

Investigating Serious Adverse Drug Reactions in Patients Receiving Erythropoiesis-Stimulating Agents: A Root Cause Analysis Using the “ANTICIPATE” Framework

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Background: Unexpected serious adverse drug reactions (sADRs) affecting patients with chronic kidney disease (CKD) who received erythropoiesis-stimulating agents were identified by study co-authors. These included pure red cell aplasia (PRCA) after administration of the Eprex formulation of epoetin or the epoetin biosimilar HX575 and fatal anaphylaxis associated with peginesatide, an erythropoietin receptor agonist. We developed and applied a structured framework to describe these sADRs, including root cause analyses and eradication efforts.

Methods: A 10-step framework termed “ANTICIPATE,” focusing on signal identification, incidence, causality, and eradication guided our evaluations.

Results: Initial cases were identified by a hematologist (Eprex), clinical study monitors (HX575), and 4 nurses (peginesatide). The number of persons with individual ADRs was 13 PRCA cases for epoetin, 2 antibody-mediated PRCA cases for HX575, and 5 fatal anaphylaxis cases for peginesatide. Initial incidence estimates per 1000 treated persons were 0.27 for Eprex-associated PRCA, 11 for HX575-associated PRCA, and 0.38 for peginesatide fatalities. Likely causes were subcutaneous administration of epoetin formulated with polysorbate 80 (Eprex), tungsten leaching from pins included in product syringes (HX575), and inclusion of a phenol stabilizer (peginesatide). Eradication strategies included restricting Eprex administration to the intravenous route, excluding tungsten from HX575 syringes, and for peginesatide, proposed eradication was to return to single-dose vials without preservatives.

Conclusion: Although the number of cases of each sADR was small, eradication was successful for 2 sADRs, and a proposed eradication was developed for a third sADR. The structured framework used to describe the above 3 sADRs in patients with CKD can also be used in other clinical settings.

Keywords: serious adverse drug reactions, ANTICIPATE, framework, peginesatide, epoetin, HX575

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INTRODUCTION

Serious adverse drug reactions (sADRs) are rare, unpredictable events. Patients with chronic kidney disease (CKD) are at increased risk of sADRs, yet are often ill with comorbidities, thus making identification of sADRs more difficult. Erythropoiesis-stimulating agents (ESAs) such as Eprex (epoetin alpha), HX575 (epoetin biosimilar) causing pure red cell aplasia (PRCA), and peginesatide, a novel erythropoietin receptor agonist, causing fatal anaphylaxis are few examples¹⁻⁴ of such sADRs. Our objective was to report these 3 sADRs, including root cause analyses and eradication efforts,¹⁻¹² using a framework we developed to review the identification and monitoring of sADRs.

Epoetin-associated PRCA, an antibody-mediated syndrome, was initially reported in 1998.¹ HX575 was the first epoetin biosimilar to receive regulatory approval and has been subsequently safely administered intravenously to patients with CKD.³ Subcutaneous administration was not indicated initially but later approved for a comparative study. In 2011, laboratory evidence of neutralizing antibodies suggesting PRCA was identified among 2 patients who received subcutaneous administration of HX575, and the study was terminated.³

In early 2012, the Food and Drug Administration (FDA) approved peginesatide but restricted to patients on hemodialysis, as cardiovascular events were high in nondialysis patients compared with darbepoetin.^{11,12} By February 2013, 5 fatal cases of anaphylaxis after peginesatide injection were reported, and peginesatide was voluntarily removed from the market.⁴

METHODS

A framework, termed “A-N-T-I-C-I-P-A-T-E” guided our review of the sADRs. The framework included steps for signal detection and evaluation, incidence estimation, identification of causal factors, and toxicity eradication strategies. Although these sADRs were described previously, root cause analyses and eradication efforts have not. Review included published studies, documents from regulatory agencies and manufacturers,¹⁻²⁰ interviews of researchers and personnel at national regulatory agencies, and product manufacturers, clinicians, and epidemiologists.

RESULTS

The toxicities

Since 1988, millions of patients with CKD have received epoetin for anemia treatment. In 2002 and 2004, 13 and

181 epoetin-associated PRCA cases characterized by severe antibody-mediated anemia were reported respectively.² After the peak incidence of Eprex-associated PRCA in 2001–2002, safety interventions resulted in 83% rate reductions.² In 2011, 2 PRCA cases developed among 174 anemic predialysis patients who received HX575 as part of a phase III clinical trial.³

Peginesatide, a novel synthetic ESA, was developed to treat anemia among patients with CKD.^{12,20} Its advantages over epoetin were primarily low cost, improved immunogenicity, better administration schedule, and longer effective time than epoetin or darbepoetin.²⁰ In 2012, a large dialysis organization in the United States initiated the pilot clinical introduction of peginesatide.⁵ Between July 2012 and February 2013, a total of 61,482 doses of peginesatide were administered to 19,540 patients at 348 centers, and 2 fatal anaphylaxis events occurred among peginesatide-treated CKD patients over the first 3 months.⁴ By February 2013, a total of 5 patients had died from anaphylaxis.

