

Acute Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Accidental injection of topical thrombin continues



In late 2016, CHPSO, one of the largest federally designated patient safety organizations, created in 2008 by the California Hospital Association, published a case report about accidental intravenous (IV) administration of **RECOTHROM** (recombinant topical thrombin).¹ The PSO identified additional cases of accidental injection into wounds and a series of close calls among its database of reported errors. In 2007 and 2008, ISMP published two articles^{2,3} highlighting the danger of giving topical thrombin intravascularly, which included several fatal events.² In one case, a physician reconstituted topical thrombin and instilled it into the intravenous track of a centrally placed catheter that had been removed and was still oozing blood. Within minutes, the patient arrested and died. In another case, a surgical patient was accidentally given thrombin 5,000 units intravenously. Soon after, the patient arrested, and resuscitation efforts were unsuccessful.

Given the ongoing, potentially harmful errors and close calls identified by CHPSO, we obtained permission to publish the CHPSO article¹ with minor edits.

Background

Thrombin, a component in the coagulation cascade, can be used for topical hemostasis or off-label to treat pseudoaneurysm by direct injection. Topical thrombin is meant only for application to the surface of tissues to stop oozing blood and minor bleeding from capillaries and small venules or from areas surrounding vascular access sites, percutaneous tubes, or catheters. It is also employed in the treatment of epistaxis. Topical thrombin should never be allowed to enter large blood vessels because extensive intravascular coagulation and death may result. It has long been known that inadvertent IV injection can be rapidly fatal. In a study published in 1990, rabbits died within 30 seconds of IV injection of thrombin.⁴

Packaging could lead to IV administration

The vial-and-syringe packaging of some topical thrombin products makes them look like they might be parenteral products. However, most thrombin formulations currently available avoid including a Luer-tip syringe in the reconstitution kit to minimize the risk of mistaking the final product as an IV-safe medication. Recothrom, a recombinant thrombin preparation, does not; Luer-tip syringes are provided in the kits along with labels, which are intended to be affixed to the Luer-tip syringes when preparing the reconstituted final product. Unfortunately, the combination of an easily forgotten step—attaching the label—and a Luer tip that attaches to an IV connector increases the risk of an administration error, despite labeling on the thrombin vial that warns against injecting the product. Since Recothrom is the only available human recombinant thrombin, it may be necessary to continue its use in many settings, as the other available forms of thrombin (bovine, human-pooled plasma) have their own drawbacks.⁵

Recent case report

A patient was receiving both IV coagulation factor for hemophilia and topical recombinant thrombin (Recothrom) to treat surgical wound oozing. The nurse took both syringes con-

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SAFETY briefs



Fatal route of administration recommended in journal. An article in *Hematological Oncology* (Yellu MR, et al. Overview of recent trends in diagnosis and management of leptomeningeal multiple myeloma. *Hematol Oncol.* 2016;34[1]:2-8) lists chemotherapy agents that can be used to treat leptomeningeal multiple myeloma intrathecally (IT), including methotrexate, cytarabine, dexamethasone, and thiotepea. VinCRiStine was also listed, but of course giving this by the intrathecal route would be a fatal mistake. The specific error appears in two places in the publication, including in the article text and in a table. The journal has agreed to retract the article, including removal of online access. But it shows how mistakes can be made even in respected peer-reviewed publications, so don't immediately accept everything you read, especially when a recommendation seems questionable.

This is similar to another case we published in 1994 (Cohen MR. Hazard warning-vinCRiStine overdose. *Hosp Pharm.* 1994;29:53) in which the use of a dash mark in a cancer journal (Lopez TM, et al. Small noncleaved continued on page 2—[SAFETY briefs](#) >

ISMP Survey on Verbal Orders

Pharmacists and nurses: We are interested in learning more about the use of verbal orders for new medication orders by telephone or face-to-face (but not including order clarifications). Do you still receive verbal orders, given the significant increase in electronic prescribing? We'd like to know which drug classes you most commonly receive verbal orders for, and how often you have the opportunity to read back verbal orders. Please participate in our short survey (see page 5) by visiting: www.ismp.org/sc?id=2851, and submit your responses by **March 3**.

