Contemporary Clinical Trials Communications 4 (2016) 64–67

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Methods to reduce medication errors in a clinical trial of an investigational parenteral medication

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ARTICLE INFO

Article history:
Received 27 April 2016
Received in revised form
31 May 2016
Accepted 22 June 2016
Available online 1 July 2016

Keywords:
Intravenous drugs
Protocol deviations
Infusions
Medication errors
Administration errors
Patient safety

ABSTRACT

There are few evidence-based guidelines to inform optimal design of complex clinical trials, such as those assessing the safety and efficacy of intravenous drugs administered daily with infusion times over many hours per day and treatment durations that may span years. This study is a retrospective review of inpatient administration deviation reports for an investigational drug that is administered daily with infusion times of 8–24 h, and variable treatment durations for each patient. We report study design modifications made in 2007–2008 aimed at minimizing deviations from an investigational drug infusion protocol approved by an institutional review board and the United States Food and Drug Administration. Modifications were specifically aimed at minimizing errors of infusion rate, incorrect dose, incorrect patient, or wrong drug administered. We found that the rate of these types of administration errors of the study drug was significantly decreased following adoption of the specific study design changes. This report provides guidance in the design of clinical trials testing the safety and efficacy of study drugs administered via intravenous infusion in an inpatient setting so as to minimize drug administration protocol deviations and optimize patient safety.

1. Introduction

Clinical trials conducted in the United States investigating the efficacy and safety of a new drug or a new indication for an approved drug are strictly regulated by institutional review boards (IRBs) and are heavily scrutinized by the United States Food and Drug Administration (FDA). The integrity and durability of any clinical trial, and the preservation of patient safety, depend on adherence to carefully considered, reviewed, and approved protocols for investigational drug administration. However, clinical studies with complex components are susceptible to protocol deviations. For example, study drugs administered in the inpatient setting that are not limited to patients treated by a particular medical service or inpatient ward are susceptible to administration errors due to lack of familiarity with the study protocol. Study drugs with non-standard administration procedures, such as infusion times and treatment durations that vary for each patient, are also susceptible to administration errors.

Prior work characterizing the scope of problems related to the administration of commonly prescribed intravenous drugs has demonstrated that administration errors are not uncommon occurrences [1]. Clinical trials that include elements of complexity in study drug administration protocols can be at increased vulnerability to administration deviations. For such studies, achieving adequate education and oversight to guarantee correct study drug administration can present unique challenges. This study describes a multi-modal strategy of modifications that reduced administration errors in a clinical trial involving daily use of an investigational parenteral medication at a pediatric teaching hospital.

Omegaven® (Fresenius Kabi, Bad Homburg, Germany) is a fish oil-based intravenous lipid emulsion. In the United States, Omegaven® is not approved by the FDA for use as a fat source in parenteral nutrition (PN). In 2004, a single-center study was initiated by investigators at Boston Children's Hospital (BCH) through a

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http://dx.doi.org/10.1016/j.conctc.2016.06.005

compassionate use protocol permitted by the FDA to assess the efficacy and safety of this study drug in the treatment of parenteral nutrition-associated liver disease (PNALD) in the pediatric population [2,3]. PNALD is characterized by hepatic inflammation and cholestasis that can progress to hepatic fibrosis, cirrhosis, and end-stage liver disease requiring liver transplantation. The design of this study allows for any PN-dependent patient who develops cholestasis, defined as a sustained direct bilirubin >2 mg/dL, with no other diagnosis of liver disease, to receive the study drug, regardless of which medical or surgical service is caring for the patient. The study drug is administered daily over an infusion time of at least 8 h. In 2007, in response to observations by the BCH IRB that inpatient protocol deviations were commonly the result of administration errors, the principal investigators of the study and hospital staff who participated in the care of study patients performed a root-cause analysis of the errors. This resulted in a series of protocol amendments and educational efforts aimed at minimizing these errors. Changes focused on specifying a subset of personnel to administer the study drug to inpatients and providing specialized training, as well as adopting systems-level modifications.

The purpose of this study is to describe and assess the effectiveness of these initiatives aimed at reducing inpatient infusion errors of an investigational medication and to provide guidance for research groups designing similar clinical trials.

