

Preprocedural administration of nanofiltered C1 esterase inhibitor to prevent hereditary angioedema attacks

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ABSTRACT

Patients with hereditary angioedema (HAE) may have attacks triggered by dental, medical, or surgical procedures. This analysis evaluated the efficacy and safety of preprocedural administration of nanofiltered C1 esterase inhibitor (C1 INH-nf; human) for the prevention of HAE attacks during and after dental, medical, or surgical procedures. Data were reviewed retrospectively from two acute treatment trials in which at least 1000 U of C1 INH-nf was administered i.v. within 24 hours before an emergency or noncosmetic medical, surgical, or dental procedure. Dosing data, HAE attacks reported within 72 hours, and adverse events (AEs) reported within 7 days after a preprocedural dose of C1 INH-nf were analyzed to assess efficacy and safety. Forty-one unique subjects (8 children and 33 adults) received C1 INH-nf for 91 procedures (40 in children and 51 in adults). The majority of procedures (56%) involved dental work and 44% involved a variety of surgical or medical procedures. A single 1000-U dose of C1 INH-nf was administered for 96% of procedures. An HAE attack did not occur within 72 hours after C1 INH-nf dosing for 98% (89/91) of procedures. Two HAE attacks were reported after the procedure, and both were treated with C1 INH-nf and achieved relief. None of the reported AEs were judged to be related to C1 INH-nf or were associated with an HAE attack. This analysis supports the efficacy and safety of preprocedural administration of C1 INH-nf for the prevention of HAE attacks.

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Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by mutations in the C1 inhibitor (C1 INH) gene and reduced synthesis of this protein.^{1–6} C1 INH deficiency is characterized by recurrent attacks of intense, localized edema that can involve the face, larynx, extremities, abdomen, or genitalia and may be painful, disfiguring, and disabling. HAE attacks may be triggered by trauma such as den-

tal and elective medical procedures or surgery.^{7–9} Invasive dental work that irritates the oral mucosa can trigger facial attacks, with subsequent migration to the larynx causing laryngeal edema and, in some cases, fatal asphyxiation.⁷ As a result, patients with HAE may avoid dental work because of the fear of triggering an attack.^{9,10} However, mild manipulation during dental work is not likely to precipitate an attack and may not require prophylaxis, unless such procedures have previously triggered an attack.¹¹ Prophylactic therapy may be beneficial for patients having substantial dental work or work that involves an injection of a local anesthetic, which in itself may cause an attack.¹¹ The rate of angioedema complications after medical or dental procedures may be as high as 20% and can lead to a potentially life-threatening upper airway obstruction.^{12,13} Therefore, preprocedural prophylaxis should be considered in all patients with HAE undergoing invasive medical procedures or surgery.

C1 INH replacement therapy, attenuated androgens (administered at high doses daily for at least 1 week before the procedure), antifibrinolytics, icatibant, and fresh frozen plasma have been reported to prevent HAE attacks when administered before dental, medical, or surgical procedures.^{13–18} Nanofiltered C1 esterase inhibitor (C1 INH-nf; human; CINRYZE; ViroPharma Inc., Exton, PA) is currently approved in the United States for routine prophylaxis in adolescents and adults with HAE and by the European

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Table 1 Summary of procedures for which preprocedural C1 INH-nf was administered

Procedure	Subjects <18 yr of Age		Subjects ≥18 yr of Age		All Subjects	
	No. of Subjects	No. of Procedures	No. of Subjects	No. of Procedures	No. of Subjects	No. of Procedures
Dental work	6	36	11	15	17	51
Surgical or medical procedure	3	4	25	36	28	40
Total	8*	40	33*	51	41*	91

*Data are shown for unique subjects. A subject may have received a preprocedural dose of C1 INH-nf for both dental work and surgery during a study; these subjects are counted once in the total.

C1 INH-nf = nanofiltered C1 inhibitor (human).

Medicines Agency for treatment, preprocedure prevention, and routine prevention of HAE attacks in adolescents and adults. The objective of this analysis was to retrospectively evaluate the efficacy and safety of preprocedural administration of C1 INH-nf for the prevention of HAE attacks during and after dental, medical, or surgical procedures.

METHODS

Written Institutional Review Board/Independent Ethics Committee approvals for the protocols and informed consent documents were obtained before the study was initiated. A signed, informed consent document was obtained from each subject or their authorized representative before they were entered into the study.

