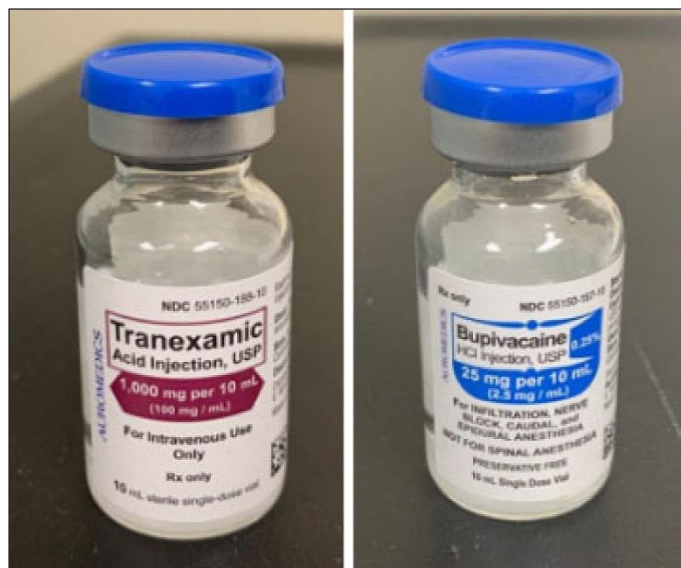


## Unraveling a Recurrent Wrong Drug-Wrong Route Error—Tranexamic Acid in Place of Bupivacaine: A Multistakeholder Approach to Addressing this Important Patient Safety Issue

### Introduction

Notwithstanding technological advances and the ongoing efforts of patient safety advocates, medication administration errors routinely occur in health care facilities across the country.<sup>1-2</sup> Each day, anesthesia professionals overcome challenges that commonly contribute to medication errors, such as a lack of standardization, drug shortages, production pressures, high-stress work environments, and limited resources. The World Health Organization estimates the global cost of medication errors to be \$42 billion.<sup>3</sup> A momentary lapse in concentration or, more frequently, systemic issues in workflow, contribute to medication errors. In addition, a medication error involving the wrong drug and the wrong route can have dire consequences for the patient.

To illustrate, we have identified a concerning trend in which anesthesia professionals have inadvertently administered tranexamic acid (TXA) intrathecally when performing neuraxial blocks. The mortality rate associated with this medication error is approximately 50%.<sup>4</sup> In the last 10 years, Preferred Physicians Medical (PPM), an anesthesia-specific professional liability carrier, received six reported incidents involving TXA-bupivacaine mix-ups (most occurring in the last four years). All six occurred during orthopedic procedures; however, a retrospective study suggests this TXA-bupivacaine wrong drug-wrong route medication error has also occurred during caesarean deliveries and other abdominal procedures.<sup>4</sup> The use of TXA has increased in recent years based on the results of several studies, including the POISE-3 trial which demonstrated decreased bleeding by up to 25% with TXA use.<sup>5-7</sup> As TXA is administered more frequently, it is imperative that measures are taken to prevent medication administration errors.



*Submitted to the APSF Lookalike Vial Gallery by  
Andrea Regan, MscS, MSA, CAA.*

### ***Mortality Rate Can Be as High as 50% When Accidentally Administering TXA Intrathecally***

In this article, we examine a case involving a TXA-bupivacaine mix-up, share perspectives from a multidisciplinary group of contributors, and offer recommendations to avoid recurrence of these catastrophic medication errors.

### Case Study

A 67-year-old male presented for left total knee arthroplasty. The patient's medical history was significant for morbid obesity, hypertension, and coronary artery disease. The anesthetic plan was a

subarachnoid block with monitored anesthesia care. An anesthesia professional was also expected to administer TXA intraoperatively at the request of the surgeon. The hospital's policies and procedures stated TXA must be ordered from the pharmacy in prefilled infusion bags.

However, this practice was seldom followed by the surgical team in the patient's Operating Room (OR). Accustomed to the OR's practice, the anesthesia professional removed 10 mL vials of TXA and bupivacaine from the automated dispensing cabinet in preparation for the case.

