

MEDICATION SAFETY IN SECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

ANTIDOTE FOR FLUOROURACIL OVERDOSE: A REMINDER TO REVIEW VA PRACTICES FOR PREVENTION AND TOXICITY MANAGEMENT

Submitted by: Bernadette (Berni) Heron, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, VHA Pharmacy Benefits Management Services

The FDA approval of uridine triacetate (Vistogard, by Wellstat Therapeutics) brings renewed interest into the cause of fluoropyrimidine overdoses, as well as the methods to prevent them. Uridine triacetate received FDA approval in December 2015, following expedited review, for patients who have received an overdose of fluoropyrimidines (e.g. fluorouracil or capecitabine) or who exhibit early onset life-threatening toxicity from fluoropyrimidines.¹

Uridine triacetate was studied in two compassionate use, open-label trials. These trials were conducted in the United States, Europe, Canada and Australia. Both pediatric and adult populations were included. Patients were eligible to receive uridine triacetate if they had received an overdose of a fluoropyrimidine (e.g. fluorouracil or capecitabine) or

if they presented with early onset severe toxicity. Out of a total of 173 patients treated with uridine triacetate, 147 patients received the antidote secondary to fluoropyrimidine overdose. The most common causes of fluorouracil overdose were due to (1) infusion pump programming errors (2) pump malfunction and (3) miscalculation of infused doses. Causes of capecitabine overdose include children (n=3) accidentally ingesting a relative's medication and adult (n=6) suicide attempts.²

Fluoropyrimidines have been a mainstay of anticancer therapy for years. They have been an essential component in the management of many solid tumors such as colorectal, pancreatic, head and neck, breast and gastric malignancies. Fluorouracil is not orally bioavailable and therefore administered as an injectable formulation for cancer indications. Many

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VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

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NEWSWORTHY...

from the pbm

- Look-Alike/Sound-Alike Confusing Name Pairs Specific to VA: UPDATED LINKS - [Cumulative VA LASA list 2016](#); [VA LASA list 2016](#)

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from the fda (continued from page 1)

CONTRAST AGENTS

[FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs: review to continue](#)

5/22/2017

FDA evaluated adverse event reports associated with gadolinium-based contrast agents (GBCAs) in scientific publications and those submitted to FDA. These publications and reports show gadolinium retention in organs such as the brain, bones, and skin, with *linear* GBCAs causing collection of more gadolinium in the brain compared to *macrocytic* GBCAs. FDA's review did not identify adverse health effects related to this brain retention. A recent review by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) also observed no adverse health effects with gadolinium retention in the brain, but that Committee recommended suspending the marketing authorization of certain *linear* GBCAs because they cause a greater retention of gadolinium in the brain compared to *macrocytic* GBCAs. FDA continues to assess this safety issue and will update the public when new information becomes available.

As previously stated in [Issue 7; Volume 5; July/August 2015](#) FDA continues to recommend that providers should:

- Consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary; and
- Reassess the necessity of repetitive GBCA MRIs in established treatment protocols.

ENDOCRINOLOGY

[FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects](#)

05/10/2017

FDA continues to review fluoroquinolone antibiotics. Findings from published studies and patient cases identified by the FDA do not support reports that these medicines may result in retinal detachment or aortic aneurysm and aortic dissection. FDA will update the public as needed.

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regimens include fluorouracil given as intermittent bolus doses, or as continuous intravenous infusions. Depending on the disease and regimen, continuous intravenous infusions of fluorouracil may be delivered over 24 – 120 hours or lower doses can be given over 21 days as an adjunct to radiation therapy.

The National Institutes of Health reports more than a quarter million Americans receive fluorouracil annually. Approximately 8000 have a toxic reaction and ~ 1300 die due to toxicity.³ The recent availability of a commercial antidote is a good reminder to evaluate practices for dispensing and administering fluorouracil in our VA facilities. Despite best practices, overdoses may occur. In addition to optimizing our procedures to **prevent** overdose, procedures to **manage** a suspect overdose are equally important. The Acute Care ISMP newsletter reminds us of steps to prevent errors as well as manage toxicity.⁵

Preventing Errors

- **Prescriptive orders should be clear.** Fluorouracil should be ordered as a single daily dose with instructions to infuse continuously over a specific time period (e.g. number of days or hours).
- **Ensure chemotherapy competency.** Review certification processes of all staff who order, dispense and administer chemotherapy. Ensure that an appropriate level of competency is achieved before staff work independently and maintained while working with chemotherapy.
- **Utilize infusion pumps with safeguards.** The need to infuse a drug over a prolonged period necessitates the use of programmable infusion pumps. Use only one type of ambulatory pump throughout the facility, to avoid confusion and

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Getting the most from our safety surveillance

DIGOXIN MONOTHERAPY FOR ATRIAL FIBRILLATION: CONSIDER ALTERNATIVES WHEN APPROPRIATE

Submitted by: Muriel Burk, Pharm.D.

