Helping to achieve safe medication use

VA STUDY RAISES POSSIBILITY OF HIGHER RISK OF DEATH WITH PPI USE

A recent longitudinal observational cohort study conducted by Xie and colleagues evaluated associations between proton pump inhibitor (PPI) use and risk of death as well as whether the risk of death increased with long-term use. Researchers used Department of Veterans Affairs (VA) administrative databases to identify a cohort of new users of acid suppression therapy (N = 349,312; 275,977 people prescribed a PPI as first acid suppression therapy and 73,335 initiated on H2 receptor antagonists [H2 blockers]) between October 2006 and September 2008, following patients for up to nearly 6 years (until 2013 or death). Additional cohorts included PPI use compared to no PPI use (n = 3,288,092) and PPI use versus no acid suppression therapy (n = 2,887,030).

Results suggested that PPI use was associated with an elevated risk of death compared to reference groups: PPI versus H2 blocker use (hazard ratio [HR] 1.25, 95% confidence interval [CI] 1.23 to 1.28); PPI use versus no known exposure to PPI (HR 1.15, 95% CI 1.14 to 1.15); and PPI use versus no known exposure to acid suppression therapy (PPIs or H2 blockers) (HR 1.23, 95% CI 1.22 to 1.24). In order to examine risk of death in a lower risk cohort, the study identified a group without GI conditions (defined as gastroesophageal reflux disease [GERD], upper gastrointestinal [GI] tract bleeding, ulcer disease, H. pylori infection, Barrett’s esophagus, achalasia, stricture, and esophageal adenocarcinoma). Risks were similar in the group with no known gastrointestinal problems: PPI versus...

(continued on page 4)
PAIN MANAGEMENT

FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

9/20/2017

The Food and Drug Administration (FDA) advises that buprenorphine and methadone, medication assisted treatment (MAT) used to manage opioid addiction, should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). Although the combined use of these drugs increases the risk of serious side effects including overdose and death, the morbidity and mortality caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks, since the combined use may continue outside the treatment setting. FDA recommends that health care professionals:

- Educate patients about the risks of concomitant use of benzodiazepines, sedatives, other prescribed opioid analgesics, alcohol, and illicit drugs.
- Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine or methadone treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required.
- Current evidence does not support dose limitations or arbitrary caps of buprenorphine or methadone as a strategy to address benzodiazepine or other CNS depressant use in MAT-treated patients. However, if a patient is sedated at the time of buprenorphine or methadone dosing, a healthcare professional should evaluate the cause of sedation. Omitting or decreasing the dose of buprenorphine or methadone may be appropriate.
- Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with MAT medicines. In some cases, monitoring at a higher level of care for tapering may be appropriate. In others, gradually tapering off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose is appropriate.
- For patients receiving buprenorphine or methadone treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider other medicines and nonpharmacologic treatments to address anxiety or insomnia.
- Recognize that patients may require MAT medications indefinitely, and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
- Ensure that other health care professionals prescribing benzodiazepines or other CNS depressants are aware of the patient’s methadone or buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use. Take measures to confirm that patients are taking their medicines as prescribed and are not supplementing with illicit drugs. Toxicology screening should test for use of prescribed and illicit benzodiazepines or other CNS depressants.

ANTIDOTES

FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs

9/6/2017

The Food and Drug Administration (FDA) recommends patients to avoid taking sodium polystyrene sulfonate (brand name Kayexalate and generic brands Kalexate, Kionex, and SPS, as well as non-branded generics) at the same time as other medicines taken by mouth. Sodium polystyrene sulfonate products treat hyperkalemia by binding with potassium in the intestines so it can be removed from the body. A study found that sodium polystyrene sulfonate binds to many commonly prescribed oral medicines, decreasing the absorption and therefore effectiveness of those oral medicines. The medicines studied included amlodipine, metoprolol, amoxicillin, furosemide, phenytoin, and warfarin. Based on these findings, FDA concluded that sodium polystyrene sulfonate would also likely bind to many other oral medicines, and separating its dosing from other oral medications by 3 hours (6 hours if the patient has gastroparesis) would reduce the risk of binding. FDA will update the sodium polystyrene sulfonate drug labels to include information about this dosing separation.
Getting the most from our safety surveillance

