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Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Safety investigations from across the pond: Deep learning from England's HSIB

ISMP recently became aware of the Healthcare Safety Investigation Branch (HSIB) (www.ismp.org/ext/552), an organization that conducts independent investigations of various patient safety concerns in National Health Service (NHS)-funded healthcare across England. The organization, which was established in 2017, is funded by the Department of Health & Social Care and hosted by NHS England and NHS Improvement. HSIB has a team of investigators and analysts with diverse experience in healthcare, human factors, and safety science, who investigate patient safety concerns, identify contributing factors that have led to harm or have the potential to cause harm, and recommend strategies to improve healthcare systems and processes. Central to this is a commitment to a no-blame approach, with investigations providing a 'safe space' for participants, including patients, families, and staff, to share information.

HSIB undertakes patient safety investigations through two programs: 1) national investigations of patient safety concerns brought to its attention via an array of information sources, including reports from healthcare organizations and families, and the organization's own research and analysis; and 2) investigations of all maternity incidents occurring in the NHS. HSIB decides what to investigate based on the scale of risk and harm, the impact on individuals involved, the level of public confidence in healthcare, and the potential for learning to prevent future harm. HSIB recommendations range in scope from those intended for frontline healthcare providers to those directed at the highest levels of national healthcare policy, regulation, and professional standards.

HSIB Investigative Reports

HSIB national investigations focus on patient safety concerns that have occurred in NHS-funded healthcare after April 2017, and investigations of maternity incidents that have occurred after April 2018. These extensive investigations cover a wide variety of topics, from management of coronavirus (COVID-19) disease transmission risk in hospitals to neonatal collapse during maternal skin-to-skin contact immediately after birth. Medication-related investigations are one of more than a dozen investigative themes. To date, there are four completed and two ongoing medication-related investigations:

- The role of clinical pharmacy services in helping to identify and reduce high-risk prescribing errors in hospital (completed)
- Electronic prescribing and medicines administration systems and safe discharge (completed)
- Potential under-recognized risk of harm from the use of propranolol (completed)
- Inadvertent administration of an oral liquid medicine into a vein (completed)
- Prescribing and administering insulin from a pen device in hospital (ongoing)
- Residual drugs in cannulae and extension lines (ongoing)

Some investigations of patient safety concerns that also involve medications are categorized under different themes, such as "never events" (Administering a wrong site nerve block), "acute" (Timely recognition and treatment of suspected pulmonary embolism in inpatients), "equipment and technology" (Procurement, usability and adoption of "smart" infusion

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SAFETY briefs

HIGH-ALERT

Area to tear open patch wrapper can destroy the barcode. We received a report about Mallinckrodt fenta**NYL** transdermal patches related to the position of the tear-open slit area on the back of the outer wrapper, which is next to the product barcode (**Figure 1**). The reporter mentioned that tearing the package open to remove the patch destroys the barcode, so scanning becomes impossible. A barcode on the front of the package (not pictured) does not include the national drug code (NDC). Some nurses may try to scan that, which usually will not work, causing confusion.

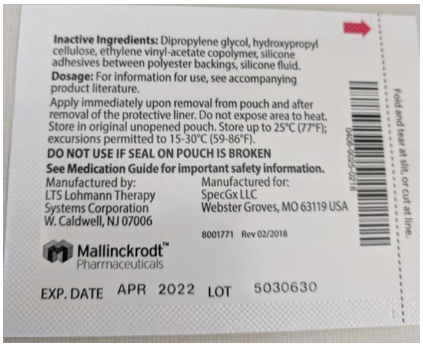

Figure 1. Mallinckrodt's fenta**NYL** patch has a dotted line on the back of the package to fold and tear open the package, which can destroy the barcode that should be used for scanning.

We agree that the tear-open slit and barcode are too close to one another, but it also struck us that nurses should be scanning the barcode on the package before opening it, so the correct drug and strength can be verified against the patient's medication administration record. Scanning should be performed before removing the medication from the package (before administration). The practitioner who reported the issue to us agreed but thought it was still best to ask the manufacturer to reposition the barcode.

