Potassium chloride for injection concentrate: Time for a risk evaluation and mitigation strategy

CAITLIN A. KNOX, WEI LIU, AND DAVID B. BRUSHWOOD

Case Law is intended to provide pharmacists with timely information about recent court decisions that may affect pharmacy practice. Each installment includes pertinent background information, excerpts from the opinion of the court, and brief commentary. The contributing editor for the section is David B. Brushwood, B.Pharm., J.D., Professor, Pharmaceutical Outcomes and Policy, College of Pharmacy, Health Sciences Center, University of Florida, Box 100496, Gainesville, FL 32610 (brushwood@cop.ufl.edu).

Patient safety is the responsibility of all individuals and institutions involved in health care. Effective patient safety programs often focus on the system of health care delivery and conduct human factors research to determine potential failure modes based on experiences of the past, with the goal of reducing the probability of future failures. The majority of medication safety programs use this systems approach.

Within a medication safety program, a distinction is often made between “thing responsibility” and “agent responsibility.” The evaluation of thing responsibility focuses on the pharmaceutical product and considers aspects of the molecule, the dosage form, the packaging, the labeling, and the distribution chain that can lead to unsafe product use and bad outcomes for patients despite the best efforts of health care personnel to use the product safely. In considering thing responsibility, an evaluator of past experiences may conclude, “The product caused an adverse effect.”

An assessment of agent responsibility focuses on people who manage and practice within the medication-use system. These administrative and clinical personnel can make technical or judgmental errors that lead to unsafe product use and bad outcomes for patients despite the inherent safety of the product used. In considering agent responsibility, an evaluator of past experiences may conclude, “The failure to use the product correctly caused an adverse effect.”

A legal case from the Court of Appeals of Louisiana provides an opportunity to consider the interface between thing responsibility and agent responsibility. The case was particularly poignant because it involved the legal claim of a family who sued a hospital, alleging that the i.v. push administration of potassium chloride for injection concentrate caused the death of their mother. The administration of potassium chloride for injection concentrate by i.v. push is widely recognized as a “never event” (i.e., an egregious and preventable medical error) because it is usually fatal. A long history of patient fatalities from the erroneous administration of potassium chloride for injection concentrate presents a challenge for the Food and Drug Administration (FDA) in the regulation of the product and for health care institutions in the system of product distribution. The appellate court affirmed a lower court verdict in favor of the family for damages exceeding $1 million.¹

Broad FDA medication safety initiatives. The third reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2007 broadened and strengthened FDA’s drug safety program. One of the performance goals committed to by FDA was to implement measures to reduce medication errors, particularly those related to drug product design.

In December 2012, FDA’s Center for Drug Evaluation and Research released a draft guidance for indus-
try titled “Safety Considerations for Product Design to Minimize Medication Errors.” The aim of the guidance was to address the safety of drug product design in order to minimize the risk of medication errors.

The guidance cites the 2006 Institute of Medicine report that urged FDA to include better standards in addressing issues surrounding drug labeling and nomenclature. Moreover, FDA responded by stating that some medication errors may not be corrected with product labeling or education: “Drug product design features that predispose end users to errors may not always be overcome by product labeling and health care provider or patient education; it is therefore preferable to eliminate these risk factors from the drug product design to reduce the risk of medication errors.”

Although it is not possible to predict all medication errors, some may be avoided with proactive risk assessments. FDA compels sponsors of new drug applications to build safety into the drug product design in early development and throughout the product’s life cycle. Design considerations include “the active ingredient, strength, dosage form, product appearance, size, shape, palatability, storage and handling, indication, type of container/closure used to package the product, the label affixed to the container/closure, secondary packaging such as outer carton or overwraps into which the container/closure is placed, and the labeling information describing the dose, preparation, and administration that accompanies the drug product.”