IMMUNOMODULATOR THERAPY AND MYELOSUPPRESSION MONITORING

Inadequate monitoring of patients receiving immunosuppressive therapy with medications such as azathioprine or 6-mercaptopurine can be associated with the development of serious drug-related toxicities. One local site reported a fatal event associated with azathioprine monitoring that was inconsistent with guidelines and/or manufacturer recommendations. In this case, a patient diagnosed with ulcerative colitis in January 2014 was initiated on azathioprine 100 mg daily in May 2014. At that time, thiopurine (S)-methyltransferase (TPMT) enzyme activity testing identified the patient as a possible poor metabolizer of thiopurine drugs. The patient’s dose of azathioprine was increased to 150 mg daily in August 2014, when the white blood cell count was normal. In October 2014, the patient presented to the Emergency Department with bleeding, thrombocytopenia, leukopenia, anemia, fever, diarrhea, gastric bleeding, and mouth ulcers. He died with sepsis and pancytopenia less than 24 hours after admission. The facility’s default to a 90-day supply with 2 refills, a feature that appears when prescribing azathioprine via computer order entry, may have contributed to the infrequent monitoring in this case.

Immunomodulators such as azathioprine and 6-mercaptopurine have a prominent role in the management of Crohn’s disease and ulcerative colitis, although they do not have approval for these indications. Azathioprine and 6-mercaptopurine belong to the thiopurine class of medications used as steroid-sparing immunosuppressive treatment in patients with Crohn’s disease or ulcerative colitis with steroid-resistance or steroid-dependency. Both azathioprine and 6-mercaptopurine are inactive pro-drugs that must undergo extensive metabolic transformation in order to exert an effect. These agents are chemically related: azathioprine undergoes conversion in the liver to yield 6-mercaptopurine, which is further broken down into additional metabolites. The TPMT enzyme is involved in the metabolism of these agents. Enzyme activity is genetically determined; diminished TPMT activity may result in potential over-immunosuppression while high TPMT activity may cause overproduction of toxic metabolites and ineffectiveness of azathioprine and 6-mercaptopurine. Side effects associated with thiopurine therapy may include the development of hepatosplenic T cell lymphoma, bone marrow suppression, hepatotoxicity, pancreatitis, allergic reactions, and opportunistic infections.

Myelosuppression related to azathioprine and 6-mercaptopurine use warrants careful monitoring as it is dose-dependent and may lead to an increased risk of infections, sepsis, and death. Monitoring for myelosuppression is recommended by the manufacturer in product labeling as well as multiple professional organizations in practice guidelines. Although differences exist in the guidelines regarding the specific frequency of monitoring, the recommendations generally propose surveillance of hematologic parameters before initiation of therapy; during treatment (frequent during the first three months); after every dose adjustment; after co-administration of relevant drugs; and after disease relapse, infections, or adverse events. Determination of TPMT activity is suggested to help optimize dosage titration as well as prevent toxicity or therapeutic failure.

Appropriate monitoring in line with the standards put forth from major society recommendations can help to reduce unwanted harmful effects. The World Gastroenterology Organization recommends that “before starting azathioprine or 6-mercaptopurine, measuring TPMT phenotype (enzyme levels) or genotype will help direct dosing and if enzyme levels are very low, then risk may be too high to use these drugs. …Monthly CBCs are still indicated.” According to the British Society of Gastroenterology, “manufacturers recommend weekly full blood counts (FBCs) for the first 8 weeks of therapy followed by blood tests at least every 3 months. …One fairly common practice is to perform a full blood count every 2-4 weeks for 2 months and then every 4-8 weeks.” The American College of Gastroenterology endorses that “routine monitoring of complete blood count, initially every 1-2 weeks, then, at least every 3 months is recommended to avoid the risk of acute or delayed bone marrow suppression.” The American Gastroenterology Association advises that “when initiating therapy with either 6-mercaptopurine or azathioprine, measurement of complete blood count with differential is advocated at least every other week as long as doses of medications are being adjusted. Thereafter, the measurement of complete blood count with differential should be performed as clinically appropriate at least once every 3 months. Periodic measurement of liver-associated chemistries is also advocated.”

