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

Gillian L. Fell [a], Alison A. O'Loughlin [a], Prathima Nandivada [a], Alexis K. Potemkin [a], Paul D. Mitchell [b], Judith Mahoney [c], Kathleen M. Gura [d], Mark Puder [a, *]

[a] Vascular Biology Program and Department of Surgery, Boston Children's Hospital, Boston, MA 02115, USA
[b] Clinical Research Center, Boston Children's Hospital, Boston, MA 02115, USA
[c] Nursing Patient Services, Boston Children's Hospital, Boston, MA 02115, USA
[d] Department of Pharmacy, Boston Children's Hospital, Boston, MA 02115, USA

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

* Corresponding author.
E-mail address: mark.puder@childrens.harvard.edu (M. Puder).

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.

Table 1
Improvements initiated in 2007–2008.

Personnel
Dedicated research nurse
Only full-time nurses at study institution may administer study drug
Limit use of the study drug to a few units in the hospital
Training
Mandatory electronic learning module
Competency testing
Information/Protocol binder on each ward
Mandatory staff meetings with nurse managers and nurses
Annual review of protocol material and testing
Systems
Electronic point of care medication administration (bar coding)
Different color delivery bags for study drug
Make "Investigational" label of study drug more obvious
Store study drug separately from other intravenous fluids
Double check pump after initiating study drug
Two methods of patient identification

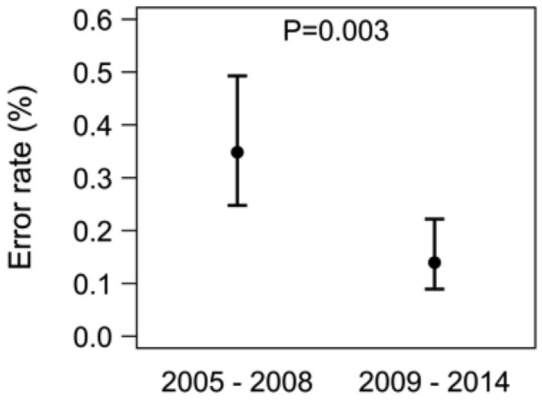

Fig. 1. Average annual rate of Omegaven administration errors. Shown are mean (95% confidence interval) and *P* value from exact Poisson regression for the time periods 2005–2008 (prior to initiation of improvement strategies) and 2009–2014 (after adoption of improvement strategies).

3. Results

3.1. Study drug administration error rates decreased with improvement initiatives

Table 2 shows the number of study drug administration deviations of incorrect dose, incorrect infusion rate, incorrect patient, and incorrect drug for each year included in the study. The average annual error rate for the time period prior to the adoption of study improvements (2005–2008) was 0.35%. Following the adoption of improvements from 2009 to 2014, the average annual error rate was decreased ($P = 0.003$) to 0.14% (Fig. 1). This represents a 60% (95% CI: 25–79%) reduction in the error rate from 2005 to 2008 after accounting for a 9% decrease in the rate of administered doses over 2009–2014.

4. Discussion

Here we demonstrate changes in clinical research protocol design that successfully decreased the number of inpatient infusion errors of a study drug. These interventions included limiting personnel and inpatient units allowed to administer the study drug, specialized training to educate inpatient caregivers about the protocol and specific study drug requirements, and systems improvements aimed at making it easier to differentiate the study drug from other similar drugs and more difficult to administer the wrong drug or to the incorrect patient. Additionally, these protocol modifications effectively heightened awareness among staff of the need and rationale for strict adherence to the research protocol of an investigational drug.

The infusion error rate in this study prior to the adoption of the changes was low, at 0.35% annually, compared to published error rates of infused medications which are reported as 5%–30% [5–7]. Although the infusion error rate in this study was low prior to adoption of the changes, standards for administration of investigational drugs are more rigorous than the standard of care, and for maximization of patient safety and study integrity the goal in clinical trials is to achieve an error rate as close to zero as possible. A statistically and clinically significant step toward attaining a near zero error rate was achieved through initiation of these changes in the study design.

Efforts to understand the etiology of medication administration errors have been undertaken previously. Several groups have identified interruptions in the medication verification process as highly associated with medication administration error rates [8], and others have attempted to define strategies to reduce errors related to interruptions in drug verification and administration [9]. Elements of the study design changes in this study, including a mandatory independent double-check of the pump settings to ensure correct infusion rate, requiring two modes of patient identification, have promoted increased awareness in the verification and administration processes. Although inquiry into the specific etiologies of medication administration errors is beyond the scope of this report, the fact that interventions aimed at minimizing the impact of disruptions or distractions in drug and patient verification support the idea that these factors may contribute to administration errors.