Recent findings on all-cause mortality in patients with atrial fibrillation (AF) in the absence of heart failure (HF) prompted a medication use evaluation (MUE) of digoxin monotherapy within the VA. Results from TREAT-AF (The Retrospective Evaluation and Assessment of Therapies in Atrial Fibrillation), a study that evaluated data in Veteran patients, suggested an association between treatment with digoxin and mortality.¹ Results of this analysis, along with additional retrospective evaluations, may have implications for clinical practice, especially in patients prescribed digoxin for rate control in AF, and where other effective therapies are available, although, data are conflicting.²⁻⁶

Analysis	All-Cause Mortality HR (95% CI)	p-value
TREAT-AF¹		
Digoxin vs. No Digoxin	1.21 (1.17 to 1.25)	<0.001
HF diagnosis	1.28 (1.21 to 1.36)	NS for interaction
AFFIRM (Whitbeck et al)³		
Digoxin vs. No Digoxin	1.41 (1.19 to 1.67)	<0.001
HF diagnosis	1.41 (1.09 to 1.84)	0.010
No HF diagnosis	1.37 (1.05 to 1.79)	0.019
AFFIRM (Gheorghiadu et al)⁴		
Digoxin vs. No Digoxin	1.06 (0.83 to 1.37)	0.640
HF diagnosis	1.08 (0.80 to 1.47)	0.609
No HF diagnosis	1.08 (0.69 to 1.69)	0.743
RACE II* (Mulder et al)⁵		
Digoxin vs. No Digoxin	0.41 (0.19 to 0.89)	NA

* Included patients with HF (~ 65% NYHA Class I; ~ 30% Class II; ~ 5% Class III)

The goal of this MUE was to assess Veterans with AF without HF, who were on digoxin monotherapy with no prior or concomitant use of guideline-preferred therapies, beta blockers or non-dihydropyridine calcium channel blockers (target population). Volunteer VA Medical Centers (VAMCs) conducted chart reviews to confirm target population criteria and collect the following data: contraindications to preferred AF therapy; indication, dose, and duration of digoxin therapy; monitoring of serum chemistries and digoxin levels; prescriber specialty; demographics. Reviewers used clinical judgment to adjudicate whether a patient could benefit from discontinuation of digoxin and initiation of preferred therapy. The abstraction tool created site-level summaries that were submitted to the coordinating center where they were averaged for report.

Sixteen VAMCs reviewed 323 patients meeting criteria. The mean patient age was 80 years, and 72% of patients were co-managed by VA and non-VA physicians. Many (64%) received care at a VA community-based outreach clinic. Digoxin prescriptions were first ordered by primary care in 58% of patients

and renewed by primary care in 92%. Eighty-eight percent had a documented indication for digoxin, while 3% had a documented risk/benefit assessment for digoxin monotherapy. Fifty-eight percent had been on digoxin for > 6 years. Contraindications or past intolerance to preferred therapy was documented in 6%. Co-morbidity of potential concern was present in 44% of patients. Reviewers adjudicated that 61% of patients would benefit from re-evaluation of digoxin therapy.

Results revealed that few patients on digoxin monotherapy had a contraindication to treatment with current preferred AF therapy. The cohort's long duration of digoxin therapy and advanced age likely reflect prescribing habits from an era with different treatment standards for AF. The high rates of co-management and primary care renewals present an opportunity for provider education, and suggest the need for improved VA/non-VA provider communication.