We contacted the manufacturer to discuss the barcode positioning. However, we are concerned that repositioning the barcode could further facilitate scanning after the

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pumps), and "mental health" (Medicine omissions in learning disability secure units).

Investigation of Inadvertent IV Administration of an Oral Liquid Medication

In April 2019, HSIB published an independent report of its investigation of inadvertent administration of an oral liquid medication (midazolam) into a vein.[1] An overview of this 88-page investigative report follows.

Background Information. HSIB was made aware of this wrong-route error after the "never event" was reported to the National Reporting and Learning System (NRLS). The investigative report first provides relevant information and cites important literature on medication errors (particularly wrong-route errors), "never events" (particularly intravenous [IV] administration of an oral liquid medication), and midazolam to support the HSIB decision to investigate the safety concern. HSIB concluded that the outcome of inadvertent IV administration of an oral liquid medication can be serious, citing rare deaths and more frequent psychological harm and prolonged patient hospitalization. HSIB concluded that the systemic risk was wide given the evidence from national reporting systems and research that wrong-route errors continue to occur despite initiatives aimed at preventing them. HSIB also concluded that learning from the reference event and a wider investigation of the safety concern would identify best practice strategies to further reduce the risk of errors. Specifically, HSIB set out to examine the reference event to understand the context and causal factors; to review similar incidents to identify common factors; and to examine the role of human factors in inadvertent IV administration of oral liquid medications.

Reference event description. *A 9-year-old child (37 kg) was admitted to an ambulatory surgery unit (ASU) for a renal biopsy under moderate sedation. The ASU had not implemented electronic health records (EHRs), so a resident wrote an order for IV midazolam on the patient's chart, noting a maximum dose of 10 mg (based on official dosing guidelines of 0.4 mg/kg with a 10 mg maximum dose). The resident was unfamiliar with the ASU and asked a nurse to help prepare the midazolam. The nurse who typically prepared medications was absent on the day of the procedure, and an inexperienced nurse was filling in. Fifteen minutes later, the nurse prepared the dose in the treatment room with the resident who had the patient's chart and order.*

*In the controlled substance storage location, midazolam ampules (1 mg/mL) were kept alongside a 100 mL bottle of oral liquid midazolam (2.5 mg/mL). The nurse, who was only familiar with oral midazolam, picked up the oral liquid bottle and drew 4 mL (10 mg) of the clear oral medication into an oral/enteral syringe with a purple barrel with the expectation that the medication would be given orally (**Figure 1**). The nurse and resident verbally checked the medication name, expiration date, dose (based on the patient's weight), and volume of medication in the syringe. However, they never verified the formulation or route of administration, and neither recognized the error. Furthermore, the resident was unfamiliar with oral/enteral syringes and did not respond to the purple enteral syringe and the "For enteral feeding/med only" warning. The nurse handed the unlabeled syringe to the resident, who took it into the procedure room.*

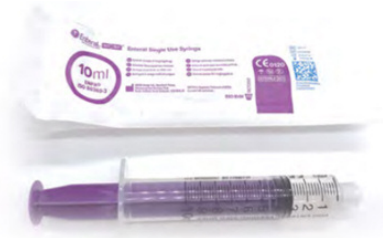

Figure 1. Purple enteral/oral syringe.

In the procedure room, the resident handed the unlabeled syringe to the physician performing the procedure, who clarified the prescribed dose with the resident. When the physician attempted to administer the medication, the syringe would not connect to the IV line, so he asked the resident if the medication in the syringe was IV midazolam. Having been told it was, he asked the resident to put the medication in a "normal" syringe. The resident decanted the contents of the oral/enteral syringe into a Luer lock syringe by

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fact. Learning about this type of concern could also indicate that some practitioners may not truly understand the importance of scanning the barcode prior to, and not after, drug administration. We mention this because we are aware that sometimes barcode scanning takes place after the fact as a way to cut corners to speed up the drug administration process; however, this increases the risk of errors.