Reports have been published providing guidance for minimizing errors in the administration of chemotherapeutic agents, which are often part of oncologic research protocols. The American Society of Health-System Pharmacists published guidelines in 2015 for maximizing the safety of chemotherapy infusions, including specialized training for personnel administering chemotherapy, open access to the study protocols of their patients, and the use of bar coding and checklists to avoid infusion errors [10]. Chemotherapy infusions typically take place in specialized inpatient units

Table 2
Annual study drug administration deviations.

	Administration errors 2005–2008						Administration errors 2009–2014							
	2005	2006	2007	2008	Total	Mean/yr	2009	2010	2011	2012	2013	2014	Total	Mean/yr
Total inpatient doses	1013	1478	2784	3623	8898	2224.5	1838	2451	1828	1557	2516	1999	12189	2031.5
Error: wrong dose	2	2	6	4	14	3.50	1	0	2	1	1	1	6	1.00
Error: wrong rate	0	4	3	4	11	2.75	3	1	1	2	3	0	10	1.67
Error: wrong drug	0	0	0	2	2	0.50	0	0	0	0	0	0	0	0.00
Error: wrong patient	0	1	3	0	4	1.00	0	0	0	0	1	0	1	0.17
Total errors	2	7	12	10	31		4	1	3	3	5	1	17	
Error rate	0.20	0.47	0.43	0.28	0.35		0.22	0.04	0.16	0.19	0.20	0.05	0.14	

and are administered by staff specialized in the care of oncology patients. Furthermore, chemotherapy protocols include fixed durations of therapy. PN-dependent patients who develop PNALD and meet criteria to receive the study drug in this report may be treated by any of several care teams on nearly any inpatient unit in the hospital. Furthermore, the duration of PN-dependence and need for the study drug are different for each patient enrolled in the study. As part of the improvement strategy reported here, steps were taken to limit the nursing staff who may administer the study drug, incorporate training, and place the study protocol on each inpatient unit where the study drug was administered to minimize administration errors.

Studies in the anesthesiology field have reported systems-level measures to reduce medication administration errors in the operating room. These measures include improved labeling of drugs and use of color-coded systems to make drug identification and verification easier, use of pre-filled syringes, and use of barcoding systems to improve medication administration records [11,12]. In this report, similar improvements in labeling, storage, and use of electronic bar codes for the investigational drug were all strategies that contributed to minimizing administration errors.

Several studies exist that investigate methods to reduce medication administration errors in other settings, however, results are inconsistent and overall evidence for the effectiveness of any single intervention remains questionable. A meta-analysis of 10 studies aimed at reducing interruptions of nurses during medication administration reported mixed effectiveness of efforts to reduce interruptions [13]. Of the 10 studies included, only three reported the effect of administration interruption on medication administration errors, however all three reported reductions in errors after intervention to decrease interruptions. Two of the 3 showed significant reductions in percentage of administrations with errors from 16.6% to 2% over 12 months and 14.6%–4.2% over 18 months. The third study had a low pre-intervention percentage of administrations with errors at 2%, which was reduced to 0% at 6 months following intervention. A second meta-analysis of 24 studies investigated methods to reduce medication errors in adult ICU patients. This study included mostly pre- and post-intervention observational comparison studies, and two prospective randomized controlled trials. This study reported mixed results for a variety of interventions that included computerized physician order entry, changes in work schedule, medication reconciliation, automated intravenous pump systems, modes of education, pharmacist involvement, protocols and guidelines, and support systems for clinical decision-making [14]. Of the two prospective randomized controlled trials included, one focused only on changes in intern work hours and reported small reductions in medication errors committed by interns with reduced work hours. The other focused on the effect of automated infusion pump systems, and found no significant improvement in errors with use of such systems.

Our study is an observational pre- and post-intervention comparison of a multi-modal approach aimed at decreasing administration deviations of a study drug. While a prospective randomized-controlled trial would have been ideal for investigating the impact of new interventions to decrease administration errors, such a design was not possible in this study as the intervention strategies were developed and implemented at the request of the Institutional Review Board and required for all patients enrolled in the study. Furthermore, in utilizing a multimodal approach, it was not possible to conclude which strategies had the greatest impact on administration deviations because all measures were initiated within a short period as part of a comprehensive strategy to reduce administration deviations of the study drug.