Research has shown that nomenclature, labeling, and packaging are key elements in medication use and that a failure in any of those elements can cause medication errors. Sponsors should design drug products to minimize the chance of end-user mistakes:

For a drug product, the end users include, but are not limited to, the patient, patient’s caregiver, the prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, and administration of medications (e.g., medication technicians). Sponsors should evaluate and understand essential characteristics of all intended user groups for the purpose of evaluation and design activities using proactive risk assessments. All individuals in the intended user population should be able to use the drug product without making unintentional errors or without being exposed to unnecessary safety risks.

This can only be done if the sponsors consider the users, as well as the environments in which the product will be used, during the initial development of the drug product design. The environment of use is very important to consider in the development of the drug product design because it typically will not be changed to fit the use of the drug product.

FDA maintains that the most useful strategy to handle use-related medication errors would be to focus on advancing the design of the interface between drug product and user; this is because a well-designed interface will discourage actions that may result in a medication error while also promoting correct actions. A well-designed interface is particularly important in instances where proper drug handling in the user environment is key for the successful administration of the drug (e.g., potassium chloride for injection concentrate).

A litany of tragic errors. The first issue of the Joint Commission’s Sentinel Event Alert series, published in 1998, dealt with the once common practice of storing potassium chloride for injection concentrate on nursing units. The Institute for Safe Medication Practices (ISMP) identifies the agent as a high-alert medication because it can be fatal if administered incorrectly. In a review of more than 200 sentinel events over a two-year period conducted around the time of the 1998 alert, the Joint Commission found that potassium chloride for injection concentrate was the drug most frequently implicated in events involving medication errors. Ten such incidents that resulted in a fatality were found to be a direct result of improper administration of potassium chloride for injection concentrate; 8 of these deaths were due to the direct infusion of potassium chloride for injection concentrate, and in 6 cases the product was mistaken for another product with similar packaging or labeling. In Canada, 23 incidents associated with potassium chloride for injection concentrate were reported between 1993 and 1996; those incidents involved episodes of misadministration similar to those found in the Joint Commission study.

Since the 1980s, ISMP, the United States Pharmacopeial Convention (USP), the Joint Commission, and the Institute for Healthcare Improvement have tried to draw attention to the medication errors commonly associated with potassium chloride for injection concentrate and urge its removal from patient care areas. In 1987, ISMP organized a national meeting at which USP and FDA established federal requirements mandating that potassium chloride for injection concentrate be packaged with black caps and closures, with warning statements to prevent confusion with other parenteral drugs. These requirements, coupled with a change in the product’s official USP-designated name (to “potassium chloride for injection concentrate”), were implemented in 1991. In 2000, Abbott Laboratories, which at the time manufactured 80% of potassium chloride for injection concentrate, stopped packaging potassium chloride for injection concentrate for its Universal Additive Syringe line, thus precluding direct
injection of the undiluted product into an i.v. port.\textsuperscript{11}

The changes in the product and nomenclature standards and limiting the access to potassium chloride for injection concentrate have reduced fatal errors. Nevertheless, this high-alert medication still presents a serious threat to patient safety, largely due to issues of agent responsibility (e.g., mix-ups occurring in the pharmacy).

**Factual background of the case.**

The patient whose children sued the Louisiana hospital arrived at the hospital emergency department (ED) on February 12, 2001, at 7 p.m. with complaints of abdominal pain, epigastric pain, vomiting, and diarrhea.\textsuperscript{1} Her daughter and the daughter’s boyfriend were present in the ED treatment room with her. The ED physician’s impression was that the patient had simple gastroenteritis. Intravenous access was established, and the patient received i.v. ketorolac and promethazine, to which she responded well. When the patient’s blood pressure dipped, the physician ordered i.v. therapy with 0.9% sodium chloride injection for presumed dehydration. The patient was taken for a computed tomography (CT) scan, during which laboratory results indicating that the patient’s potassium level was low were reported to the ED.