HIGH-ALERT

Ready to use but not ready to administer. Until recently, both e**PHED**rine and phenylephrine injection were not available in a concentration that was suitable for direct intravenous (IV) bolus injection. Historically, e**PHED**rine has been available in 50 mg/mL vials or ampules. When treating hypotension, product labeling calls for doses of 5 to 10 mg as needed, not to exceed 50 mg, and all doses must first be diluted to 5 mg/mL. Phenylephrine injection, also used to treat hypotension, has been available as a 10 mg/mL injection that also needs to be diluted to 100 mcg/mL before administration.

Since these products are available in 1 mL containers (phenylephrine is also available in larger vials labeled as pharmacy bulk packages), the small container size has sometimes misled healthcare professionals into believing the amount in the container represents the dose. Thus, overdoses have occurred when these products were administered without first diluting the product to the correct concentration. From that standpoint, we were happy to see the introduction of **EMERPHED**, which is a "pre-diluted" e**PHED**rine injection 50 mg/10 mL (5 mg/mL), and **BIORPHEN**, a "pre-diluted" form of phenylephrine injection 500 mcg/5 mL (100 mcg/mL). However, these drugs are only available in a vial (Emerphed) and an ampule (Biorphen); neither drug is available in a prefilled syringe. Ready to use products are certainly safer than the previously available products, and we support companies that submit applications to the US Food and Drug Administration (FDA) for ready to use products. But prefilled, pre-labeled syringes that are ready to administer, not just ready to use, would further enhance safety. Ready to use products still pose risks due to the potential for an unlabeled or mislabeled syringe, lack of a barcode on the syringe, accidental contamination, waste of

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connecting the tips of each syringe together and transferring the medication from one to the other. The physician connected the syringe to the patient's IV line but found it difficult to push the plunger. After administering about 1.5 mL (3.75 mg) of the dose, he stopped and a small amount of the medication leaked onto his gloved hand, feeling sticky and smelling sweet. The physician suspected an error, flushed the line with saline, and asked the resident to clarify the medication with the nurse who prepared it. As soon as the nurse noticed the resident was carrying a parenteral syringe, she recognized the error and the procedure was halted. The patient's mother was informed of the error, and the child was monitored for the next 24 hours without apparent adverse effects. The next day, the child had the renal biopsy under general anesthesia and was later discharged.

HSIB Investigation

The report describes the HSIB investigation process and conclusions based on their findings. In addition to reviewing medical records, the event report, and policies and procedures, as well as interviewing involved staff, patients and family members, subject matter experts, and national organizations, the investigative process also included:

National review of similar incidents. When reviewing similar errors reported to national reporting programs, HSIB found that wrong-route errors have shown the largest increase in reporting among all medication event types. The most frequent medications involved in these events were oral liquid morphine, oxy**CODONE**, sodium valproate, and dispersible aspirin. In 40% of these errors, oral medications had been drawn into IV syringes. In other cases, the medication had been drawn into oral/enteral syringes but decanted into IV syringes, or oral/enteral syringes were not available.

Review of the literature. While researching inadvertent IV administration of an oral medication, the investigators discovered that the Royal College of Emergency Medicine reported in 2017 that, in a 2-year period, 30% of "never events" occurring in emergency departments were related to the inadvertent IV administration of oral morphine solution.

Observation. Direct observation of staff related to IV and oral medication storage, prescribing, preparation, and administration found a mismatch in terms of how the work is designed in procedures and guidelines (e.g., work as imagined) and how the work is really carried out (e.g., work as done). Observations of electronic prescribing systems, automated dispensing cabinet storage and retrieval, and barcoded medication administration was also conducted to review opportunities for technological interventions.

