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MEDICATION SAFETY IN SECONDS

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VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

LOW-DOSE METHOTREXATE: ERRORS WITH DAILY DOSING AND SAFETY CONSIDERATIONS

Submitted by: Paul Fina, Pharm.D., PGY-2 Medication Use Safety Resident

Disclaimer: This article is a general overview of methotrexate, highlighting some important points of use. Recommendations are intended to assist practitioners in providing consistent, safe, high quality, and cost effective drug therapy. They are not intended to interfere with clinical judgment. Providers should should consider new clinical information, as available and applicable when using dated material.

Methotrexate is a folate antimetabolite indicated for certain forms of cancer using a wide range of treatment schedules; at low immunomodulatory and anti-inflammatory doses (10–25 mg once weekly), methotrexate is FDA-approved for the treatment of psoriasis, rheumatoid arthritis (RA), and active polyarticular juvenile idiopathic arthritis (pJIA). Low-dose methotrexate is also used off-label for several systemic inflammatory disorders including psoriatic arthritis and Crohn's disease. Methotrexate can be given via injectable (e.g. intravenous, intramuscular, subcutaneous) or oral routes. The oral route is used most frequently for rheumatologic conditions.

Extra caution must be used when prescribing, dispensing, and administering methotrexate. Clinicians and patients are very familiar with daily dosing of medications, but methotrexate's dosing varies depending on a number of factors, including the indication, renal and hepatic function, concomitant medications, and route of administration. Potentially fatal dosing errors can occur when once-weekly methotrexate doses are mistakenly administered on a daily basis.

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NEWSWORTHY...

from the pbm

- Addendum - Procrit® (epoetin alfa) 1 mL Single-Dose, Preservative-Free Solution: Recall Due to Presence of Glass Particles – 09/25/17—National PBM Patient Level Recall Communication
- Medtronic Recall of MiniMed Infusion Sets Due to Potential Over-Delivery of Insulin – 09/18/17—National PBM Patient Level Recall Communication
- Vancomycin Hydrochloride for Injection, USP, 750 mg/vial: Recall Due to Glass Particulate in Vial – 09/08/17 - National PBM Patient Level Recall Communication ****TARGETED to affected sites only****
- Procrit® (epoetin alfa) 1 mL Single-Dose, Preservative-Free Solution: Recall Due to Presence of Glass Particles -09/01/17 - National PBM Patient Level Recall Communication

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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.

EDITOR-IN-CHIEF

Marie Sales, Pharm.D.
VA Pharmacy Benefits Management Services [PBM] & Center for Medication Safety [VA MedSAFE]; 1st Avenue—1 Block North of Cermak Road | Building 37; Room 139 | Hines, Illinois | 60141; www.pbm.va.gov

NEWSWORTHY...

from the fda

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HEPATIC IMPAIRMENT

FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease
9/21/2017

Obeticholic acid (Ocaliva) was approved by the Food and Drug Administration (FDA) in May 2016 for the treatment of primary biliary cholangitis. On 9/21/2017, the FDA issued a warning that obeticholic acid is being incorrectly dosed in some patients with moderate to severe hepatic impairment. In patients with normal hepatic function, obeticholic acid is dosed 5mg once **daily** and increased to 10mg **daily** depending on the patient's response. Patients with moderate or severe hepatic impairment (Child-Pugh class B or C) should initially be treated with obeticholic acid 5mg once **weekly** and may be increased to 10mg twice **weekly** (at least 3 days apart) based on response and tolerability. A higher frequency of doses increases a patient's risk of serious liver injury and death. In the 13 months after the approval of obeticholic acid, the FDA received reports of nineteen cases of death and eleven cases of serious liver injury associated with its use. Eight cases of death provided information about the patient's cause of death. In seven of eight of those cases, patients with moderate to severe hepatic impairment received Ocaliva 5mg daily instead of the recommended dose. Six of the eleven patients with severe liver injury were also associated with incorrect dosing in patients with moderate to severe hepatic impairment. Of these six, three died, which were included in the aforementioned nineteen deaths.

FDA recommends that healthcare professionals:

- Determine the patient's baseline liver function prior to initiation of obeticholic acid.
- Monitor frequently for disease progression and liver injury (worsening liver function inconsistent with the patient's extent of disease).
- Discontinue if liver injury is suspected. Weigh benefits versus risks if considering re-initiation of treatment.
- Educate patient on the potential symptoms of liver injury, such as new or worsening fatigue, diarrhea, weight loss, abdominal pain, decreased appetite, nausea and vomiting.