Once the patient arrived in the OR, the anesthesia professional drew up what he believed to be bupivacaine into a syringe labeled "Marcaine/Fentanyl." The anesthesia professional had difficulty administering the block due to the patient's body habitus, and he called the supervising anesthesiologist to assist. The anesthesiologist administered a 2.5 mL dose, but the block did not induce the intended effect. Within minutes, the patient reported pruritus in his perineum. The anesthesia team assumed the patient's discomfort was the result of a failed block, and they elected to convert the case to a general anesthetic. After induction, the patient was noted to have minor leg twitching. Once the procedure

progressed to the point TXA was needed, the anesthesia professional discovered the TXA vial was opened, while the bupivacaine vial remained sealed and unused on the anesthesia cart. Upon recognizing the patient had received a 250 mg dose of TXA intrathecally, the anesthesia professional alerted the anesthesiologist and surgeon, and they decided to complete the procedure and evaluate the patient in the PACU.

The patient remained intubated and on a propofol infusion upon transfer to the PACU, where he began experiencing seizures a short time later. The patient was transferred to the Neurological Intensive Care Unit (Neuro-ICU) for evaluation. There, the decision was made to take the patient back to the OR to undergo a cerebral spinal lavage. After the procedure, the neurology critical care physician elected to leave the patient on isoflurane until the seizures stopped or the inhalation agent was no longer tolerated. Isoflurane was subsequently discontinued in favor of propofol and ketamine, and the seizures were suppressed by postoperative day (POD) #3.

The patient had a lengthy and eventful stay in the neuro-ICU. He experienced delirium due to toxic and

metabolic encephalopathy, and myoclonic status epilepticus requiring prolonged intubation. He was extubated on POD #14, and the nasogastric tube was removed on POD #17. The patient exhibited cognitive deficits, including both short- and long-term memory impairment.

He was discharged to a rehabilitation hospital on POD #23. During his 2-week admission, the patient's cognition, memory, and motor function gradually improved. The patient was also treated for shoulder pain, which was attributed to a rotator cuff tear resulting

**>50%**  
of TXA-associated intrathecal injections resulted in **death** (36%) or **permanent harm** (19%)

**PRE-MIXED BAGS**

The **SINGLE MOST EFFECTIVE** measure to reduce the incidence of wrong drug-wrong route TXA-bupivacaine errors

The infographic features a blue background with a blurred image of a syringe and vial. A white line-art icon of a pre-mixed bag is positioned to the right of the statistics. The text is in white and yellow, with 'PRE-MIXED BAGS' in a larger, bold font.

from seizures. The patient required skilled nursing care for several weeks post-discharge. Fortunately, the patient went on to make a remarkable recovery, and his neurologist noted his executive and motor functions returned to baseline approximately 13 months after the event.

The patient and wife subsequently filed a lawsuit against the anesthesia professionals involved, the anesthesia group, the hospital, and the orthopedic surgeon. The anesthesia professional acknowledged liability at the outset of the case, and the parties conducted discovery to fully evaluate the plaintiffs' damages. The parties mediated the case a year later, and the plaintiffs settled with the anesthesia professional and the anesthesia group within the policy limits.

## Discussion

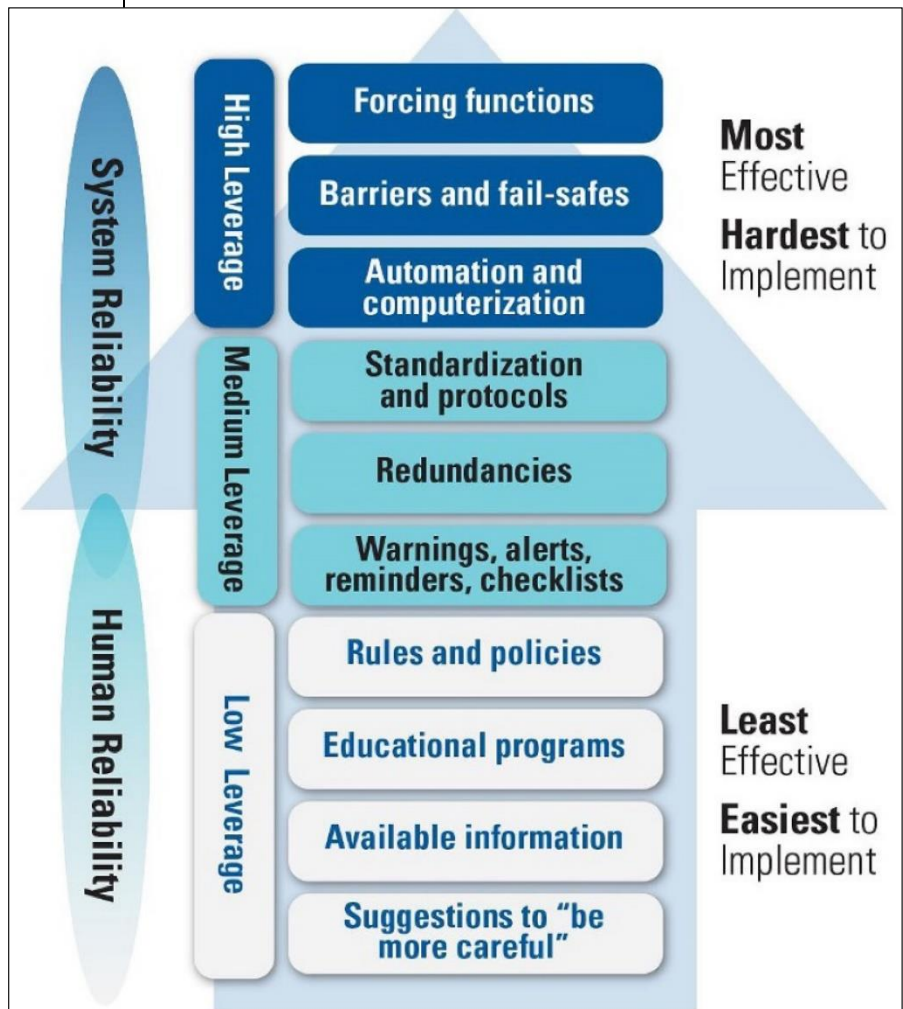
### Unacceptably High Accidental Injections of TXA into the Intrathecal Space Continue to Occur

