# Reporting of Adverse Drug Reactions with Parenteral Drugs for the On-Demand Treatment of Hereditary Angioedema Attacks – Analysis of the FAERS Database 2009 to 2022

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## Background

- Hereditary angioedema (HAE) is characterized by recurrent and unpredictable episodes of subcutaneous or submucosal swelling affecting the abdomen, extremities, genitals, face, and larynx
- Results from clinical trials suggest that currently available on-demand treatments for HAE are associated with adverse events such as hypersensitivity reactions, thromboembolic events, injection site reactions, and headache[1-4]
- Few studies have examined the prevalence of adverse drug reactions (ADRs) associated with on-demand HAE treatments using real-world data
- This analysis assessed the post-marketing reporting rates for ADRs in patients treated with parenteral on-demand HAE drugs utilizing the FDA's Adverse Event Reporting System (FAERS)

## Methods

- We searched FAERS data 10/1/2009-3/31/2022 for human C1-inhibitor (pdC1-INH), ecallantide, icatibant, and recombinant C1-inhibitor (rhC1-INH)
  - The FAERS database contains information on adverse event and medication error reports submitted to FDA by healthcare professionals (such as physicians, pharmacists, nurses, and others) and consumers (such as patients, family members, lawyers, and others)
- Cases were only included if the HAE drug was listed as the 'primary suspect' potentially leading to an ADR
- The ADRs of interest to this study included those from clinical trials denoted on approved HAE drug US package inserts
- Analysis was conducted on a single ADR (headache) and four ADR composites
- ADR composites (**Table 1**) were comprised of preferred terms derived from the Medical Dictionary for Regulatory Activities (MedDRA) and included: gastrointestinal disorders, hypersensitivity reactions, thromboembolic events, and injection site reactions (compared to same route-of-administration drugs)
  - An FDA report with at least one of the preferred terms in the composite was flagged as an ADR in the current study
- For each drug-event pair, the Reporting Odds Ratio (ROR) and the Empirical Bayesian Geometric Mean (EBGM) were calculated to detect drug-ADR pairs with higher-than-expected reporting rates versus all other drugs (except for injection site reaction that was compared to same route-of-administration drugs) in the FDA registry
- ROR estimates with a two-sided lower 95% confidence bound >1.0 were considered significant
- One-sided 95% lower confidence bound of the EBGM was generated, with values >1 considered significant
- A strong signal of a disproportionately high event rate for a drug-event pair was declared when both the ROR and EBGM were significant
- When both RORs and EBGM values were above 1, but not both significant, it was reported as an indication of a trend toward higher-than-expected reporting rates

### Table 1. ADR composites and associated preferred terms

| Composite | Preferred Terms |
|---|---|
| Gastrointestinal Disorders | Abdominal discomfort |
| | Abdominal pain |
| | Nausea |
| | Vomiting |
| | Diarrhea |
| Hypersensitivity Reactions | Hypersensitivity |
| | Anaphylactic reactions |
| | Rash |
| Thromboembolic Events | Thrombosis |
| | Basilar artery thrombosis |
| | Carotid artery thrombosis |
| | Cerebral thrombosis |
| | Myocardial infarction |
| | Pulmonary embolism |
| | Inferior and superior vena cava thrombosis |
| | Internal jugular vein thrombosis |
| | Peripheral venous thrombosis |
| | Multiple pulmonary microemboli |
| | Renal vein thrombosis |
| | Sagittal sinus thrombosis |
| Injection Site Reactions | Injection site reactions |
| | Injection site pain |
| | Injection site redness |
| | Injection site pruritus |
| | Injection site irritation |
| | Injection site urticaria |
| | Injection site bruising |
| | Injection site hematoma |
| | Injection site hypoesthesia |
| | Injection site edema |
| | Injection site swelling |
| | Injection site warmth |
| | Injection site burning |
| | Injection site numbness |
| | Injection site pressure sensation |

