 of 9 patients), steroids (2 of 9 patients), famotidine (1 of 9 patients), intravenous fluids (2 of 9 patients), or ondansetron (2 of 9 patients). One patient identified as having anaphylaxis did not receive epinephrine or go to the ED. This patient developed itchy hands; redness of the face, arms, and hands; and an unusual feeling in her throat shortly after the ecallantide infusion. The patient was treated with 50 mg of oral diphenhydramine, 50 mg of intravenous diphenhydramine, and 500 mL of normal saline, and all the symptoms improved. The nurse was in contact with the managing physician and with the improvement of symptoms; the patient did not go to the ED.

Although HAE is inherited in an autosomal dominant fashion, many studies have found female predominance of attacks and disease.^{3–5} One study investigating the humanistic burden of hereditary angioedema reported that 75% of HAE attacks were in

females.⁶ This female predominance of disease and attacks is reflected in our data. The 9 HSRs seen in the program demonstrate the potential adverse effect of ecallantide therapy. The rate of HSR from our data is 0.76% (9 of 1,177 patients), which is significantly lower than the Food and Drug Administration package insert rate of 2.7%. However, the rate generated by our data may not be reflective of all patients receiving ecallantide therapy. Patients were excluded from this program for geographic reasons, having laryngeal attacks only, or being pediatric patients. In addition, our data only reflect patients receiving ecallantide for nonlaryngeal HAE attacks. All 9 HSRs were managed appropriately and resolved without sequelae.

There is also a projected cost savings using the nursing infusion program.^{7,8} The direct medical costs per patient are \$25,884 annually, with medical treatment of HAE attacks accounting for 82.4% of these expenses.⁸ Hospital stays and ED visits account for most medical expenses associated with HAE.⁸ The substantial cost savings is generated by avoiding an ED visit in lieu of the home nursing visit.⁷ The mean cost of an ED visit for an HAE attack is \$2,603, which is substantially more than a home nursing infusion visit of \$150.^{7,8} However, we acknowledge that these data were collected before the approval of newer therapies in the United States, which would change the cost of HAE care currently.

These data support the home infusion program as a safe and effective solution for treating nonlaryngeal HAE attacks. Nurse response and treatment of an HAE attack with ecallantide occurred rapidly and efficiently after an HAE patient having an attack called the home infusion company. All HSRs were managed appropriately and resolved without hospitalization.

James Kuhlen, MD*
Autumn Guyer, MD†
Tricia Morpew, MSc‡
Raffi Tachdjian, MD§
Aleena Banerji, MD*

*Massachusetts General Hospital

†Beth Israel Deaconess Medical Center
Boston, Massachusetts

‡Children's Hospital of Orange County
Orange Cove, Florida

§Ronald Reagan UCLA Medical Center
Santa Monica, California
jkuhlen@partners.org

References

- [1] Sheffer AL, Campion M, Levy RJ, Li HH, Horn PT, Pullman WE. Ecallantide (DX-88) for acute hereditary angioedema attacks: integrated analysis of 2 double-blind, phase 3 studies. *J Allergy Clin Immunol*. 2011;128:153–159.
- [2] Kalbitor (Ecallantide) [package insert]. Burlington, MA: Dyax Corporation; 2009.
- [3] Longhurst H, Cicardi M. Hereditary angioedema. *Lancet*. 2012;379:474–481.
- [4] Agostoni A, Cicardi M. Hereditary and acquired C1 inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine*. 1992;71:206–215.
- [5] Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs and course. *Am J Med*. 2006;119:26–27.
- [6] Bouillet L, Gompel A. Hereditary angioedema in women: specific challenges. *Immunol Allergy Clin*. 2013;33:505–511.
- [7] Toscani M, Riedl M, Geffen D. Meeting the challenges and burdens associated with hereditary angioedema. *Managed Care*. 2011;20:44–51.
- [8] Wilson DA, Bork K, Shea EP, et al. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:314–320.