In a 2023 narrative review of 22 recent reports of TXA-associated intrathecal toxicity occurring from July 2018 to September 2022, it was found that 36% of the patients died and 19% had permanent harm. The permanent harm ranged from residual muscle weakness, chronic pain, T10 and L1 spine fractures associated with convulsions, mild cognitive impairment, and multiple neurological deficits to extreme chronic pain causing the patient to be bed-bound.<sup>5</sup> A dose-response relationship has not been determined. Patient responses have been variable, such as some patients have died after receiving 160–200 mg, whereas other patients have survived after doses of 300–350 mg. It was also noted that the lack of recognition by the perioperative team of the characteristics of the TXA toxicity caused a delay in diagnosis. The severity of patient injury in a wrong drug intrathecal administration is typically related to the toxicity of the drug that is inadvertently administered.<sup>8</sup> When TXA is given intrathecally, it is a potent neurotoxin that can cause neurological injury, seizures, paraplegia, ventricular fibrillation, and death.<sup>9–12</sup> The Human Factors Analysis Classification System was used to assess and classify human and systemic factors that contributed to the errors. Mistaking look-alike TXA ampules or vials for local anesthetics was the predominant cause of the 22 events. The authors suggested that double checking the medication with another human or technology such as a barcode scanner could have possibly prevented the errors.

The same error occurring multiple times with the accidental administration of TXA into the intrathecal space warrants a call for implementation of reliable prevention strategies in every perioperative area.<sup>8,10–12</sup> In 2010, the Anesthesia Patient Safety Foundation (APSF) Stoelting Conference on Medication Safety developed recommendations for new strategies for “predictable prompt improvement” of medication use in the OR.<sup>12</sup> The implementation of many of the recommendations has not been

as widely adopted as safety experts would have liked. One of the recommendations was routine provider-prepared medications should be discontinued whenever possible and that high-alert medications should be prepared by pharmacy in a ready-to-use (bolus or infusion) form that is appropriate for both adult and pediatric patients.

The ISMP developed the hierarchy of effectiveness of risk-reduction strategies, which ranked various strategies for preventing errors from least to most effective (Figure 1).<sup>13</sup> Risk-reduction strategies such as



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Figure 1. ISMP’s hierarchy of effectiveness of risk-reduction strategies. High-leverage strategies are most effective because they can eliminate the risk of errors and associated harm by “designing out” hazards; however, they often require complex implementation plans. Medium-leverage strategies, which are easier to implement, reduce the likelihood of errors or minimize harm; however, they may need periodic updating and reinforcement. Low-leverage strategies, which aim to improve human performance, are easy and quick to implement; however, they are the least effective strategies for error prevention although frequently relied upon.