Study Design

Data were collected and compiled retrospectively from two completed studies in which C1 INH-nf (human; CINRYZE) was administered before an emergency or noncosmetic surgical or dental procedure (*i.e.*, preprocedural). Subjects in both a placebo-controlled treatment trial (clinicaltrials.gov identifier, NCT00289211)¹⁹ and its open-label extension trial (clinicaltrials.gov identifier, NCT00438815)²⁰ were eligible to receive prophylaxis with a single dose of C1 INH-nf 1000 U administered *i.v.* within 24 hours before the procedure when possible. Dosing records were used to determine whether a preprocedural dose of C1 INH-nf had been administered. Investigators who indicated that a preprocedural prophylactic dose of C1 INH-nf was administered were subsequently sent a case report form to document the type of procedure for which prophylaxis was provided and the date of the procedure. Information on HAE attacks within 72 hours and adverse events (AEs) within 7 days after a prophylactic dose were compiled retrospectively from the existing databases for the individual studies.

Study Outcomes

No *a priori* formal analysis was planned to evaluate the efficacy and safety of administration of C1 INH-nf before procedures in preventing HAE attacks. Efficacy for the prevention of HAE attacks was assessed based on dosing data and reported HAE attacks that occurred within 72 hours of the procedure. Safety was assessed by monitoring vital signs pre- and postinfusion and recording AEs up to 7 days after a preprocedural dose.

RESULTS

Study Population

Seven subjects in the placebo-controlled trial¹⁹ and 36 subjects in the open-label extension trial²⁰ received ≥1 preprocedural dose of C1 INH-nf. Among these subjects, two participated in both studies, which resulted in a total of 41 unique subjects who received preprocedural administration of C1 INH-nf in this analysis. Eight (20%) subjects were children (<18 years old) and 33 (80%) were adults. The mean age of the subjects was 37 years, with a range of 6–80 years. Thirty-one (76%) subjects were female patients and 10 (24%) subjects were male patients.

A total of 91 procedures were performed in the 41 subjects who received preprocedural C1 INH-nf (Table 1). The majority of the procedures (56%; 51/91), involved dental work and 44% (40/91) involved surgeries or medical procedures ranging from gastrointestinal endoscopy to major cardiac surgery. Children accounted for 44% (40/91) of the procedures, and among children, 90% (36/40) of the procedures involved dental work. In adults, the majority of procedures (71%; 36/51), were surgical or medical.

Individual subjects received from 1 to 18 doses of C1 INH-nf for preprocedural prophylaxis depending on how many procedures were performed while enrolled in the studies. A single preprocedural dose of C1 INH-nf 1000 U was administered before 96% (87/91) of

Table 2 Dosing of C1 INH-nf for preprocedural prophylaxis

Dosing Regimen	Dental Work	Surgery/Medical Procedure	Total No. of Procedures
C1 INH-nf, 1000 U $\times$ 1 dose	51	36	87
C1 INH-nf, 1000 U $\times$ 2 doses within the same day	0	3*	3
C1 INH-nf, 1000 U $\times$ 2 doses over a 48-hr period	0	1#	1
Total	51	40	91

*One CABG surgery (two infusions given over 20 minutes); one CABG surgery (unknown time between infusions); one upper gastrointestinal endoscopy (two infusions administered 1 hr apart).

#One labor/delivery (second infusion administered 1 day after delivery).

C1 INH-nf = nanofiltered C1 inhibitor (human); CABG = coronary artery bypass graft.

all procedures (Table 2). Although all subjects received at least 1 dose of C1 INH-nf, 2 doses of C1 INH-nf 1000 U were administered on the same day for three procedures (two coronary artery bypass graft [CABG] surgeries and one gastrointestinal endoscopy). For one of the CABG surgeries, the 2 doses of C1 INH-nf were administered sequentially over 20 minutes. For the other CABG surgery, it was preplanned that 1 dose of C1 INH-nf 1000 U was to be administered preoperatively and another dose was administered postoperatively, $\sim$ 4 hours later. A prophylactic dose was then administered immediately before extubation, which was considered to be a separate procedure from the surgery. For the subject who underwent gastrointestinal endoscopy, 2 doses of C1 INH-nf were administered 1 hour apart as preplanned by the investigator for this procedure.