Providers should recognize that digoxin is not recommended as first-line therapy for AF to control ventricular rate; rather, beta blockers or nondihydropyridine (non-DHP) calcium channel blockers (CCB) are preferred.⁷ Digoxin may be considered in combination with a beta blocker or non-DHP CCB for patients not controlled on initial therapy. Digoxin can be beneficial in patients with Heart Failure with reduced Ejection Fraction (HFrEF), unless contraindicated, to decrease hospitalizations for HF.⁸

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maintain consistency. Technology of infusion pumps has evolved over time, with programs capable of alerting clinicians of potential unsafe therapy during pump programming. Smart pumps, as they are commonly called, include dose error-reduction software to maximize safety features such as dose alerts, dosing, flow rate limits and operator feedback. One of the ISMP Safety Best Practices for 2016-2017 includes the use of programmable infusion pumps with dose error-reduction software for the administration of high-alert intravenous infusions. High-alert medications are defined as those drugs that bear a heightened risk of causing significant patient harm if given in error.⁶

- **Educate staff and validate competency.** Staff education for programming and connecting infusion pumps is essential. Ensure ongoing competency validation is maintained.
- **Enhance independent double checks.** Encourage the staff to use critical thinking skills while preparing and checking chemotherapy. Devise a structured process to perform and document independent double checks following preparation and prior to administration. Consider the use of checklists to help facilitate the order check process. As there may be times when only one practitioner is on duty, develop a process so that staff may conduct and document independent double checks, if necessary.
- **Standardize pharmacy labels.** Ensure prominent display of key information necessary to program an infusion pump (e.g. total volume, concentration, hourly rate of infusion) on the pharmacy label. Eliminate extraneous information that may lead to confusion (e.g. milliliters [mL] per 24 hours). Communicate infusion rates as an hourly rate only and verify that the specific version of your infusion devices used by your institution allow programming in mL per hour.
- **Educate patients.** Teach patients and caregivers about the drug they are prescribed. If receiving fluorouracil via infusion pump, inform patients and caregivers about the total dose, and length of time the infusion should last. Instruct them to report symptoms and to call with questions or concerns. Periodically check in on them to ensure the drug volume is not infusing too quickly.

Managing Toxicity

- **Develop treatment protocols for overdose situations.** Establish a plan so that decisions can be made promptly when an overdose is identified. Another ISMP New Best Practice for 2016-2017 includes having appropriate antidotes, reversal and rescue agents readily available. In addition, standardized protocols and/or order sets should be in place to facili-

tate emergency use, as well as readily available instructions for use.⁶ Clear instructions on how to obtain uridine triacetate should be available within inpatient and outpatient oncology areas, the emergency department and the pharmacy. Uridine triacetate is on the VA National Formulary with Criteria for Emergency Use. The Criteria also contain VA ordering information, as well as dosing and administration for either oral or enteral routes. This document may be accessed internally within the VA system via: <https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Forms/AllItems.aspx?RootFolder=%2Fcmop%2FPBM%2FClinical%20Guidance%2FCriteria%20For%20Use&FolderCTID=0x0120006BA3B2280F536A41A2C5A1B0F4AFC943&View={43999405-C9A2-47A4-AE17-15518717FA3E}>

- **Recognize overdoses and toxicity promptly.** Staff who administer and/or monitor patients who receive fluorouracil should be aware of the signs and symptoms of early onset drug toxicity and overdose. Education to those who triage calls from patients regarding the onset and severity of fluoropyrimidine-related signs and symptoms is essential to prompt management of potentially serious clinical situations.^{4,5}
- **Provide prompt treatment.** When an overdose or early-onset toxicity is identified, uridine triacetate should be administered within 96 hours of the overdose. Establish an account for your facility with Cardinal Health (pharmaceutical distributor) in advance of having to provide it for a first case to reduce delivery time. While awaiting procurement of the antidote, consider admitting patients to an inpatient unit and provide supportive care provided to reduce symptom severity. Examples of supportive care that may be needed include intravenous hydration, electrolyte replacement, management of diarrhea, mouth and skin care, granulocyte colony-stimulating factor administration, continuous cardiac monitoring.
- **Avoid contraindicated medications.** Drugs that might interfere with the clearance of fluorouracil or capecitabine should be avoided in these situations. Examples include metronidazole, leucovorin, cimetidine and thiazide diuretics.
- **Monitor patient closely post-hospitalization.** Fluorouracil overdoses may cause delayed toxicity, therefore patients should be closely monitored post-hospitalization for these delayed adverse effects, especially throughout the neutrophil nadir.⁷ Use of human granulocyte colony stimulating factors and antibiotics may need to be extended.

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