Human factors investigation. A human factors expert attended a reconstruction of the reference event and a simulation of what should happen according to documented policies and procedures and identified additional contributing factors, including the similarity of the two formulations of midazolam (both clear liquids); the lack of interaction and communication between team members on the day of the event; ambiguity about what is meant by a two-person check (double check), which is rarely independent; and the overreliance on oral/enteral syringes that are not well-understood by physicians.

Investigative Findings

The report draws dozens of conclusions, a few of which follow:

- Using oral/enteral syringes does not always prevent wrong-route administration
- Decanting medication from an oral/enteral syringe into an IV syringe is not an isolated event
- There appears to be a lack of understanding about the use and purpose of oral/enteral syringes among physicians
- There is no national standard for two-person checking of medication preparation and administration

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drug remaining in the vial or ampule, and so on. Also, when the drug is stored outside of the pharmacy, practitioners may not realize ampules require the use of a filter needle. While errors are still possible if the patient's dose is less than contained in a prefilled syringe and the entire syringe of medication is administered, ready to administer products still enhance medication safety.

In the past, pharmacists and anesthesiologists have overcome the dilution problem (and the lack of a prefilled syringe) either by having pharmacy prepare diluted products or by purchasing diluted prefilled syringes in exact patient doses through 503B outsourcers.

Given that prefilled and prelabeled dosage forms are safest for patients, it was discouraging to learn that attorneys for Eton Pharmaceuticals, manufacturer of Biorphen, have been sending letters to pharmacists to let them know that since FDA has approved their client's Biorphen product, it is now unlawful for outsourcing facilities to market compounded phenylephrine injections that are "essentially a copy" of Biorphen. The letters mention that compounding of such products could subject an outsourcing facility to enforcement action by FDA. We are hearing from hospitals that have already stopped purchasing prefilled syringes due to receiving this letter. Unfortunately, patient safety is not being served.

We certainly understand that, except in times of a drug shortage, FDA does not allow 503B compounders to commercialize drugs that are essentially a copy of an FDA-approved drug using active pharmaceutical ingredients. However, it is unclear to us if FDA would prohibit a 503B compounder, or a 503A pharmacy for that matter, to prepare prefilled syringes from commercially available 10 mg/mL phenylephrine products, creating a product that would then be available in a dosage form (prefilled syringe) not commercially available from the vendor. We have, therefore, entered an inquiry with the FDA compounding branch and hope to have an answer for readers soon.

Helping patients avoid insulin pen mix-ups. A pharmacist recently heard from two patients who mixed up their insulin pens and gave themselves the wrong insulin. The first

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- The training of medical students, residents, and doctors in the preparation and administration of oral and IV medicines is variable, with no formal mandatory standard drug administration training and practical competencies for doctors in hospitals
- Labeling of practitioner-prepared syringes is inconsistent
- Staffing shortages combined with good intentions to support colleagues may lead to staff carrying out unfamiliar tasks, resulting in knowledge-based errors

Recommendations

Based on findings from the investigation, HSIB makes recommendations aimed at the local level (specific for the involved organization), organizational level (for all organizations), and national level (for professional, regulatory, and standards organizations). A few examples from each level follow:

Local

- Develop and implement policies and procedures for invasive procedures that require sedation, including minimum staffing and skill-mix requirements.
- Educate all clinical staff who prescribe, prepare, and/or administer medications about strategies to prevent wrong-route administration of medications, including the appropriate use of purple oral/enteral syringes.

Organizational level

- Separate different formulations of the same medication in storage areas.
- Label practitioner-prepared syringes of medications that are not immediately administered; the person who prepares the medication should administer it.
- Staff with a responsibility for medication safety should be able to demonstrate how they are learning from medication-related patient safety incidents.
- HSIB, supported by a teaching hospital, has produced a simulation of what happened during the reference event (www.ismp.org/ext/555) along with a supplementary teaching aid to increase awareness of this type of error.
- The investigation team reviewed the opportunities for technological interventions including electronic prescribing systems, automated dispensing cabinets (to limit access to the formulation not ordered), and barcoded medication administration. However, another HSIB investigation was focusing on these technologies; therefore, findings were shared for inclusion in the technology report to prevent duplication.