The evaluations

A-N-T-I-C-I-P-A-T-E framework

The ANTICIPATE framework described below includes 3 steps for signal detection (Awareness of signal, Notification of personnel, and Timely field discussions), 4 steps for analysis of signal/data and incidence estimation (Investigation of safety signals, Comparison of sADR data, Interim, and Postsafety intervention data analysis), 2 steps for causal factor determination (Association of plausible causes and Technical/manufacturing issues), and 1 step for toxicity (Eradication).

Signal detection

Awareness of the first cases

Thirteen epoetin-associated PRCA cases were reported from Europe in 2002.¹ Awareness of these cases facilitated identification of 181 epoetin-associated PRCA cases in 2004.² In 2011, clinical trial monitors of a phase III trial of HX575 became aware of 2 laboratory-defined PRCA cases based on identifying neutralizing antierythropoietin antibodies in prospectively obtained plasma samples.³ For peginesatide, clinician monitors of the phase IV safety trial became aware of 2 fatal anaphylaxis events occurring in the first 3 study months; however, it was noted that several other drugs had also been administered within minutes of peginesatide administration. This awareness in the early phase of the trial prompted vigilance to identify 3 more fatal anaphylaxis events later in the postmarketing study of peginesatide.⁴

Notification of safety personnel

In 2003, 1 year after the seminal report of the first epoetin-associated PRCA cases, epoetin manufacturer personnel were notified of the reported PRCA cases.² In 2011, monitors of the HX575 trial notified the manufacturer regarding laboratory evidence of PRCA, who in turn, reported to the European Medicines Agency.³ Nurses from 3 dialysis centers reported to clinical trial monitors of the phase IV peginesatide safety study that 3 additional fatal anaphylaxis events had occurred after peginesatide administration.⁴

Timely field discussions

In all the above examples, timely field discussions quickly led to hypotheses that toxicities were probably product related. Reporting of the first 13 epoetin-associated PRCA cases identified that 12 patients had received the Eprex formulation.¹ Timely discussion of the 2 instances of anti-erythropoietin-associated antibodies developing after initiation of subcutaneous HX575 helped track the cause, which terminated the study.³ Nurses observing peginesatide administration in the phase IV trial, when queried by FDA investigators, reported that the fatal anaphylaxis events occurred immediately after peginesatide administration, which in their opinions was the most likely proximate cause.⁴

Analysis of safety signals/data and outcomes

Investigate safety signals closely

After 13 Eprex-associated PRCA cases were reported in 2002, a collaboration of epidemiologists, nephrologists, and hematologists initiated a country-wide epidemiologic study in Canada reporting in 2004, high PRCA rates with subcutaneous Eprex administration versus low rates with other epoetin products administered subcutaneously or intravenously or with the Eprex formulation administered intravenously.⁶ For HX575, studies noted that the 2 patients with laboratory evidence of antibodies received HX575 from 2 specific batches of the product.³ After becoming aware in the first 3 months of a phase IV study of peginesatide that severe anaphylaxis had occurred within minutes of intravenous administration of peginesatide, the clinical trial monitoring committee mandated that no other medication be administered intravenously within 1 hour of intravenous peginesatide administration.⁵

Comparison of sADR rates from different settings

For Eprex-associated PRCA, incidence rates reported from the Canadian epidemiologic study were 0.175 per 100 patients with CKD with subcutaneous Eprex administration versus <0.05 per 100 patients with CKD with

subcutaneous or intravenous administration of other epoetins or intravenous administration of Eprex.^{2,6,7} For HX575, 1 phase III multicenter trial of 174 predialysis patients receiving HX575 subcutaneously identified 2 cases of laboratory-identified PRCA cases versus none among 489 predialysis patients receiving HX575 intravenously in a different clinical trial.^{3,8} There were 5 fatal anaphylaxis events in the phase IV study of 19,540 patients with CKD who received peginesatide intravenously from multidose vials with stabilizers versus no anaphylaxis cases among 2124 peginesatide-treated CKD patients in preapproval trials who had received intravenous peginesatide from single-dose vials without preservatives.^{4,5}

Interim data analyses

An interim report of the Canadian epidemiology study identified PRCA rates of 27 per 100,000 CKD patient years who received epoetin formulated with polysorbate 80 subcutaneously versus <1 per 100,000 CKD patient years who received that product intravenously or other epoetin products subcutaneously or intravenously.⁶ The HX575 interim analyses of phase III clinical trial data had identified the 2 instances of neutralizing antierythropoietin antibodies among 174 patients with CKD who received subcutaneous HX575 versus no instances among 165 patients with CKD who received branded epoetin subcutaneously.^{3,9} In 2013, the interim analyses of possible sADRs during the initial phase of the peginesatide clinical trial helped identify more sADRs later in the study, which became one of the pivotal reasons for the manufacturers' reassessment of the product safety.