Getting the most from our safety surveillance

PROCESS FOR ADDRESSING PRESCRIPTIONS TRANSMITTED TO CMOP FOR METHOTREXATE DOSED DAILY

Submitted by: Paul Fina, Pharm.D., PGY-2 Medication Use Safety Resident

In June 2017, a production floor pharmacist at VA's Consolidated Mail Outpatient Pharmacy (CMOP) identified a 30-day prescription for oral methotrexate 2.5 milligrams (mg) with the sig "Take 4 tablets by mouth twice a day" and a quantity of 240 tablets. CMOP cancelled back the prescription to the VA medical center (VAMC) requesting verification of the medication and dose. Subsequently, the prescription's directions were changed and a new prescription was issued by the VAMC which was transmitted to CMOP. This incident prompted further review by CMOP. The CMOP Data Analytics Resource Team (DART) queried CMOP's Central Database and found that 50,102 prescriptions for methotrexate 2.5 mg tablets had been transmitted to CMOP between March 23, 2017 and August 23, 2017. Using verbiage in the sig that indicated daily use, such as "daily" or "every day," a total of 12 methotrexate prescriptions were identified for review. Of these 12 prescriptions, 11 were dispensed and 1 was cancelled back to the VAMC for review of dosing appropriateness.

DART now runs daily reports to identify all prescription orders transmitted to CMOP for methotrexate oral and injectable. Any prescription identified with sig verbiage for daily use is reviewed by a pharmacist and cancelled back to the VAMC for review to determine if the methotrexate dosing is appropriate. CMOP provides details on these cancelled prescriptions to the respective transmitting facilities and asks these medical centers to verify appropriate use and conduct follow-up as needed. CMOP continues to make improvements to this process. Updates will be provided in a future issue.

Product labeling documents overdose of methotrexate from accidental daily administration instead of weekly (single or divided doses). Exposure to more than the recommended dose of methotrexate increases risks of significant toxicities to patients including, but not limited to, gastrointestinal reactions, myelosuppression, renal toxicity, hepatotoxicity, infections, and even death. Safeguards to assure appropriate methotrexate dosing can help to prevent harm. See article addressing *Low-Dose Methotrexate: Errors with Daily Dosing and Safety Considerations* on pages 1, 3, and 4 for more details on how to lower this risk.

REFERENCES:
1. Internal CMOP data.
2. Methotrexate Tablets, USP [package insert]. Hunstsville, AL: DAVA Pharmaceuticals, Inc., a Subsidiary of Qualitest Pharmaceuticals; January 2016.

Helping to achieve safe medication use

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Daily dosing of methotrexate increases the risk of severe side effects such as myelosuppression, renal toxicity, hepatotoxicity, infections, and pneumonitis. Toxic effects can occur at all doses, but dose is a key risk factor for serious adverse drug events. In addition to dose and frequency of administration, other risk factors that may increase the potential for methotrexate toxicity include ascites, pleural effusion, hypoalbuminemia, radiotherapy, and drug interactions. Concomitant nonsteroidal anti-inflammatory drugs, proton pump inhibitors, salicylates, phenytoin, sulfonamides, tetracycline, and penicillins can all increase blood concentrations of methotrexate. Product labelling recommends close monitoring for bone marrow, liver, lung, and kidney toxicities with measurements of complete blood count with differential, serum creatinine, and liver function tests, at baseline and repeated at regular intervals during therapy.

The Institute for Safe Medication Practices (ISMP) has reported harmful or fatal errors with low-dose oral methotrexate in more than 50 of their newsletters since 1996, with most errors involving accidental daily dosing of oral methotrexate intended for weekly administration. For example, a patient died after misunderstanding the prescription directions to take 2.5 milligrams (mg) every 12 hours for three doses each week and instead took methotrexate 2.5 mg every 12 hours for six consecutive days. Another patient died after mistaking "take 10 mg every Monday" for "take 10 mg every morning." In a case of provider error, a patient was prescribed 7.5 mg daily for 2 weeks then 10 mg daily thereafter; this resulted in hospitalization. There are also many instances of transcription errors in which a patient was prescribed weekly dosing but received a prescription bottle labeled with daily dosing. One patient developed pancytopenia and a pulmonary infection after the patient was prescribed methotrexate 5 mg weekly but received a prescription from the pharmacy for methotrexate 5 mg daily.

