An analysis of fatalities in persons with congenital hemophilia A reported in the FDA Adverse Event Reporting System (FAERS) database

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Historical overview

FAERS was searched for fatalities reported between January 1, 2000 and March 31, 2020 in people receiving various coagulation products, namely factor VIII (FVIII), bypassing agents, and emicizumab. A total of 749 fatalities in people receiving coagulation products were reported: 519 were in PwcHA, or those receiving coagulation product for an unknown condition. Regardless of the coagulation product used, the most common cause of fatality in this population was hemorrhage. Overall, 749 fatalities alongside coagulation product use were identified: 422 in PwcHA, 230 in acquired HA (AHA), and 97 in PwcHA or those receiving coagulation product for an unknown condition reported to the FAERS database.

Methods

The FAERS dashboard was searched for all AEs associated with FDA-approved coagulation product use between January 1, 2000 and March 31, 2020.

- The coagulation products that were searched included:
  - FVIII – plasma-derived and recombinant; standard and extended half-life.
  - Bypassing agents – activated prothrombin complex concentrate (aPCC), recombinant activated FVII (rFVIIa).
  - Emicizumab.

- The ‘outcome’ column was filtered to show cases labeled as ‘killed’ only.
- Cases assessed to be duplicates were removed.
- When individuals were exposed to multiple coagulation therapies at the time of death, the first therapy reported was used for classification.
- Using a framework for assessing mortality,1 each case was categorized per common causes of fatality in the hemophilia A (PwC) and non-PwC populations.

Results

Overall, 749 fatalities alongside coagulation product use were identified: 422 in PwcHA, 230 in acquired HA (AHA), and 97 in unknown conditions.

Excluding 414, 519 fatalities were reported worldwide in the last 20 years (Figure 1).

The median age at time of death was 54 years, and a large proportion of cases were reported with cardiovascular risk factors (Figure 2).

- In total, 16 fatalities (16/519, 3.1%) were reported in infants aged 0-2 years.

When applied to a mortality framework,2 the most common (22.2%, 115/519) cause of fatality across all products was hemorrhage (Figure 3).

- Fatalities from infection/pancreatitis (10.2%), malignancy (6.9%), and cardiac dysfunction (non-thrombotic, 3.9%) were reported for all coagulation products.
- Fatalities associated with human immunodeficiency virus/hepatitis C virus (1.3%) were only reported in persons taking FVIII.
- Over a quarter (26.4%) of fatalities reported did not specify a cause of fatality.

Conclusions

- Fatality from hemorrhage was the most common (22.2%, 115/519) cause of fatality across all products (Figure 3).
- Around half (48.7%, 56/115) of all hemorrhagic fatalities were reported as intracranial hemorrhage (ICH), a rare but life-threatening complication of HA (Figure 5).
- There is a need for improved reporting of adverse events, including fatalities, that would enable better evaluation of mortality risk in persons with congenital hemophilia A.

References

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2. Hay CRM, et al. Presented at NHF 2020; poster #32; Employee of and holder of stocks in, and receipt of expenses from F. Hoffmann-La Roche Ltd.; Employee of, holder of stocks in, and receipt of expenses from Genentech, Inc.; Employee of, holder of stocks in, and receipt of expenses from F. Hoffmann-La Roche Ltd.

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