In this analysis, there were two pregnant subjects who received preprocedural C1 INH-nf for their deliveries. One of the pregnant subjects received 2 doses of C1 INH-nf 1000 U. The first dose was administered before delivery on day 1, and the 2nd dose was given postpartum on day 3. For the other pregnant subject, a single C1 INH-nf 1000 U dose was administered before Caesarean section. Both subjects delivered full-term healthy neonates.

Study Outcomes

An HAE attack did not occur within 72 hours after a preprocedural dose of C1 INH-nf for 98% (89/91) of procedures. Of these 89 procedures, 50 were performed in subjects $\geq$ 18 years old (Fig. 1) and 39 were performed in subjects <18 years old (Fig. 2). Overall, dental procedures were the most common types of procedures performed, and these procedures ranged from extractions, implants, root canals, and osseous surgery to orthodontic procedures and routine cleanings. Both age groups also reported successful preprocedural administration of C1 INH-nf before obstetric, orthopedic, and ear, nose, and throat procedures. In adults, genitourinary, gastrointestinal, and cardiac pro-

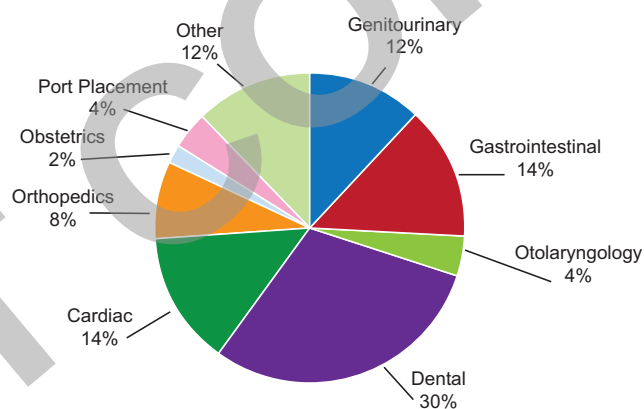


Figure 1. Types of procedures ($n = 50$) that did not result in a hereditary angioedema (HAE) attack within 3 days of the preprocedural administration of nanofiltered C1 inhibitor (C1 INH-nf; human) in subjects $\geq$ 18 years of age. Genitourinary: kidney transplant, bladder lift, cystoscopy, hysteroscopy, urethral dilation, and transvaginal urethropexy. Gastrointestinal: colonoscopy, laparoscopic cholecystectomy, hemorrhoidectomy, esophagogastroduodenoscopy, ventral herniorrhaphy, abdominal herniorrhaphy, and upper GI endoscopy. Otolaryngology: adenoidectomy and thyroidectomy. Dental: extractions, implants, root canal, crown replacement, wisdom teeth removed, right osseous surgery, routine cleaning, and not specified. Cardiac: coronary artery bypass graft (CABG) surgery, mitral valve repair, and heart catheterization. Orthopedics: repair of fractured foot, knee arthroscopy, reconstructive knee surgery, and back surgery. Obstetrics: Caesarean section.

cedures combined accounted for more than one-third of the procedures. Of note, one subject had dental work and a colonoscopy performed on the same day but received only 1 preprocedural dose of C1 INH-nf 1000 U the day before the procedures.

Among the 91 procedures performed, two HAE attacks were reported within 72 hours of dosing. One subject had a moderate genitourinary attack that occurred 2 days after a preprocedural dose of C1 INH-nf 1000 U was administered before having her braces tightened. This 16-year-old female patient was treated with C1 INH-nf 1000 U within $\sim$ 17 hours of attack