The ED nurses’ notes indicated that the patient returned from the CT scan to the ED at 9:40 p.m., and the physician was summoned. A nurse expert witness testified that when her mother returned from the CT scan, the nurse entered the room and stated, “Here is what your mother needs . . . potassium.”\textsuperscript{1} The daughter said the nurse was holding three syringes of equal size and that she administered all three medications directly into the patient’s i.v. port. According to the daughter, the patient began screaming that her arm was burning and went into seizure-like convulsions.

The daughter’s boyfriend testified that the nurse told him the three syringes contained meperidine, promethazine, and potassium.\textsuperscript{1} He testified that he observed the nurse administer all three medications directly into the i.v. port, that within 60 seconds the patient was frothing at the mouth and convulsing, and that within 90 seconds the patient was no longer breathing.

A physician expert witness testified that the patient’s reaction was consistent with an i.v. push of concentrated potassium and that this injection caused her death.\textsuperscript{1} The expert opined that the hospital’s lack of written policy regarding the handling of undiluted potassium chloride was well below the standard of care. The physician expert witness cited testimony by the hospital’s director of pharmacy, who referred to a directive from a year earlier mandating that all potassium chloride be removed from patient care areas due to its lethal nature when administered without dilution. The director of pharmacy testified that if undiluted potassium chloride is dispensed, the pharmacist takes it to the patient care area and injects it into the i.v. infusion bag containing 0.9% sodium chloride injection.

A nurse expert witness testified that the “medical records contain timing inaccuracies and . . . the pharmacy record was inconsistent with the patient’s chart regarding medications.”\textsuperscript{1} In particular, this expert showed that a dose of potassium chloride was dispensed by the pharmacy and was not accounted for in the patient’s chart.

The hospital contend that potassium chloride for injection concentrate was not available in the ED at the time the patient died.\textsuperscript{1} However, two physicians who had been involved in a medical review panel considering this incident acknowledged that “the second dispensation of 40 mEq of potassium as reflected in the record does not appear anywhere else in the medical records, i.e., it is not documented as having been given or destroyed.” At trial, the director of pharmacy “reluctantly agreed that undiluted potassium was obtainable from the pharmacy and could have left the pharmacy in a syringe.”

The ED nurse blamed for giving the deadly injection denied that she administered potassium chloride for injection concentrate by i.v. push.\textsuperscript{1} She stated that the daughter and her boyfriend were lying when they testified that she had entered the room and told them she was bringing potassium for administration to the patient; instead, the nurse explained, she had brought syringes of meperidine, promethazine, and 0.9% sodium chloride injection to flush the i.v. line.

The jury returned a verdict in favor of the patient’s family, and the hospital appealed.\textsuperscript{1}

**Appellate court ruling.** In ruling on the case, the Louisiana appellate court said\textsuperscript{1}

> It is undisputed that the administration of undiluted potassium IV push falls below the standard of care. As previously stated, the jury in this case found by a preponderance of evidence that [the ED nurse] breached the standard of care in her treatment of [the patient] by injecting undiluted potassium directly into the [i.v.] port, which caused the cardiac arrhythmia that caused [the patient’s] death.
review of the record reveals a reasonable basis for this conclusion.

First, the jury heard repeated testimony concerning the inaccuracy of the medical records and the inconsistencies between the pharmacy records and the medical records. Second, [the director of pharmacy’s] testimony was subject to differing interpretations regarding the availability of undiluted potassium to nurses from the pharmacy. In addition, there was no written policy dictating the handling of undiluted potassium; rather the staff was informed via internal memo in February 2000 that undiluted potassium would no longer be available in patient care areas. [The director of pharmacy], however reluctantly, testified that undiluted potassium was available from the pharmacy. Moreover, [the ED physician] testified that he was unaware that undiluted potassium was not supposed to be available to ED nurses and he ordered that the potassium be added to the bag of normal saline that had already been hung. Third, all witnesses, albeit somewhat reluctantly, testified that there was a 40 [meq] dose of potassium dispensed by the pharmacy, but not accounted for in the medical chart as having been given to the patient or discarded. Finally, all expert witnesses agreed that [the patient’s] cardiac arrhythmia and the reactions as described by [the daughter and her boyfriend] were consistent with the patient having received undiluted potassium IV push. Collectively, this evidence could reasonably lead a fact finder to conclude that undiluted potassium was available to [the ED nurse] from the pharmacy and was administered [by i.v.] push to [the patient].