education, training, and policies are considered low-leverage strategies and are least effective. Although these practices do have some benefits, they rely on humans and have not been shown to be as effective as system-focused, high-leverage strategies. The risk-reduction strategies that are most effective for error prevention are forcing functions, barriers and fail-safes, automation, and computerization.<sup>13</sup> One such example of forcing function and fail-safe is the adoption of NRFit™ Neuraxial Connectors in Japan, which are designed to prevent misconnections and prevent wrong-route delivery of medications. This was made possible through advocacy with the Japan Ministry of Health, Labor, and Welfare.<sup>14</sup> Unfortunately, such efforts in the United States were met with resistance.<sup>15</sup>

Applying ISMP's hierarchy of the topmost effective risk-reduction strategies of using barriers and forcing functions is appropriate for TXA-associated intrathecal errors. This would involve restricting or eliminating TXA vials/ampules and only allowing manufacturer-prepared ready-to-administer TXA 1,000 mg per 100 mL bags or pharmacy-prepared IV bags. This strategy would likely create a constraint to avoid the look-alike problem with local anesthetic and TXA vials or ampules.

Removing vials of medications that cause patient harm from patient care areas is not a new concept. In the 1990s, concentrated potassium chloride vials were commonly stocked and readily available on patient care units. After the vials were found to have caused patient

deaths, a national movement began that only potassium chloride in a diluted form should be allowed in patient care units.<sup>16</sup>

### Medical-Legal Perspective

Medical malpractice claims arising from medication mix-ups, such as the one described in the case study above, are indefensible from a standard-of-care perspective. In addition to targeting the responsible clinicians, plaintiff's attorneys commonly assert negligence claims against facilities. This is particularly true when evidence or testimony comes to light to suggest the medication error was a consequence of the facility prioritizing labor efficiencies or other cost-saving measures over patient safety. These objectives are shortsighted and can lead to outcomes that harm both patients and the facility's bottom line. When medication errors result in catastrophic injuries, such as brain damage or death, patients and their families commonly seek millions of dollars in damages, particularly when patients require ongoing medical care or are unable to return to work.

In addition to civil litigation, clinicians who are responsible for medication administration errors may become the subject of licensing board investigations and criminal charges. While each board operates under its state's laws and regulations, some practice acts empower licensing authorities to pursue formal disciplinary action against clinicians in the wake of medication errors. At the facility level, medication errors can result in scrutiny from regulators and accrediting bodies, which can have significant implications from both financial and reputational standpoints.<sup>17</sup>

The need to report near misses and medication errors and to review systems issues at the department and hospital level in a nonpunitive manner cannot be overstated. In addition, having a system in place to provide appropriate confidential peer support when an event occurs will reduce the long-term negative impact that exists with a second victim.<sup>18</sup> Since peer review protections are generally established under state law, a hospital's ability to facilitate a meaningful analysis of these problems largely depends on its geographic location. In states lacking adequate protections, policymakers should pursue the adoption of laws that will enable facilities to



implement appropriate, confidential peer-review practices so clinicians are free to review and discuss clinical care without fear of information being used against them during litigation. These efforts mitigate reoccurrence of adverse events, encourage reporting, and improve patient outcomes.<sup>18</sup>

### Manufacturer's Perspective

To identify potential solutions, it is important to understand the complexity that results from the large and diverse number of suppliers for a particular product, including the variability in product appearance from one manufacturer to another. According to IQVIA (formerly Quintiles and IMS Health Inc.) data, currently, there are 13 companies that manufacture TXA for the U.S. market. The TXA presentation consists of vials (81.5%), premixed bags (16.9%) and ampules (1.6%). Eight companies manufacture bupivacaine, mostly in vials (98.7%) with some ampules (1.3%).<sup>19</sup>

While this diversity helps ensure a robust supply of these drugs, it also creates the potential for variability that can lead to product look-alikes. Manufacturers can incorporate an understanding of how drugs are stored into their packaging and labeling decisions, particularly in cases where products are stored together that are inherently higher risk, such as the combination of TXA and bupivacaine.

Another way manufacturers can help improve medication safety is by offering ready to administer (RTA) products. At the 2010 APSF Stoelting Conference on Medication Safety, manufacturer-prepared RTA products were not as prevalent as they are today. With the recent availability of manufactured RTA TXA 1,000 mg per 100 mL bags, implementing the APSF and ISMP recommendation to utilize preprepared dosage forms is a realistic and achievable means to prevent future TXA-bupivacaine errors.<sup>20</sup> Use of RTA products is recommended by major scientific and regulatory organizations including the Joint Commission.<sup>21-22</sup> Premixed bags and prefilled syringes do not require assembly at the point of care, which eliminates medication preparation steps where errors can occur.<sup>21-22</sup> In addition, FDA-approved manufacturer-prepared RTA products contain all required information on the manufacturer label and a barcode to help verify the proper drug and dose prior to administration, promoting safe medication delivery.<sup>23-24</sup> The FDA has a rigorous approval process for manufacturers seeking to introduce combination products integrating drugs and delivery systems. While a select number of manufacturers have

this manufacturing capability, the growing segment of RTA products signifies a pivotal advancement in medication delivery, offering enhanced safety measures.