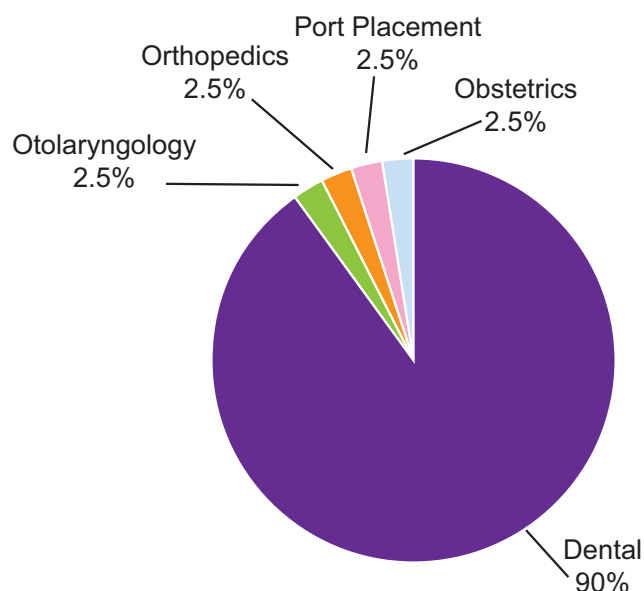


Figure 2. Types of procedures ($n = 39$) that did not result in a hereditary angioedema (HAE) attack within 3 days of the preprocedural administration of nanofiltered C1 inhibitor (C1 INH-nf; human) in subjects <18 years of age. Dental: wisdom teeth extraction, braces tightened, dental expander and braces, and not specified. Otolaryngology: tonsillectomy. Orthopedics: fractured finger with possible surgical intervention. Obstetrics: labor/delivery.

onset and achieved relief within 30 minutes. Another subject, a 25-year-old woman, had a mild laryngeal attack not requiring intubation that occurred 3 days after a preprocedural dose of C1 INH-nf 1000 U was administered before laparoscopy. She was treated with C1 INH-nf 1000 U within ~1.25 hours of attack onset and achieved relief within 60 minutes.

Of the 41 subjects who received preprocedural C1 INH-nf, a total of 12 AEs in seven subjects were reported within 7 days after dosing (Table 3). Three of the 12 AEs (procedural pain, intestinal perforation, and B-cell lymphoma) were considered serious AEs. The only AE reported by more than one subject was mild constipation (two subjects). Other events included single reports of coronary artery disease, back pain, adenoidal hypertrophy, increased blood glucose, herpes simplex virus, upper abdominal pain, and renal transplant. Most of these events were caused by the condition for which the procedure was being performed or were the result of other preexisting conditions; none of the AEs was considered by the investigators to be related to study drug and none was associated with an HAE attack.

DISCUSSION

In our retrospective analysis, 98% of medical, dental, and surgical procedures did not result in an HAE attack within 3 days of the preprocedural administration of C1 INH-nf. C1 INH-nf was administered before

a wide variety of procedures in subjects ranging in age from 6 to 80 years. In these subjects, 39/40 procedures in children and 50/51 procedures in adults did not result in an HAE attack. Among all subjects, the majority of procedures involved dental work (56%). In children, 90% of the procedures were dental and included wisdom teeth extraction, tightening of braces, applying of dental expanders, and applying of braces. HAE attacks precipitated by endothelial trauma from a procedure occur unpredictably. Results of observational studies suggest that minor trauma, including that from mild dental work and even injection of a local anesthetic, can precipitate attacks.^{6,9,11} Preventing HAE attacks in children and young adults who are undergoing dental procedures is particularly important because it has been established that laryngeal edema is most prevalent in HAE patients between the ages of 11 and 45 years.⁸

Patients with HAE are at risk for attacks after dental, medical, and surgical procedures.⁷⁻⁹ In particular, invasive dental procedures or other surgeries or manipulations near the airway are associated with potentially fatal upper airway obstruction that may occur up to 30 hours after treatment.^{7,21} Consensus guidelines recommend C1 INH replacement therapy for preprocedural administration to patients with HAE having substantial dental work performed, but data are primarily limited to case reports.^{6,11,22} Previous studies have shown the safety and efficacy of C1 INH with long-term prophylactic use to prevent HAE attacks^{19,23} and for the acute treatment of HAE attacks.^{20,24-29} However, few studies have examined the preventive effects of preprocedural therapy in patients with HAE. A recent analysis of 171 patients with HAE showed that facial swelling or potentially life-threatening laryngeal edema, or both, followed 21.5% (124/577) of tooth extractions without prophylaxis compared with 12.5% (16/128) of extractions with C1 INH concentrate prophylaxis.¹³ On a per-patient basis, C1 INH prophylaxis led to a 44.1% reduction in angioedema attacks. On a per-attack basis, C1 INH prophylaxis led to a 41.9% reduction in attacks.