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taining the IV coagulation factor and the Recothrom into the patient's room. After being interrupted by other urgent care needs, the nurse accidentally picked up the Recothrom syringe and administered the product intravenously. The patient coded but was successfully resuscitated, largely because the nurse quickly recognized and acknowledged the error, enabling the code team to provide appropriate and timely treatment. While the treatment provided to this patient was not disclosed, the literature describes successful treatment of accidental thrombin infiltration with antithrombin and heparin.⁶

Additional case reports

A search of the CHPSO database found other errors associated with topical thrombin.

- After a personnel change in the operating room (OR), an unlabeled syringe of Recothrom was confused with lidocaine and infiltrated into the wound.
- During surgery, an unlabeled medicine cup of thrombin was mixed with a local anesthetic and injected into the wound.
- During surgery, a steroid injection and Recothrom were drawn up in syringes and passed to the surgeon together when only the steroid injection was needed. The error was noticed prior to injecting both medications.
- During surgery, what was thought to be a cup of heparin on the table was actually thrombin. The error was discovered prior to use.
- A nurse reconstituted Recothrom believing it was Factor VIII and was about to administer the product IV. Just then, a pharmacy technician delivered the syringe of Factor VIII to the nurse. The error was noticed, and the Recothrom, intended to be used to control bleeding at an IV site, was not administered via the wrong route.
- A medication cart in the cardiothoracic OR was supplied with Recothrom instead of antithrombin III, due to the similarity of the generic product names (thrombin, antithrombin). The error was discovered when the anesthesiologist was preparing the patient for cardiopulmonary bypass, after retrieving what she initially thought was antithrombin III from the cart.
- A radiologist asked a nurse to pick up Recothrom from the pharmacy. The nurse returned with a syringe of antithrombin III, which was injected into a pseudoaneurysm. After no response to the injection, the error was identified and the patient was successfully treated with Recothrom. Investigation showed multiple episodes of confusion between "human thrombin" and "human antithrombin" by nurses, pharmacists, and the radiologist as one cause of the error.

Recommendations to prevent errors

To use topical thrombin products safely, continued scrutiny of use of these products in surgical and procedural areas is required, as these are common sites of use and frequent locations of events reported to CHPSO and ISMP. The recommendations to prevent errors with topical thrombin from the 2007 and 2008 ISMP newsletters^{2,3} are still relevant. A summary of these recommendations follows:

- Apply auxiliary warning labels to vials and final reconstituted products in syringes and bowls/cups, making it clear the drug should only be administered topically.
- Whenever possible, have the pharmacy dispense the reconstituted thrombin with appropriate warning labels, including doses used in the OR or procedural areas.
- Never leave a topical thrombin vial or syringe at the patient's bedside, as it can later be confused as a parenteral product.
- Sequester or separate topical thrombin from parenteral products once drawn into a syringe or placed into a cup or bowl on the sterile field.
- Communicate the presence of topical thrombin when placing it on the sterile field.

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cell lymphoma in adults: superior results for stages I-III disease. *J Clin Oncol.* 1990;8[4]: 615-22) contributed to an accidental overdose of vinCRISStine. A protocol in the article called for "vinCRISStine 1.4 mg/m² days 1-8." This should have been listed as "days 1 and 8," but doctors, pharmacists, and nurses interpreted the dash to mean days 1 through 8. The patient received daily doses for 3 days until painful peripheral neuropathy developed. The error was later recognized upon closer review of the case. It's important to ensure that all who prescribe, dispense, and administer chemotherapy are qualified to manage the use of these specialized high-alert medications. Such staff would be in the best position to recognize and prevent a potentially fatal overdose.



Educate fluorouracil home infusion patients about accidental overinfusion.

