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Fluoropyrimidines and routine screening for DPYD genetic variants

A hospital recently reported that over a three-week period two patients experienced seizures following administration of injectable fluorouracil. The first patient experienced seizures after two separate injections were administered, approximately two weeks apart. The second patient experienced multiple seizures, with the first occurring within 30 hours after exposure. While the first patient had prior exposure to fluorouracil, the second patient was treatment naïve. At the reporting organization, routine screening for dihydropyrimidine dehydrogenase (DPD) deficiency was not standard practice prior to initiating fluoropyrimidine therapy, therefore, both patients had not undergone testing. Although we are not certain of the cause of the seizures or other contributing factors, neurotoxicity, including seizures, has been reported with fluorouracil administration, and patients with reduced DPD activity are at increased risk.[1,2] "DPYD is the gene that encodes the DPD enzyme. Genetic variants of DPYD are known to affect the risk of severe toxicity and drug exposure in patients receiving fluoropyrimidines."[3]

DPYD Screening

ISMP is aware of several reports of patients who suffered severe toxicities or even death from fluorouracil or **XELODA** (capecitabine), an oral prodrug that is metabolized to fluorouracil. Both are fluoropyrimidine chemotherapy drugs. In our acute care newsletter, in a July 15, 2021 article, Screening for Dihydropyrimidine Dehydrogenase (DPD) Deficiency in Fluorouracil Patients: Why Not?, and a May 2, 2024 article, Utilizing Pharmacogenomic Testing Can Improve Medication Safety and Prevent Harm, we reinforced our continued support for universal screening of this deficiency prior to fluorouracil administration.

In January 2025, the US Food and Drug Administration (FDA) issued a safety announcement to increase awareness of recent updates to the product labeling of fluorouracil and capecitabine related to risks associated with DPD deficiency. FDA emphasized that all healthcare providers should be aware of the risks, inform patients prior to treatment about the potential for serious and life-threatening toxicities, and discuss testing options for DPD deficiency with their patients.[4]

In addition, the latest version of the National Comprehensive Cancer Network's (NCCN's) Colon Cancer guidelines, released in October 2025, now recommends considering testing for DPYD genetic variants prior to initiating fluoropyrimidine therapy. The NCCN panel endorses identifying patients at the greatest risk for severe fluoropyrimidine toxicity, emphasizing that discussion of DPYD genetic variant testing should occur with patients prior to fluoropyrimidine therapy, and should be considered within the context of the patient's individual circumstances.[3]

In March 2024, the fluorouracil prescribing information was updated to include a warning regarding the increased risk of serious or fatal adverse reactions in patients with low or absent DPD activity, and to consider testing for genetic variants of DPYD prior to initiating fluorouracil to reduce the risk of serious adverse reactions if the patient's clinical status permits and based on clinical judgment. Furthermore, in October 2025, FDA added a Boxed Warning for Xeloda that includes the statement, "Test patients for genetic variants of DPYD prior to initiating Xeloda unless immediate treatment is necessary."[5] However, fluorouracil does not have the same Boxed Warning, which ISMP advocates for FDA to consider adding.

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SAFETYwire

Include implantable medication pumps in patients' medication histories. A patient presented to the emergency department (ED) with abdominal pain, severe constipation, and somnolence. The pharmacist completing the medication history interviewed the patient's spouse and reviewed the patient's clinic notes and prescription history. The pharmacist documented that the patient was taking several medications, including insulin via an external pump. The prescriber placed an order to discontinue the patient's insulin pump upon admission due to the patient's somnolence and inability to self-manage the pump.