### Preventing Medical Errors

#### Using Ready-to-Administer Products Can Reduce Medication Error

Providing forcing function and barriers as discussed above in having TXA available only in a premixed bag rather than in a vial form in the perioperative environment is the single most effective measure to reduce the incidence of wrong drug-wrong route TXA-bupivacaine errors. ISMP has included safeguards against wrong-route errors with TXA in the 2024–2025 ISMP Targeted Medication Safety Best Practices.<sup>25</sup> Some of the recommendations are listed below.

#### System Safeguards

- Use barcode-assisted medication safety checks, if available, when preparing and prior to administering medications in surgical and obstetrical areas.
- Develop protocols to use premixed intravenous (IV) bags of TXA or pharmacy-prepared infusion bags to prevent mix-ups.
- Foster culture of safety
- Maintain a high level of vigilance when these two medications are given during a case.
- Meet with key stakeholders to review their workflow when ordering and administering TXA to ensure safe practices.
- Evaluate workload to ensure workload pressures will not result in unsafe workarounds and practices.
- Report near misses and unsafe medication practices.
- Conduct regular reviews and discussions of medication events and close calls reported in your institution.

## Conclusion

Wrong drug-wrong route medication errors involving TXA and bupivacaine will continue to harm patients unless effective change is made. Regulatory authorities have the ability to work with stakeholders and impart this change. We have provided insight from multiple stakeholders with a commitment to help foster this change.

The authors of this article believe that TXA is a necessary and a beneficial medication for many surgeries and should continue to be available in the perioperative areas. However, TXA vials or ampules should be removed from the perioperative areas and RTA 100 mL bags from either the manufacturer, 503 B compounding facility, or institution's pharmacy should be the sole TXA dosage form available in the perioperative areas. The cost of a premixed bag may vary by regions, contracts, discounts, group purchasing organizations, and suppliers, and this cost is inconsequential when compared to the cost of a medication error involving significant morbidity and mortality. The time to act is now.

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*Tricia Meyer is a speaker for Eagle Pharmaceutical and has consulted for Heron.*

*The remaining authors have no additional conflicts of interest.*

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## In This Issue - Reprinted with APSF Permission

Preferred Physicians Medical recently collaborated with a multidisciplinary group of professionals to publish an article in the *APSF Newsletter* about a concerning loss trend we have identified involving a particular wrong-drug, wrong-route medication error: tranexamic acid (TXA) inadvertently administered intrathecally during neuraxial blocks. Since PPM first addressed this medication error in *Anesthesia & the Law* Issue 44 in 2017, seven additional TXA-bupivacaine mix-ups have been reported to our company. Most alarming, five of these events occurred within the last 12 months. A total of nine events involving a bupivacaine and TXA mix-up have been reported to PPM, including five within the last 12 months. In this issue, we reprint the article, “Unraveling a Recurrent Wrong Drug-Wrong Route Error—Tranexamic Acid in Place of Bupivacaine: A Multistakeholder Approach to Addressing this Important Patient Safety Issue.” Like the authors, PPM strongly encourages our insureds to promptly implement high-leverage risk reduction strategies to prevent these catastrophic medication errors from occurring. In particular, anesthesia professionals should advocate for the removal of TXA vials from operating rooms. Instead, TXA infusion bags should be prepared before procedures by perioperative pharmacists. Alternatively, facilities should procure ready-to-administer TXA products from suppliers or prepared spinal kits with local anesthesia medications included. If these options are not feasible, anesthesia professionals should engage stakeholders at their facilities to ensure TXA vials and ampules are never stored in close proximity to local anesthetics. Finally, the anesthesia provider responsible for the surgery must ensure that spinal anesthetic syringes are separated in time and space from other medications to be utilized during the anesthetic.

**Note:** The purpose of this newsletter is to provide information to policyholders and defense counsel regarding professional liability issues. Risk management analysis is offered for general guidance and is not intended to establish a standard of care or to provide legal advice.

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