## Results

### Table 2. Reporting odds ratio and empirical Bayesian geometric mean values for HAE on-demand parenteral drugs

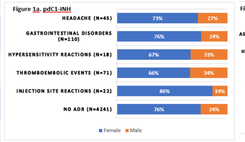
| HAE Drug (FDA approval date) | Adverse Drug Reaction | N of 'Primary suspect' cases | ROR (95% CI[a]) | EBGM (95% CI Lower Bound[a]) |
|---|---|---|---|---|
| pdC1-INH (Oct 12, 2009) N=4,790 ADRs | Headache | 47 | 0.93 (0.70-1.24) | 0.80 (0.63) |
| | Gastrointestinal disorders composite | 111 | 0.77 (0.64-0.94) | 0.69 (0.59) |
| | Hypersensitivity reactions composite | 18 | 0.57 (0.36-0.90) | 0.50 (0.34) |
| | Thromboembolic events composite | 72 | 1.05 (0.83-1.32) | 0.91 (0.75) |
| | Injection site reactions composite (vs other IV)[b] | 22 | 3.59 (2.36-5.46) | 1.97 (1.39) |
| Ecallantide (Dec 1, 2009) N=3,170 ADRs | Headache[c] | 45 | 1.35 (1.00-1.81) | 1.20 (0.94) |
| | Gastrointestinal disorders composite | 95 | 1.01 (0.82-1.24) | 0.95 (0.80) |
| | Hypersensitivity reactions composite[b] | 56 | 2.70 (2.07-3.52) | 2.23 (1.79) |
| | Thromboembolic events composite | 25 | 0.54 (0.37-0.81) | 0.52 (0.37) |
| | Injection site reactions composite (vs other SC) | 41 | 0.39 (0.28-0.53) | 0.38 (0.29) |
| Icatibant (Aug 25, 2011) N=6,787 ADRs | Headache[c] | 88 | 1.23 (1.00-1.52) | 1.08 (0.90) |
| | Gastrointestinal disorders composite | 170 | 0.84 (0.72-0.98) | 0.76 (0.67) |
| | Hypersensitivity reactions composite | 41 | 0.91 (0.67-1.24) | 0.79 (0.61) |
| | Thromboembolic events composite | 87 | 0.89 (0.72-1.10) | 0.79 (0.66) |
| | Injection site reactions composite (vs other SC)[c] | 252 | 1.15 (1.01-1.30) | 1.00 (0.90) |
| rhC1-INH (July 16, 2014) N=5,005 ADRs | Headache | 58 | 1.10 (0.85-1.42) | 0.73 (0.58) |
| | Gastrointestinal disorders composite | 120 | 0.80 (0.67-0.96) | 0.54 (0.47) |
| | Hypersensitivity reactions composite | 23 | 0.68 (0.45-1.02) | 0.45 (0.32) |
| | Thromboembolic events composite | 33 | 0.50 (0.35-0.70) | 0.34 (0.26) |
| | Injection site reactions composite (vs other IV)[c] | 19 | 2.85 (1.82-4.48) | 1.32 (0.90) |

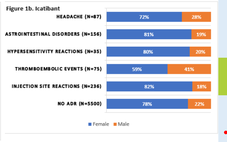
ADRs adverse drug reactions, CI confidence interval, ROR reporting odds ratio, EBGM empirical Bayesian geometric mean, IV intravenous, SC subcutaneous

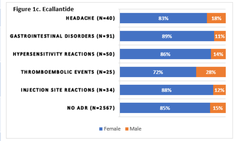
[a] Two-sided CI for ROR; one-sided CI for EBGM
[b] Both ROR and EBGM lower-bound CI values were >1
[c] ROR or EBGM lower-bound CI values >1

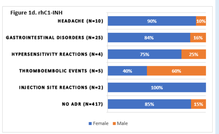
- PdC1-INH showed a statistically significant elevated risk of injection site reactions (**Table 2**)
- A statistically significant elevated risk of hypersensitivity reactions was found for ecallantide (**Table 2**)
- A non-significant trend toward increased risk of headaches was found for ecallantide (**Table 2**)
- Icatibant showed non-significant trends toward increased risks of headaches and injection site reactions (**Table 2**)
- RhC1-INH showed a non-significant trend toward increased risk of injection site reactions (**Table 2**)

### Figure 1. Sex distribution by ADR for each HAE drug




- The majority of ADRs were reported by females (**Figure 1a-1d**)
- A nominal increased reporting rate in males was observed for:
  - Hypersensitivity in pdC1-INH (33% vs 24%)
  - Thromboembolic events in icatibant (41% vs 22%), ecallantide (28% vs 15%), and rhC1-INH (60% vs 15%)
- Age distributions did not show any discernable patterns with respect to ADRs by drug

## Discussion

- Although adverse events are underreported in spontaneous reporting systems (reporting estimated to represent just 6% of actual events)[5], data mining of such databases may reveal clinically important associations to help guide clinical decision-making[6]
- This real-world analysis suggests the currently approved parenteral on-demand therapies for HAE attacks are associated with an elevated risk of specific ADRs similar to those reported in clinical trials and FDA-approved labels
  - The increased risks of reporting were found for hypersensitivity, headache, and injection site reactions
- Overall ADR reporting was more frequent for women. In addition, male patients were at a greater risk for hypersensitivity and thromboembolic events

## Limitations

- It should be noted that due to the nature of the FAERS registry, there are a number of limitations:
  - ADR rates are not exposure-adjusted and are based on spontaneous reporting and, thus, cannot be used to estimate incidence
  - Reporting rates may not be similar across included drugs
  - Reporting rates may vary over time, with the highest reporting rates typically in the first two years of commercial availability[6]

## Conclusions

- Adverse events reported in clinical trials and subsequently in product labels are reflected in the FAERS registry
- FAERS real-world data suggest that patients with HAE experience substantial treatment burden due to adverse events associated with currently approved parenteral on-demand therapies for HAE attacks

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