We recently received a call from a family member of a patient with cancer who was to receive a 7-day infusion of fluorouracil at home via an ambulatory elastomeric infusion pump. For an unknown reason, the entire infusion ran in over 4 days. The patient was very sleepy for the next 2 days and had "terrible diarrhea." Even though the infusion was empty, they waited until the patient's scheduled appointment 4 days later to report the mishap. The doctor hospitalized the patient and treated the patient with IV hydration. It's unclear why the antidote uridine triacetate was not administered, but the safety and efficacy of uridine triacetate initiated more than 96 hours following the end of fluorouracil or capecitabine administration has not been established. The patient was discharged after 7 days of hospitalization.

We are learning more about the pump issue that occurred, but this incident points to the need to educate patients with ambulatory infusion pumps about specific details in regards to how the pump works, what to expect over the course of the treatment, infusion rates, how long the infusion should last, how much should be left in the container each day, and the need to immediately report any incident to their care team should

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Try to delay placing it there until all parenteral products have been administered.

- Consider using spray kits for topical thrombin. However, if a syringe is used for reconstitution, never leave it unlabeled before attaching the spray mechanism.
- To help differentiate the topical product from parenteral products, consider using the topical thrombin in powder form on oozing surfaces or adding it to an absorbable gelatin sponge.

Additional recommendations from CHPSO and ISMP include the following:

- Avoid placing or dispensing topical products in Luer-tip syringes. For example, unless the order is for use in a pseudoaneurysm, the pharmacy should transfer Re-cothrom from the kit's Luer-tip syringe into an oral or topical syringe.
- Label all bowls, cups, syringes, and containers of medications and solutions used in the OR with the name (and strength/dose, if appropriate) of the drugs or solutions, both on and off the sterile field. Note that this is also a Joint Commission standard.
- Sequester topical thrombin away from injectable products in storage areas in the pharmacy, OR, and other procedural areas.
- The terms "human thrombin" and "human antithrombin" can be confused, so take measures to differentiate the two.

References

- 1) CHPSO. Recothrom: error-prone packaging. 2016. www.ismp.org/sc?id=2845
- 2) ISMP. Danger of giving topical thrombin intravascularly. *ISMP Medication Safety Alert!* 2007;12(3):2-3. www.ismp.org/sc?id=2846
- 3) ISMP. Risk of IV administration of topical thrombin products. *ISMP Medication Safety Alert!* 2008;13(22):3.
- 4) Wesley JR, Wesley RE. A study of the lethal effects of intravenous injection of thrombin in rabbits. *Ann Ophthalmol.* 1990;22(12):457-9.
- 5) Lomax C. Safety of topical thrombins: the ongoing debate. *Patient Saf Surg.* 2009;3:21. www.ismp.org/sc?id=2847
- 6) Nielsen VG, Paidy SR, McLeod W, et al. Treatment of accidental perianal injection of topical thrombin with intravenous antithrombin. *JThrombThrombolysis.* 2016 Oct 28. doi:10.1007/s11239-016-1447-z.

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the container empty sooner than anticipated. Dangerous delays have been known to occur because patients are often asymptomatic in the first few hours and days. But rapid identification of an overdose allows prompt treatment with the antidote to minimize serious side effects and the risk of a harmful or fatal outcome. Patients need to be educated about rapidly reporting events so an antidote can be administered.

**Soy lecithin long gone from Atrovent and Combivent products.**

We received an inquiry last month about peanut allergy concerns when prescribing **ATROVENT** (ipratropium) given that the current package insert does not list this as a warning or contraindication. At one time, prescribing information for Atrovent Inhalation Aerosol and **COMBIVENT** (ipratropium and albuterol) Inhalation Aerosol stated that these products were contraindicated in patients with hypersensitivity to soy lecithin (previously an inactive ingredient in these products) or related products such as soybeans and peanuts. A 1998 ISMP article (www.ismp.org/sc?id=2849) described the issue when we received a report about a patient who developed anaphylaxis after receiving what was reported to be Atrovent Inhalation Aerosol.