Postsafety interventions should be evaluated closely

It was hypothesized that the incidence of Eprex-associated PRCA could be reduced by intravenous administration.² After regulatory agencies mandated this change, follow-up studies found PRCA rates with intravenous administration were lower or similar to rates observed with comparator epoetins administered intravenously or subcutaneously.² For HX575, no additional laboratory-identified cases of antierythropoietin antibodies were detected after glass syringes with high levels of tungsten in the plunger of the vial were withdrawn.^{3,9,10} Reports from the initial 6 months of the phase IV clinical trial of peginesatide were the data sources for the first few fatal peginesatide-associated anaphylaxis cases. After the trial was redesigned mandating no coadministration of other drugs within 1 hour of intravenous peginesatide, 3 additional fatal peginesatide-associated anaphylaxis events occurred over a 2-day period, which prompted product removal from the market a week later.⁴

Causal factors

Association of plausible causes

For Eprex-associated PRCA, early theories focused on cold chain storage and supply chain. Later theories focused on leachates that seemed to form in response to the polysorbate stabilizer in the product and increased immunogenicity with subcutaneous versus intravenous administration.^{2,7} For biosimilar epoetin HX575-associated PRCA, soluble tungsten derived from pins used to manufacture glass syringes seemed to be causal.^{3,9} Spiking of epoetin alfa with sodium polytungstate or an extract of tungsten pins used to manufacture HX575-containing glass syringes induced aggregate formation.⁹ Subcutaneous route of administration was another causal factor of HX575-associated PRCA.^{2,7}

For peginesatide, initial studies focused on supply chain management, cold storage, and/or manufacturing production. One FDA scientist conducted a study in which the peginesatide formulation was combined one at a time with different preservatives and found that the sample with phenol preservative induced anaphylaxis in rats, whereas peginesatide admixed with the other preservatives did not.¹⁴

Technical/manufacturing-related product-specific causes

Manufacturing decisions seemed to be central to these sADRs, although additional factors are possible.¹⁷ Exchanging albumin with polysorbate 80 as a stabilizer for Eprex² and manufacturing HX575 in syringes that contained high residual tungsten levels^{3,9} are few examples. Spiking of epoetin alfa with sodium polytungstate, which has denaturing property, or an extract of tungsten pins used to manufacture HX575-containing glass syringes induced aggregate formation.⁹ Adding phenol as a preservative for multidose peginesatide preparation was suggested as a cause.^{14,15}

Eradication

Eradication strategy

Toxicity eradication is the cornerstone of drug safety, although it is not always possible. Analysis of safety signals, comparison of sADR data from different settings, interim data analysis, causal factor identification, and postsafety intervention outcome analysis are pivotal in formulating prevention strategies. Identification of causal factors and correlation with any product/manufacturing specific causes helped develop an eradication plan.

For Eprex and HX575-associated PRCA, manufacturing process changes were successful. For peginesatide-associated anaphylaxis, a proposed strategy of using single-unit vials is under consideration.

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DISCUSSION

SADRs are rare, but early identification is crucial and a system to achieve it is pivotal in drug safety. Although there are several sADRs reporting systems, there is no structured framework to help identify and facilitate root cause analysis to develop eradication strategies. FDA and manufacturers conduct pharmaceutical safety investigations postmarketing. Most of these are based on data mining and may miss some sADRs, as reporting is dependent on multiple factors. ANTICIPATE is developed with an aim to facilitate a structured approach to optimize the signal detection and identify plausible causes.

In interpreting our evaluations, several factors should be considered. Signal detection is the most important step. Awareness of the first cases of each sADR was the impetus for the corresponding investigation. Investigators' experiences and awareness of potential signals were key to sADR detection in all the cases.¹⁷ Investigators' long history of studying PRCAs and awareness of the potential for PRCA to occur with epoetins played a significant role in the PRCA investigations.^{1,2,6,7,11,13,19}

For HX575, investigators were aware of potential PRCA events with epoetins, although none had been reported previously after intravenous administration of HX575 before the subcutaneous HX575 clinical trial.^{16,18,19} Prospective monitoring identified serum antibodies, which were correlated with a high tungsten level in the syringes. With the introduction of a low-tungsten-level syringes, HX575 received European Commission (EC) approval for subcutaneous use by April 2016 as a part of the SENSE trial,^{16,18,19} and the study was completed in Europe in 2017.^{18,19} Study patients who received at least 1 dose per week subcutaneously did not show any development of neutralizing or clinically relevant antibodies during the 12-month study.^{18,19}

A hematologist with experience in sADR evaluation of erythropoiesis-stimulating agents reported the first case series of peginesatide-associated anaphylaxis.⁵ Nurses involved in the peginesatide clinical trial who were vigilant for safety events in conjunction with study monitors and the clinical trial safety committee identified peginesatide-induced anaphylaxis.⁵ Within 2 years of withdrawal of peginesatide, trial investigators, the manufacturer, and FDA scientists identified phenol preservative as the most likely causal agent.¹⁵

In conclusion, this study provides a platform to anticipate sADRs. Often elusive and uncommon, sADRs are unpredictable and may go unrecognized unless we learn to anticipate the more often potentially

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missed or overlooked sADR's by conventional evaluation methodologies. Utilization of such a structured platform will help identify those rare sADRs, which are crucial to patient safety. Although the ANTICIPATE framework was developed to investigate sADRs associated with patients with CKD, this could be extrapolated to be a structured framework useful in other clinical settings.

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