5. Conclusions

Based on these results, we recommend a multifactorial approach that integrates use of a dedicated study nurse, limiting the personnel allowed to administer the study drug and inpatient units where the drug may be administered, educational initiatives to train personnel in protocol requirements, mandatory medication and patient verification procedures, and use of labeling, color coding, and electronic bar codes that make it easier to differentiate the study drug from other drugs. These represent experience-based guidelines meant to provide investigators with tools for developing optimal protocols for clinical trials of intravenously infused drugs that include strategies for minimizing administration deviations and optimizing patient safety.

Acknowledgments

We gratefully acknowledge the Boston Children's Hospital Surgical Foundation for funding of our studies. Additional funding was provided by National Institutes of Health Grant 1F32DK104525 (GLF), and the Joshua Ryan Rappaport Fellowship (PN). A license agreement for the use of Omegaven® has been signed by Boston Children's Hospital and Fresenius Kabi, and a patent has been submitted by Boston Children's Hospital on behalf of M. Puder and K.M. Gura.

References

[1] A. Vijayakumar, E.V. Sharon, J. Teena, S. Nobil, I. Nazeer, A clinical study on drug-related problems associated with intravenous drug administration, J. Basic Clin. Pharm. 5 (2014) 49–53, http://dx.doi.org/10.4103/0976-0105.134984.

[2] M. Puder, C. Valim, J.A. Meisel, H.D. Le, V.E. de Meijer, E.M. Robinson, et al., Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury, Ann. Surg. 250 (2009) 395–402, http://dx.doi.org/10.1097/SLA.0b013e3181b36657.

[3] K.M. Gura, S. Lee, C. Valim, J. Zhou, S. Kim, B.P. Modi, et al., Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease, Pediatrics 121 (2008) e678–e686, http://dx.doi.org/10.1542/peds.2007-2248.

[4] A.C. Cameron, P.K. Trivedi, Regression Analysis of Count Data, first ed., Cambridge University Press, Cambridge, 1998.

[5] A. Valentin, M. Capuzzo, B. Guidet, R. Moreno, B. Metnitz, P. Bauer, et al., Errors in administration of parenteral drugs in intensive care units: multinational prospective study, BMJ 338 (2009) b814.

[6] S.E. McDowell, S. Mt-Isa, D. Ashby, R.E. Ferner, Where errors occur in the preparation and administration of intravenous medicines: a systematic review and Bayesian analysis, Qual. Saf. Health Care 19 (2010) 341–345, http://dx.doi.org/10.1136/qshc.2008.029785.

[7] E. Tissot, C. Cornette, P. Demoly, M. Jacquet, F. Barale, G. Capellier, Medication errors at the administration stage in an intensive care unit, Intensive Care Med. 25 (1999) 353–359.

[8] V. Prakash, C. Koczmara, P. Savage, K. Trip, J. Stewart, T. McCurdie, et al., Mitigating errors caused by interruptions during medication verification and administration: interventions in a simulated ambulatory chemotherapy setting, BMJ Qual. Saf. 23 (2014) 884–892, http://dx.doi.org/10.1136/bmjqs-2013-002484.

[9] L. Colligan, E.J. Bass, Interruption handling strategies during paediatric medication administration, BMJ Qual. Saf. 21 (2012) 912–917, http://dx.doi.org/10.1136/bmjqs-2011-000292.

[10] B. Goldspiel, J.M. Hoffman, N.L. Griffith, S. Goodin, R. DeChristoforo, C.M. Montello, et al., ASHP guidelines on preventing medication errors with chemotherapy and biotherapy, Am. J. Health. Syst. Pharm. 72 (2015) e6–e35, http://dx.doi.org/10.2146/sp150001.

[11] A.F. Merry, C.S. Webster, J. Hannam, S.J. Mitchell, R. Henderson, P. Reid, et al., Multimodal system designed to reduce errors in recording and administration of drugs in anaesthesia: prospective randomised clinical evaluation, BMJ 343 (2011) d5543.

[12] A.F. Merry, D.H. Shipp, J.S. Lowinger, The contribution of labelling to safe medication administration in anaesthetic practice, Best Pract. Res. Clin. Anaesthesiol. 25 (2011) 145–159, http://dx.doi.org/10.1016/j.bpa.2011.02.009.

[13] M.Z. Raban, J.I. Westbrook, Are interventions to reduce interruptions and errors during medication administration effective?: a systematic review, BMJ Qual. Saf. 23 (2014) 414–421, http://dx.doi.org/10.1136/bmjqs-2013-002118.

[14] E. Manias, A. Williams, D. Liew, Interventions to reduce medication errors in adult intensive care: a systematic review, Br. J. Clin. Pharmacol. 74 (2012) 411–423, http://dx.doi.org/10.1111/j.1365-2125.2012.04220.x.