However, by the end of 2013, both products had been reformulated to be in compliance with rules to reduce chlorofluorocarbons (CFC) aerosol propellants, which decrease the ozone layer, and soy lecithin was removed as an inactive ingredient at that time. Thus, currently available Atrovent HFA and Combivent Respimat inhalers do not contain CFC or soy lecithin. Therefore, an allergy to soy lecithin or peanuts is no longer an issue with these drugs. More information is available from the American Academy of Allergy, Asthma & Immunology at: www.ismp.org/sc?id=2850.

Incidentally, after the 1998 incident was reported, follow-up information was obtained that indicated the patient had received Atrovent solution by nebulization. But Atrovent solution for nebulizers never contained soy lecithin. This was clarified in our November 4, 1998 newsletter.

**Concomitant use of Entresto and ACE inhibitors can lead to serious outcomes**

PROBLEM: **ENTRESTO** (sacubitril/valsartan) is an angiotensin II receptor-neprilysin inhibitor (ARNI) used to reduce the risk of cardiovascular death and hospitalization in patients with chronic heart failure and reduced ejection fraction. It contains the angiotensin II receptor blocker (ARB) valsartan and the neprilysin inhibitor sacubitril. Entresto is contraindicated with concomitant use of angiotensin converting enzyme (ACE) inhibitors because the inhibition of neprilysin from the sacubitril component in Entresto combined with an ACE inhibitor increases the risk of angioedema.¹ Also, the dual renin-angiotensin-aldosterone system blockade that occurs when valsartan is combined with ACE inhibitors increases the risk of hypotension, acute kidney injury, and hyperkalemia. Thus, Entresto should not be administered within 36 hours of switching from or to an ACE inhibitor. Still, the US Food and Drug Administration (FDA) has received 55 cases reporting concomitant use of Entresto and an ACE inhibitor, with several cases describing serious outcomes.

The cases submitted to FDA describe patients who were taking an ACE inhibitor and were prescribed Entresto, and patients who started taking Entresto in the hospital and inadvertently restarted their ACE inhibitor after discharge. Several cases described a washout period of less than 36 hours when switching from an ACE inhibitor to Entresto. Eleven patients were hospitalized. The most common adverse events reported due to this drug interaction were angioedema, hyperkalemia, acute kidney injury, and hypotension.

Entresto is used to lessen morbidity and mortality, and replaces an ACE inhibitor or ARB in
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patients with chronic symptomatic heart failure (NYHA class II or III) with a reduced ejection fraction (HFrEF) who tolerate an ACE inhibitor or ARB.² Due to the previous standard of care, many patients starting Entresto are already taking ACE inhibitors. This could lead to serious adverse events if the ACE inhibitor is not discontinued, or if the patient continues taking the previously prescribed ACE inhibitor at home. These errors may be related to the lack of familiarity with Entresto. But since approval in 2015, the drug's use has increased. It was added in the updated 2016 heart failure guidelines published by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA). The new guidelines recommend either an ACE inhibitor, an ARB, or an ARNI (e.g., Entresto) for patients with chronic HFrEF, but **not** in combination (Table 1, prepared by ISMP).

Table 1. ACE inhibitors/ARBs to avoid with Entresto

ACE Inhibitors	ARBs
benazepril (LOTENSIN)	azilsartan (EDARBI)
captopril	candesartan (ATACAND)
enalapril (VASOTEC)	
enalaprilat	eprosartan (TEVETEN)
fosinopril	
lisinopril (PRINIVIL, ZESTRIL)	irbesartan (AVAPRO)
	losartan (COZAAR)
moexipril	olmesartan (BENICAR)
perindopril (ACEON)	
quinapril (ACCUPRIL)	telmisartan (MICARDIS)
ramipril (ALTACE)	
trandolapril (MAVIK)	valsartan (DIOVAN)

SAFE PRACTICE RECOMMENDATIONS: Please consider the recommendations below to help prevent the concomitant use of Entresto and ACE inhibitors.