The appellate court noted that the jury clearly had made a credibility determination in accepting as true the testimony of the daughter and her boyfriend while rejecting the testimony of the ED nurse. A jury is afforded great deference in making such credibility determinations, and the court found no abuse of that discretion in this case. The judgment against the hospital was affirmed.

**Analysis.** Ongoing patient safety problems involving potassium chloride for injection concentrate exemplify the struggle to resolve labeling and packaging problems in order to reduce the number of catastrophic events that occur with accidental injection of some pharmaceutical products.

Efforts to ensure the safe use of potassium chloride for injection concentrate are plagued with thorny issues, including challenges posed by the system of use and the product itself. The literature states that due to persistent ambiguities of nomenclature, potassium chloride for injection concentrate is commonly confused with other drugs. It has been suggested that pharmacies order potassium chloride for injection concentrate from a different manufacturer than other injectable forms of the salt to avoid similar labels. As an alternative measure, ISMP suggests that hospitals order premixed boluses of potassium chloride for injection concentrate from the manufacturer to completely remove the human factor from the patient safety equation. However, implementation of these suggested safety steps is not required or enforceable. Twenty-three years ago, USP required product and nomenclature changes to ensure that potassium chloride for injection concentrate, as packaged for marketing, does not look like any other drug; still, 10 years later there was no change in the number of deaths from potassium chloride poisoning. ISMP began a formal campaign in 1997 aimed at removing potassium chloride for injection concentrate from patient care units and prohibiting nurses’ access to it, thereby segregating potassium chloride for injection concentrate from other products. However, implementation of and adherence to these recommendations depend on the medication-use system to have a strong infrastructure and may require the modification of the use environment to ensure the safe use of the drug.

The manufacturers of potassium chloride for injection concentrate have adapted the labeling to improve the safe use of the drug. The label highlights the need for dilution in bold lettering in a boxed warning: “Concentrate Must Be Diluted Before Use.” Nevertheless, it is still mistakenly used in a “pushed” fashion, as seen in the Farmer v. Willis-Knighton Medical Center case; the potential for medication errors to result from this practice may have been identified in the development of the drug product. However, that potassium chloride for injection concentrate is a frequently implicated drug in fatal medical errors suggests that the changes in the design are not working.

The removal of potassium chloride for injection concentrate from the market would not be feasible, but it may be time to implement a risk evaluation and mitigation strategy (REMS). A REMS program provides the framework for FDA regulatory assurance that safe and effective drugs are used safely and effectively (Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355-1). The implementation of a REMS for potassium chloride for injection concentrate would allow FDA to enforce and promote the safe use of the drug without taking it off the market. A REMS would require prescribers to be educated on the dangers of misuse, and it would necessitate authorization before the dispensing of potassium chloride for injection concentrate so that health care providers could not remove it from the pharmacy without following the proper protocols.

**Conclusion.** Safe use of medication is a complex process. Several programs have effectively focused on the system of health care delivery and the human factors to determine
potential failures and modify the actions with the goal to achieve safe and effective patient care. In some cases, internal modification is not enough to prevent medication errors, especially when there is a flaw in the design of the drug that creates a need for the infrastructure and environment of use to ensure safe usage. The number of fatal medication errors associated with potassium chloride for injection concentrate is inexcusable.

In the interest of public health protection, FDA should use its control given to it by the PDUFA and the Food and Drug Administration Amendments Act to ensure that the benefits of using potassium chloride for injection concentrate outweigh the risks.

References
6. Institute for Safe Medication Practices. ISMP’s list of high-alert medications.