On the second day of admission, the patient's glucose became critically low at 32 mg/dL. Despite receiving an intravenous (IV) dextrose 50% injection, the patient's somnolence worsened, prompting the nurse to call a rapid response. The prescriber ordered IV naloxone, and after administration, the patient became alert. According to the medication administration record (MAR), the patient was last given 5 mg of oral oxy**CODONE** 13 hours prior. So, at that point, the nurse completed a physical assessment and identified that the patient had an intrathecal (implanted) pump infusing fenta**NYL** at 31.2 mcg/hour and **BUP**ivacaine at 0.31 mg/hour, with the ability to self-bolus 40 mcg fenta**NYL** and 0.4 mg **BUP**ivacaine up to 5 times/day with a 2-hour lockout. Unbeknownst to the care team, the patient's husband had been giving her boluses via a Bluetooth device.

While they had not specified that the patient had an intrathecal pump, the patient and her husband had previously mentioned she had used a "pain stimulator." The practitioners assumed that they were referring to a transcutaneous electrical nerve stimulation (TENS) machine, a small external device that is used to deliver low-voltage electrical currents near nerves to block or change

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Recommendations

To enhance patient safety when using fluoropyrimidines, several key considerations should be integrated into practice.

Gather a multidisciplinary team. Create a team with representatives from pharmacy, oncology, clinical laboratory, and other relevant departments to oversee fluoropyrimidine safety and conduct a comprehensive review of current testing protocols, comparing them to established guidelines to identify gaps in current practice.

Establish DPYD testing guidelines. Develop guidelines that clearly define DPYD testing criteria, provide instructions for interpreting results, and outline appropriate clinical action that includes a system to track patients initiating fluoropyrimidine treatment. For additional information, please refer to the DPYD Genotyping Recommendations[6] which aim to promote consistency in DPYD genetic variant testing across clinical laboratories.

Utilize clinical decision support. Integrate the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Fluoropyrimidines and DPYD into the electronic health record (EHR) to alert prescribers and recommend DPYD genetic variant testing before ordering fluorouracil or capecitabine. Integrate testing results with clinical decision support (e.g., alerts for contraindications, dose adjustments) directly into the EHR workflow.

Educate staff. Educate staff about your organization's guidelines and how to interpret test results and adjust or hold the fluoropyrimidine dose when needed.

Inform patients. Engage in shared decision-making with patients by reviewing their DPYD genetic variant test results before initiating therapy and explaining the implications on their treatment plan. Provide patients with detailed documentation of their test results and emphasize the importance of sharing this information with all healthcare professionals involved in their care.

Antidote availability. Ensure uridine triacetate, the antidote for fluoropyrimidine overdose or toxicity, is readily available and included in order sets that contain fluoropyrimidine drugs to ensure appropriate doses and timing for both adult and pediatric patients, should signs and symptoms of an overdose/toxicity present themselves.

Contributing author Kara Jensen, PharmD, BCPS; 2025-2026 ISMP Safe Medication Management Fellow, supported by the US Army

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the perception of pain. However, the practitioners did not ask clarifying questions to confirm this was the type of device the patient referred to as a "pain stimulator."

The ISMP Targeted Medication Safety Best Practices for Hospitals, Best Practice 21, calls for obtaining the most accurate medication list possible upon admission. This includes not only asking about prescription and over-the-counter medications but also asking about non-enteral medications such as injections and infusions, including those administered via implanted pumps. Organizations should add scripting to the medication history process to specifically prompt about implantable pumps and other devices. These devices may not be visible upon physical exam. Understand that patients and family members may use different terminology or descriptions for these devices other than what healthcare practitioners might expect. Always ask clarifying questions and physically assess patients for devices upon admission and during transitions of care.

MSB white paper on IV push practices

Learn more about current intravenous (IV) push practices by reading the white paper, ***IV Push Medication Practices: Identifying Persistent Gaps and Advancing Safety***, recently published by Med Safety Board (MSB), an ISMP company, powered by ECRI.

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Editors: Ann Shastay, MSN, RN, AOCN; Shannon Bertagnoli, PharmD; Jana O'Hara, MSN, RN, CPHQ, CPPS. ISMP, 3959 Welsh Road, #364, Willow Grove, PA 19090. Email: ismpinfo@ismp.org; Tel: 215-947-7797.