National level

- Define a national standard for independent two-person checking when preparing high-risk (high-alert) medications for administration.
- Create a national audit tool for organizations to use to measure availability of oral/enteral syringes in all clinical areas.
- The Royal College of Physicians, Royal College of Nursing, and Royal College of Midwives, in collaboration with the other professional and safety organizations, should recommend postgraduate activities to standardize professional development in medication safety processes; for example, the General Medical Council Medical Licensing Assessment could mandate skills associated with medication administration as part of the Clinical Practical Skills Assessment.

Conclusion

We hope that just a glimpse of this report will help you recognize the depth of learning that is possible when an event is fully investigated by a diverse team discussing each behavioral and system component of the event and then broadly researching all uncovered patient safety issues.

Reference

1) HSIB. Inadvertent administration of an oral liquid medicine into a vein; 12017/009. April 2019;1-88. www.ismp.org/ext/553

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patient, a 67-year-old man with type 2 diabetes, had been using an insulin degludec (**TRESIBA**) pen, 70 units once daily subcutaneously. Because his blood glucose remained uncontrolled, he was started on an insulin lispro (**HUMALOG**) pen, 5 units subcutaneously with the first bite of dinner. He inadvertently took 70 units of Huma**LOG** instead of Tresiba. He immediately realized the error and called the Poison Help line, which advised him to check his blood sugar every 15 minutes for 3 to 4 hours. He was also instructed to eat glucose-containing foods and beverages regularly during this time to combat hypoglycemia. He was able to maintain a blood sugar of 90 to 150 mg/dL.

The second patient, a 49-year-old man with diabetes, had recently been started on a multidose insulin injection regimen of Huma**LOG** 30 units 3 times a day with meals and Tresiba 60 units once daily. He inadvertently injected Tresiba 30 units at mealtime instead of Huma**LOG**. His blood sugar measurements rose to above 300 mg/dL, which led him to realize he was taking the wrong insulin with his meals. Other than hyperglycemia, he had no more adverse effects.

We have written about the potential to confuse insulin pens in the past, particularly with impaired vision. In the two cases above, neither patient had significant visual impairment. However, even though Huma**LOG** and Tresiba pens are produced by different manufacturers, the pens are similarly shaped and available in a similar shade of blue, although they have different label colors.

With both patients, the pharmacist discussed ways to avoid this type of mistake in the future, including verifying the insulin names and strengths/doses, flagging the pens with "rapid-acting" or "long-acting" stickers, and including the brand name on the sticker. Also, since insulin does not need to be kept in the refrigerator after opening, the pens can be stored in the specific physical locations where they will be administered, such as the bedroom for long-acting Tresiba, and the kitchen or dining room for rapid-acting Huma**LOG**. Always remind patients to securely store their medications up and away and out of sight and reach of children. We have also heard of using adhesive tape, a rubber band, or a hair tie wound around the pens to differentiate the insulin types.

ACD-A bags will have a barcode, but not sure when

Anticoagulant Citrate Dextrose Solution, Formula A (ACD-A) is available from Fenwal in 500 mL and 1,000 mL flexible containers and is intended for use as an anticoagulant in extracorporeal blood processing with cytapheresis devices. Although the product looks like many intravenous (IV) infusion bags (**Figure 1**), it is NOT intended for direct IV infusion, which could cause serious harm. ACD-A is also used, off-label, for continuous renal replacement therapy (CRRT) patients to prevent clotting in the extracorporeal circuitry. Its use in conjunction with CRRT brings the bags closer to patients who have venous access, increasing the risk of inadvertent IV administration. For example, bags of ACD-A might be confused with IV bags intended for administration to CRRT patients, such as premixed heparin or potassium chloride solutions, each of which are available in flexible containers that have labels printed in red font.