For Prescribers, Pharmacists, and Nurses:

- Prior to prescribing Entresto, ensure that patients are not already taking an ACE inhibitor. For patients taking an ACE inhibitor, ensure that it is stopped and allow for a 36-hour washout period prior to starting Entresto.
- Work with information technology (IT) staff to create and/or enable order entry system alerts to warn against the concomitant use of Entresto and ACE inhibitors when both of these drugs have been prescribed for the patient. If possible, configure the alert to continue for 36 hours after Entresto or the ACE inhibitor has been discontinued.
- Before dispensing or administering Entresto, review patients' medication regimens. If ACE inhibitors are listed, ensure that patients have discontinued the ACE inhibitor and wait 36 hours before starting Entresto.
- Educate patients about the importance of not taking Entresto and ACE inhibitors together.
- Conduct a thorough medication reconciliation (on admission and at discharge) to ensure that patients who are prescribed Entresto, but were taking an ACE inhibitor or ARB in the past, do not restart it upon discharge from the hospital.

For Insurers:

- Create alerts to warn against the concomitant use of Entresto and ACE inhibitors when claims are submitted for both drugs.

References

- 1) Entresto [package insert]. Novartis Pharmaceuticals Corporation. East Hanover, NJ; Aug 2015. www.ismp.org/sc?id=2848
- 2) Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Failure Society of America. *Circulation*. 2016;134(13):e282-93.

ISMP thanks Ashleigh Lowery, PharmD, BCCCP, at the US Food and Drug Administration (FDA) Division of Medication Error Prevention and Analysis, for providing this article.

Special Announcements

ISMP webinars

January 25: Starting at the Top: Strategies to Enhance the Safety of Prescribing Practices

Learn about frequent harmful errors involving breakdowns in the prescribing process, along with first-hand observations of the organizational factors that contribute to prescribing errors and the challenges hospitals face making improvements.

February 23: Medication Safety Success Stories: Implementation of ISMP's Targeted Medication Safety Best Practices

Participants will learn about the barriers that exist to fully implementing these safety strategies. Our speakers will present their success stories and list a number of strategies they used to overcome the barriers.

To register, visit: www.ismp.org/sc?id=349.

Welcome to new ISMP Fellow

ISMP welcomes **Ghadeer Banasser**, PharmD, CPHQ, as one of our newest **ISMP Safe Medication Management Fellows** for 2016-2017. Before the Fellowship, Ghadeer worked as a Pharmacy Quality Management Specialist at King Abdulaziz Medical City-Jeddah, Saudi Arabia, and was a member of their regional Medication Safety Program. Ghadeer will be with us through November.

To subscribe: www.ismp.org/sc?id=382



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ISMP Survey on Verbal Orders

Pharmacists and nurses: We would appreciate your help with a brief survey. We are interested in learning more about the ongoing use of verbal orders for new medication orders by telephone or face-to-face (but not including order clarifications). Do you still receive verbal orders, given the significant increase in electronic prescribing? We'd like to know which drug classes you most commonly receive verbal orders for, and how often you have the opportunity to read back verbal orders (receive, transcribe, and read back, not just repeat back). Any comments you have would also be appreciated. Please take the survey by visiting: www.ismp.org/sc?id=2851, and submit your responses by **March 3**. Thank you for your help!