ISMP considers methotrexate a high-alert medication due to the increased risk of causing devastating harm when used in error. Additionally, ISMP encourages consensus-based strategies (in their *2016-2017 Targeted Medication Safety Best Practices for Hospitals)* for health care institutions to follow to reduce the risk of errors and prevent adverse drug events associated with inappropriate methotrexate daily dose. Recommendations put forth by ISMP that healthcare professionals can take to reduce the risk of methotrexate toxicity include (but are not limited to):

Methotrexate Ordering Strategies

- Use a weekly dosage regimen default for oral methotrexate in electronic systems when methotrexate orders are entered.
- Require a hard stop verification of an appropriate oncologic indication for all daily oral methotrexate orders. For manual systems and electronic order entry systems that cannot provide a hard stop, clarify all daily orders for methotrexate if the patient does not have a documented oncologic diagnosis.
- When possible, dispense only a 4-week supply of methotrexate at a time.
- Provide clear written instructions that name a specific day of the week for taking the medication. Avoid choosing Monday as it could be misread as "morning."
- Consider folate supplementation to reduce gastrointestinal and hepatic toxic effects.

Patient Monitoring

- Obtain baseline hematologic, hepatic, and renal values. Monitor at regular intervals for duration of therapy. More frequent monitoring may be indicated during antineoplastic therapy; while starting therapy or changing doses; or during risk of increased methotrexate blood levels.
- Screen for Hepatitis B and C, and test for HIV in high-risk patients.
- Consider concomitant use of specific prescription and over-the-counter medications that may interact with methotrexate.
- Methotrexate blood concentrations are not an accurate predictor of either the degree of toxicity or the outcome for the patient. If a dosing error is discovered, ensure the patient receives immediate medical attention.

Patient Education

- Ensure that every patient receives verbal AND written education when discharged on oral methotrexate or when filling a prescription for oral methotrexate.
  - Ideally, electronic health records should automatically generate this written material upon discharge for patients receiving oral methotrexate.
  - ISMP provides a free high-alert medication consumer leaflet on oral methotrexate that can be found at: www.ismp.org/AHRQ/default.asp .
- Ensure that written drug information material given to patients contains correct dosage regimen and clear information to take the medication weekly and not daily (where indicated).
- Review the dosing schedule with patients.
  - Explain to patients that taking extra doses is dangerous and that the medication should not be used "as needed" for symptom control. Advise patients to contact their

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physician if they miss a dose.

- Emphasize the need to adhere to the prescribed dose and to obtain all monitoring tests ordered by the prescriber as scheduled.
- Ask the patient to repeat back the instructions to confirm their understanding of the dosing and toxicities.
- Ask for the help of a caregiver if a patient appears to have difficulties.

Within the VA, pharmacy can take the following steps inside the computerized drug-order entry system to reduce potential dosing errors with methotrexate:

- Configure systems to avoid defaulting to a daily dosing schedule.
- Require mandatory entry of an appropriate oncologic indication for selection of daily dosing for all methotrexate orders.
- Add "blue line" drug text display restriction/guideline that displays as blue text on the screen when ordering in CPRS, for example: "METHOTREXATE: VERIFY DOSE, SCHEDULE, & INDICATION". See Figure A.

The MOCHA v2.1b Project, which will provide Maximum Daily Dose Checks, is planned for national release in January 2018 and will alert clinicians when recommended dose limits are exceeded.

VA's Consolidated Mail Outpatient Pharmacy (CMOP) also addresses prescriptions transmitted to CMOP for methotrexate oral or injectable orders dosed daily. See page 2 for more information on CMOP's process.

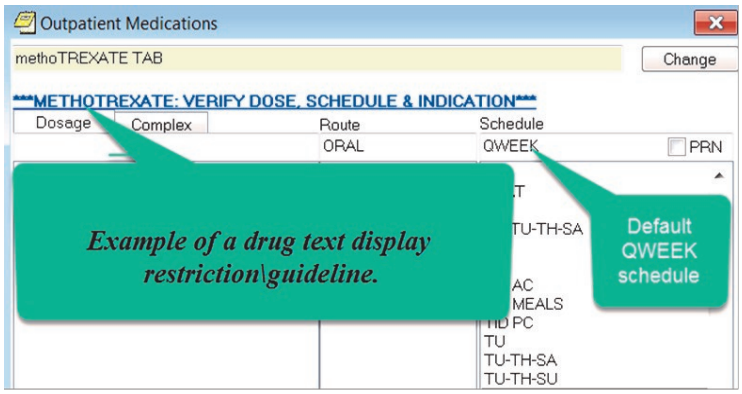

Figure A. Example of a drug text display restriction/guideline that displays as blue text on the screen when ordering as well as default schedule indicated by the green text box call outs. In this instance, the drug text display restriction/guideline alerts providers to verify dose, schedule, and indication for methotrexate prescriptions. Dose schedule is defaulted to "QWEEK".

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