ISMP and the US Food and Drug Administration (FDA) have received multiple reports about the potential for product mix-ups. Two incidents were reported to the FDA Adverse Event Reporting System (FAERS) in which ACD-A was inadvertently administered IV, causing harm to one patient. In one case, the CRRT machine was set up incorrectly and the ACD-A anticoagulant flowed directly into the patient's bloodstream instead of bathing the prefilter of the machine. This led to multiple adverse events, including dangerously low calcium levels. A small-print warning, "NOT FOR DIRECT INTRAVENOUS INFUSION," is buried within the red text midway below the product name and is difficult to see. In the other case, a patient received IV ACD-A instead of the intended **HESPAN** (hetastarch). The patient suffered bleeding, although a direct relationship to IV ACD-A administration could not be determined. Additionally, mix-ups between ACD-A and Anticoagulant Sodium Citrate bags, which also use red font on the label, have been reported to ISMP, including a case published in a ***SAFETY* brief** in our June 5, 2014 newsletter.

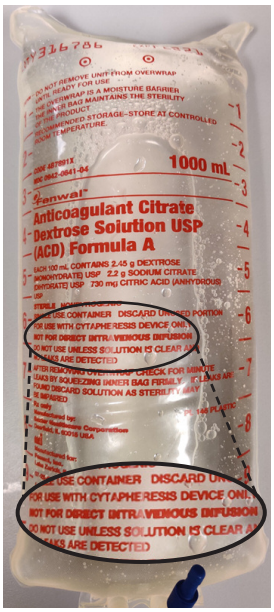

Figure 1. ACD-A, 1,000 mL bag with red font labeling (Fenwal) should not be administered IV (magnified warning says: **NOT FOR DIRECT INTRAVENOUS INFUSION**) and could be confused with other infusion bags with red font labeling.

Barcode scanning would help verify infusion products in flexible containers before use. At present, a barcode is not available on the ACD-A IV bag overwrap or immediate container label. In 2004, Fenwal was awarded an exemption from the FDA Bar Code Rule for ACD-A. The exemption request stated that use of ISBT (International Society of Blood Transfusion) 128 compliant labeling during blood collection, processing, and storage in blood centers and hospital transfusion services provided an acceptable alternative to ensure patient safety. With widespread use of barcode scanning technology in hospitals, the risk of an error would be less if a barcode was on the product. To enable barcode scanning, one pharmacy told us they label the overwrap with a barcode. According to prescribing information, the product must be kept in the moisture-barrier overwrap until use, so the pharmacy cannot place a barcode directly on the bag. However, this workaround could lead to errors. For example, the pharmacy could affix the wrong barcodes to ACD-A bags or mislabel a different product with barcodes meant for ACD-A, or the nurse could throw away or misplace the overwrap prior to scanning it.

Despite the barcode exemption, Fenwal has told us that the company is planning to add a linear and two-dimensional (2D) barcode label to the ACD-A solution overwrap. The company is also in the planning stages to print a linear and 2D barcode on the flexible container, which will eventually replace the barcode label on the overwrap. These labeling changes will require FDA review and approval prior to implementation. We hope the company will see this as an urgent need and make this change in the near future.

Special Announcements

Virtual MSI workshop

Don't miss a unique opportunity to maximize your error prevention efforts and look at your organization through the eyes of leading safety experts! Register for the first virtual ***ISMP Medication Safety Intensive (MSI) Workshop*** on **December 3-4, 2020**, and learn how to establish a medication safety program and use data for sustained improvement. For details, please visit: www.ismp.org/node/13788.

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FREE FDA webinar

The US Food and Drug Administration's (FDA) Division of Drug Information is presenting a **FREE** webinar, ***FDA Drug Topics: Labeling Made Simple: The How, What, and Where of Drug Interactions in Prescribing Information***, on **October 27**. This webinar will provide an overview of key regulations impacting drug interaction content in the prescribing information. For details, visit: www.ismp.org/ext/30, and to register, visit: www.ismp.org/ext/31.

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