2. Methods

2.1. Data collection

Safety Event Reporting System (SERS) reports of protocol deviations associated with administration of the study drug submitted to the BCH IRB from 1/1/2005–12/31/2014 were retrospectively reviewed. SERS reports included in this study were limited to those detailing inpatient administration errors of incorrect dose, incorrect infusion rate, wrong drug infused, and incorrect patient receiving the drug. An incorrect dose was defined as at least a 20% difference between what was administered and the prescribed dose. This category included missed doses of the study drug. An incorrect rate was defined as an infusion rate that was at least 0.15 g/kg/hr different from the prescribed rate infused over at least 10 min. Errors of incorrect drug were events in which a patient prescribed the study drug was administered another drug instead of the study drug. Errors of incorrect patient were instances in which a patient received study drug that was intended for another patient, regardless of whether the patient receiving the study drug was enrolled in the study.

Inpatient pharmacy records from Boston Children's Hospital were reviewed to determine the total number of inpatient doses of the study drug administered annually from 2005 through 2014. Annual administration errors and total annual doses administered were used to calculate the annual rate of study drug inpatient administration errors for each year from 2005 to 2014.

To capture the type of interventions performed, the 2007 Report of Improvement submitted to the BCH IRB by the study's principal investigators was reviewed. This report detailed system changes undertaken in 2007–2008 to minimize inpatient administration errors of the study drug. These modifications particularly targeted errors of incorrect dose, infusion rate, patient, and drug. Inpatient administration error rates for the study drug from 2005 to 2008 were compared to those from 2009 to 2014 in order to evaluate the efficacy of the modifications adopted in minimizing inpatient administration protocol deviations and maximizing the safety of patients receiving the study drug infusion.

2.2. Statistical analysis

The annual rate of study drug administration errors was calculated as the number of errors divided by the total number of inpatient doses administered. Exact Poisson regression was used to compare the error rate from 2005 to 2008 to the error rate from 2009 to 2014, via a generalized linear model with a logarithmic link function. An offset variable, defined as the natural logarithm of the number of doses administered in a given year, was used to account for different total study drug doses administered each year. There was no evidence of overdispersion as determined by the scaling parameter (deviance/df = 0.998), and a sensitivity analysis with negative binomial regression yielded results consistent with Poisson regression [4]. Point estimates of error rates, as well as for the percent reduction in error rates from 2005 to 2008 to 2009–2014, are provided with 95% confidence intervals (CI). Statistical analysis was performed with SAS version 9.3 (Cary, NC).

2.3. Protocol design changes initiated to minimize infusion administration deviations

Table 1 describes the study design improvements initiated over 2007–2008 aimed at minimizing study drug infusion administration errors. There were 3 categories of study design improvement: personnel, training, and systems.

Changes to the study personnel structure included hiring a dedicated research nurse for the study. This research nurse acts as a resource for inpatient nurses and staff who care for patients receiving the study drug but who may not be familiar with the process of administering an investigational drug and the particular study protocol. Use of the study drug was limited to specific inpatient units in the hospital to allow the cohort of staff working on those units to become familiar with the study drug and the protocol for its administration. Additionally, to ensure only those most familiar with the study protocol administer the drug, administration privileges were limited to nurses at the study institution who consistently work on the units where the study drug was administered.

Several formal training platforms were introduced, including mandatory electronic learning modules for nurses who administer the study drug followed by competency testing to assess understanding of the protocol requirements. Copies of the study protocol were placed centrally on each inpatient ward for reference, and the clinical trial staff met with inpatient caretakers to provide teaching and clarifications about the protocol. Nurses caring for study patients were required to review protocol material and undergo competency testing annually.

System improvements were established to differentiate the study drug from other, identical-appearing lipid emulsions and to utilize electronic point of care medication administration (bar coding) to render it more difficult to commit an error in the administration process. Steps to make the study drug more recognizable included using uniquely colored bags for delivering the study drug from the pharmacy to inpatient units, enlarging the auxiliary label denoting the drug as investigational, and storing the study drug separately from other intravenously infused substances on each inpatient ward. At the time of administration, a mandatory double check of the infusion pump by two independent personnel was adopted to ensure the correct pump settings and correct source container connection. To prevent wrong patient and wrong drug errors, two independent methods of patient identification prior to initiation of each infusion and prior to any change in infusion rate was adopted to ensure the correct patient received each dose of study drug.