1 Please indicate your country of practice:

- USA International

2 Please indicate your profession:

- Pharmacist Nurse Other (please specify): _____

3 Please indicate your practice location:

- Hospital Ambulatory clinic/facility Community/retail pharmacy
 Ambulatory pharmacy within a healthcare facility Long-term care facility
 Other (please specify): _____

4 If you work in a hospital, in which unit(s) do you work? (select all that apply)

- Emergency department Medical/surgical unit Intensive care unit Operating room
 Telemetry unit Cardiac catheterization lab Interventional radiology
 Endoscopy unit Obstetrical unit Specialty unit (please specify): _____
 Behavioral health Ambulatory surgery
 Ambulatory clinic within the hospital (please specify type): _____
 Inpatient pharmacy Outpatient pharmacy Other (please specify): _____

5 During the past 12 months, which method(s) have been used to communicate verbal orders? (select all that apply)

- Telephone Spoken (face-to-face) Voicemail
 We do not receive any verbal orders (please exit the survey if you receive no verbal orders)

6 During the past 12 months, what percentage of all orders did you receive as verbal orders, irrespective of mode of communication (e.g., telephone, spoken [face-to-face], voicemail)?

- 0% 1% to 5% 6% to 25% 26% to 50% More than 50%

7 During the past 12 months, what percentage of the time did you read back verbal orders (receive, transcribe, and read back, not just repeat back), regardless of the communication method, to ensure the accuracy of the verbal order? Please exclude verbal orders issued during codes or under sterile conditions in the operating room or invasive procedural areas where the orders cannot be transcribed and read back.

- 0% 1% to 5% 6% to 25% 26% to 50% More than 50%

8 During the past 12 months, for which medication classes have you received verbal orders? (select all that apply)

- Analgesics (not controlled substances) Analgesics (controlled substances)
 Other controlled substances (not analgesics) Fluids for hydration
 Blood pressure control agents Anti-infectives
 Anticoagulants Oncologic/chemotherapy Antidiabetic medications
 Antipsychotic, antianxiety, and sleep agents Gastrointestinal agents
 Respiratory agents Anticoagulation reversal Electrolytes (e.g., potassium rider)
 Emergency drugs (e.g., antihistamines, glucose elevating agents, anticonvulsants)
 Antiemetics Other medication categories (please specify): _____

9 During the past 12 months, are you aware of any errors that have occurred at your facility due to mishearing, misunderstanding, or mistranscribing verbal orders?

- No Yes. If yes, please describe: _____

Please leave any additional comments you may have about verbal orders:

Safe Medication Management Fellowships

ISMP is now accepting applications for three unique **2017-2018 Fellowship** programs

One ISMP Safe Medication Management Fellowship

Location and Term: This 12-month Fellowship, sponsored by **Baxter International Inc.**, commences summer 2017 at the Horsham, Pennsylvania (near Philadelphia) office of ISMP. Relocation to the Horsham/Philadelphia area is required.

Description: The Fellowship **offers a nurse, pharmacist, or physician with at least 1 year of postgraduate clinical experience** an unparalleled opportunity to learn from and work with some of the nation's experts in medication safety. This Fellowship is open to US citizens only. Now in its 25th year, the Fellowship allows the candidate to work collaboratively with practitioners in various healthcare settings to assess and develop interdisciplinary medication error-prevention strategies.

Sponsored by: **Baxter**

Two FDA/ISMP Safe Medication Management Fellowships

Location and Term: These 12-month Fellowships commence August/September 2017. The Fellows will spend 6 months at the Horsham, Pennsylvania (near Philadelphia) office of ISMP and 6 months at the Silver Spring, Maryland (near Washington, DC) office of the US Food and Drug Administration (FDA). Relocation to the Horsham/Philadelphia and Silver Spring/Washington, DC, area is required.

Description: The Fellowships, **open to healthcare professionals with at least 1 year of postgraduate clinical experience**, are a joint effort between ISMP and FDA's Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, and Division of Medication Error Prevention and Analysis. These Fellowships are open to US citizens only. The Fellowships allow candidates to benefit from ISMP's years of experience devoted to medication error prevention. At FDA, valuable regulatory experience is gained by working with the division focused on medication error prevention.

A competitive stipend, paid vacation, and health benefits are provided with all Fellowship programs.

How to Apply

Information and applications can be found at: www.ismp.org/profdevelopment/.
Applications can also be requested by calling 215-947-7797.

The application deadline for all Fellowship Programs is March 31, 2017.