In this analysis, a single preprocedural dose of C1 INH-nf 1000 U was administered before 96% of procedures. In certain cases, the investigator elected to administer an additional dose for more extensive procedures (e.g., CABG), although many other subjects undergoing extensive procedures (e.g., mitral valve repair and renal transplant) received only 1 dose. One subject received a single preprocedural dose of C1 INH-nf 1000 U the day before having dental work and a colonoscopy performed on the same day without receiving further prophylaxis.

Labor and delivery are potential triggers of an HAE attack, which may occur 3–7 days after delivery¹⁰ and consensus guidelines suggest that C1 INH is the safest

Table 3 AEs and severity reported within 7 days after preprocedural administration of C1 INH-nf

Subject	Procedure	AEs	Severity
1	Dental work	Constipation and upper abdominal pain	Mild
2	Heart catheterization and mitral valve repair	Constipation	Mild
3	Coronary artery bypass graft surgery	Coronary artery disease	Moderate
4	Esophagogastroduodenoscopy	Back pain	Moderate
5	Operative hysteroscopy to resect endometrial abnormality and vulvar biopsy	Herpes simplex	Mild
6	Laparoscopy	Procedural pain (abdominal)*	Moderate
7	Adenoidectomy	Blood glucose increased	Mild
		Adenoidal hypertrophy	Moderate
		Intestinal perforation* and B-cell lymphoma*	Severe
	Kidney transplant	Renal transplant	Severe

*Serious AE.

C1 INH-nf = nanofiltered C1 inhibitor (human); AE = adverse event.

prophylactic agent for HAE patients during pregnancy.¹¹ Danazol is classified as Pregnancy Category X, and its use is absolutely contraindicated in the first two trimesters of pregnancy. If C1 INH is not available, short-term danazol is recommended only in the third trimester; however, the increase in circulating C1 INH is dependent on secondary hepatic synthesis, which may vary considerably. In our analysis, two pregnant subjects received preprocedural prophylaxis with C1 INH-nf before childbirth. For the subject who delivered *via* Caesarean section, only 1 preprocedural dose of C1 INH-nf 1000 U was administered. In the other pregnant subject, a single dose of C1 INH-nf 1000 U was administered on presentation in labor and a 2nd dose was given after delivery. Although the reason for the 2nd dose before discharge was not documented, it is known that the risk of attacks may be higher in the postpartum period.^{10,15} The safety and effectiveness of danazol have similarly not been established in children.³⁰ In this analysis, preprocedural prophylaxis with C1 INH-nf was safely administered in 40 different instances in children.

One limitation of this analysis was its retrospective design in which case report forms were filed *post hoc*; however, the authors feel that good clinical practice of safety reporting during these clinical trials would accurately reflect HAE attacks precipitated by medical, dental, or surgical procedures. Another limitation of this analysis includes the lack of a control group of subjects who did not receive preprocedural prophylaxis with C1 INH-nf. Although patients with HAE may have an attack triggered by a procedure, it is possible subjects may not have had an attack, regardless of prophylaxis. Despite these limitations, these data are compelling enough to suggest that preprocedural prophylaxis with C1 INH-nf, when deemed nec-

essary for a patient with HAE, may prevent an attack potentially triggered by the trauma from a medical, dental, or surgical procedure.

This analysis also reflected the clinical reality that unless prophylactic therapy is administered "on call" to the operating room, it is difficult to precisely coordinate the timing of the preprocedural dose with the actual procedure. According to consensus guidelines, for intubation or major procedures, C1 INH should be administered 1–6 hours before surgery and as close to the time of surgery as possible.¹¹ Ideally, treatment for an HAE attack should be available throughout the procedure and repeated as deemed necessary by the treating physician until there is no further proximate risk of contact system activation. Patients should be educated about the symptoms of an attack so that treatment can be sought if an attack is precipitated by a procedure. In addition, health care providers who may not be familiar with the management of HAE but will be performing the procedures should be educated about emergency management of HAE and should be aware of medications to which patients will respond.

In conclusion, administration of a prophylactic therapy should be considered before dental, medical, or surgical procedures in patients with a history of HAE. Patients with HAE must be informed that any procedure may precipitate an attack and that many of these attacks might be prevented with appropriate prophylaxis. The results of this analysis provide further support for the efficacy and safety of preprocedural administration of C1 INH-nf (human) for the prevention of HAE attacks.

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