The Effect of Weight on the Efficacy and Safety of C1 Esterase Inhibitor Concentrate for the Treatment of Acute Hereditary Angioedema

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ABSTRACT

Background: Despite the worldwide obesity epidemic, there have been very few studies investigating the influence of body weight on treatment dosing and outcomes in patients with hereditary angioedema (HAE).

Objective: The purpose of this analysis was to determine whether the standard weight-based dosing recommendation of C1 esterase inhibitor (C1-INH) concentrate (20 IU/kg) is adequate in HAE patients with a high body mass index (BMI).

Methods: Data from patients treated for HAE attacks with 20 IU/kg of C1-INH concentrate were retrospectively analyzed from the open-label IMPACT2 study (International Multicenter Prospective Angioedema C1-INH Trial). Patients were categorized according to BMI as being normal body weight, overweight, or obese. Efficacy end points were time to onset of symptom relief and time to complete resolution of symptoms. The safety profile was evaluated according to adverse events occurring within 7 to 9 days of treatment.

Results: Of 57 patients, 24 (42%) were of normal body weight, 20 (35%) were overweight, and 13 (23%) were obese. Median (95% CI) time to onset of symptom relief was 0.37 hour (0.29–0.57) in normal-weight patients, 0.48 hour (0.39–0.53) in overweight patients, and 0.58 hour (0.41–0.94) in obese patients. Median time (95% CI) to complete resolution of symptoms was 15.2 hours (9.3–23.2) in normal-weight patients, 22.6 hours (11.3–44.6) in overweight patients, and 11.0 hours (5.6–23.6) in obese patients (differences not significant). There were no relevant differences in the incidence of adverse events in normal-weight patients (54%), overweight patients (30%), and obese patients (54%).

Conclusions: Treatment of HAE attacks with weight-based doses of C1-INH concentrate provided reliable treatment response, regardless of body weight, in these patients with HAE. (*Clin Ther*. 2014;36:518–525)

Key words: body mass index, C1 esterase inhibitor, dosing, hereditary angioedema, obesity, pharmacokinetics.

INTRODUCTION

The condition of obesity has reached epidemic proportions in the United States and is becoming widespread in Europe as well. Data gathered between 2009 and 2010 indicate that 36% of US adults and 18% of children and adolescents (aged 6–19 years) are obese.[1] A similar percentage of adults in the United States (33%) are overweight. In Europe, statistics from the World Health Organization indicate that ~23% of women and 20% of men are obese.[2] Excess body weight can affect drug pharmacokinetics and thus needs to be taken into account when designing treatment strategies for overweight patients, particularly for serious and life-threatening indications. Hereditary angioedema (HAE) is a rare, autosomal dominant disorder in which affected persons suffer periodic attacks of non-pruritic swelling, usually of the extremities or abdomen but sometimes of the genitalia, trunk, face, or larynx, the latter of which can be fatal.[3,4] No epidemiologic data are available on the prevalence of obesity in the population with hereditary angioedema (HAE), but no evidence has emerged to suggest that it varies from that of the general population.

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Table I. Avaliable treatments for hereditary angioedema.

Trade Name	Active Substance	Licensing For	Recommended Dose and Route of Administration
Berinert®[a]	Human pasteurized, nanofiltered C1-INH (pnfC1-INH)	Acute treatment, short-term prophylaxis (Europe only)	20 IU/kg, intravenous[3,6]
Cinryze®[b]	Human pasteurized, nanofiltered C1-INH (pnfC1-INH)	Europe: acute treatment and prophylaxis US: prophylaxis only	1000 IU, intravenous[7]
Ruconest®[c]	Recombinant C1-INH (rhC1-INH)	Acute treatment (Europe only)	50 IU/kg[d], intravenous (≥84 kg, 4200 IU)[8]
Firazyr®[e]	Icatibant; bradykinin B2 receptor antagonist	Acute treatment	30 mg[f] subcutaneous[9]
Kalbitor®[g]	Ecallantide, kallikrein inhibitor	Acute treatment (US only)	3 × 10mg[h], subcutaneous[10]

C1-INH = C1 esterase inhibitor.
[a]CSL Behring, Marburg, Germany.
[b]VIROPharma, Biologics, Inc, Exton, Pennsylvania.
[c]Pharming, Group NV, Leiden, the Netherlands.
[d]In case of insufficient clinical response, an additional dose can be administered. No more than 2 doses should be administered within 24 hours.
[e]Shire Orphan Therapies, Inc, Lexington, Massachusetts.
[f]In case of insufficient relief or recurrence of symptoms, additional injections may be administered at intervals of at least 6 hours. No more than 3 injections should be administered within 24 hours.
[g]Dyax Corp, Cambridge, Massachusetts.
[h]If attack persists, an additional dose of 30 mg may be administered within 24 hours.

The underlying abnormality in HAE is a deficiency of functional C1 esterase inhibitor (C1-INH), a serine protease inhibitor that regulates the complement and contact systems, including the kallkrein-kinin cascade.[5] In the absence of sufficient C1-INH activity, excessive kallikrein activity and bradykinin overproduction trigger increased capillary permeability and the hallmark angioedema. A number of effective therapies are now available for the management of HAE (**Table I**) which act by replacing the deficient protein (C1-INH), inhibiting bradykinin formation (ecallantide) or antagonizing bradykinin activity (icatibant, ecallantide).[6–10] Despite widespread access to these multiple treatment options, data regarding the potential impact of weight on pharmacokinetic parameters or clinical outcomes in the HAE population are very limited. In a recently published analysis of ecallantide clinical trial data that focused on patient characteristics, treatment was found to be less effective in obese patients (body mass index [BMI] >30 kg/m^2) compared with patients having a BMI ≤ 30 kg/m^2.[11] Ecallantide is administered subcutaneously as a fixed 30-mg dose, regardless of BMI or body weight, and the published analysis was undertaken because of concerns that the standard fixed dose might be less effective in larger patients.

C1 esterase inhibitor (C1-INH) concentrate* was first introduced in Europe (Germany) in 1985 and is now approved in >30 countries in Europe, North and South America, Asia, and Australia.[3] The manufacturing process begins with thoroughly tested plasma donations, which are then subject to a range of manufacturing steps that purify and concentrate C1-INH and inactivate and remove viruses and prions potentially present in product intermediates. In addition to the dedicated virus-reduction steps, a nanofiltration

*Trademark: Berinert® (CSL Behring, Marburg, Germany).