Monitoring hematologic and biochemistry parameters in the VA should be consistent with society guidelines. In an informal poll, the VA IBD Cooperative group suggests the following monitoring schedule when immunomodulatory therapy is initiated for management of inflammatory bowel symptoms: monitoring should occur with complete blood counts (CBCs) every 2 weeks for 2 weeks, then every month for 2 months, then every 3 or 4 months. Consider using an every 4 month frequency if a patient is also receiving concomitant infliximab every 8 weeks so that a blood draw can accompany the infliximab infusion. The monitoring schedule may be simplified to every 2 weeks for 4 weeks, then every 3-4 months. Consider monitoring CBC once weekly in the presence of concurrent allopurinol treatment.

Additional manufacturer recommendations for the monitoring of (continued on page 4)
Getting the most from our safety surveillance

**IMMUNOMODULATOR THERAPY AND MYELOSUPPRESSION MONITORING**

(continued from page 3)

myelosuppression after initiation of therapy with an immunomodulator include the following:

- Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in or persistently low leukocyte count, or other evidence of bone marrow depression.
- Leukopenia does not correlate with therapeutic effect; therefore the dose should not be increased intentionally to lower the white blood cell count.
- TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing toxicity; however TPMT testing cannot substitute for CBC monitoring.
- Patients with intermediate TPMT activity may be at an increased risk of myelotoxicity if they are prescribed conventional doses.
- Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if they are prescribed conventional doses. Dosage reduction is recommended in patients with reduced TPMT activity.
- Providers should consider alternative therapies for patients who have low or absent TPMT activity (homozygous for non-functional alleles).
- Use caution in patients with one non-functional allele (heterozygous); these patients are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given.
- Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction.
- Benefits versus risks must be weighed carefully before use of azathioprine in patients of reproductive potential because of the mutagenic potential to sperm and egg and possible fetal harm.
- Providers should inform patients receiving immunomodulator therapy about:
  - Necessary periodic blood counts while receiving the drug and the need to report any unusual bleeding or bruising to their physician.
  - The danger of infection while receiving immunomodulating agents and to report signs and symptoms of infection to their physician.
  - The increased risk of malignancy following therapy with immunomodulators.

Clinicians should use professional judgement and the best available evidence to weigh the risk-versus-benefit ratio for an individual patient. Management of immunomodulatory drugs should be undertaken by providers familiar with these agents. Appropriate monitoring can help determine therapeutic efficacy and manage toxicity. Efforts taken by some local medical centers to enforce adequate monitoring include tools to facilitate monitoring, assigning a nurse to track inflammatory bowel disease patients on immunosuppressive medications, and using order sets.

A medication use evaluation tracker (MUET) scheduled for development in Fall 2017 will follow patients with inflammatory bowel disease who are receiving treatment with azathioprine or 6-mercaptopurine. The aim of the MUET is to assess whether monitoring for myelosuppression aligns with manufacturer recommendations and practice guidelines.

**REFERENCES**

1. Internal Data.
3. PURETHINOL® (mercaptopurine) [package insert]. Sellersville, PA: Gate Pharmaceuticals, div. of Teva Pharmaceuticals USA; April 2011.

Helping to achieve safe medication use

**VA STUDY RAISES POSSIBILITY OF HIGHER RISK OF DEATH WITH PPI USE**

(continued from page 1)

H2 blocker use (HR 1.24, 95% CI 1.21 to 1.27); PPI versus no known exposure to PPI (HR 1.19, 95% CI 1.18 to 1.20); PPI versus no known acid suppression therapy (HR 1.22, 95% CI 1.21 to 1.23). The risk of death increased with longer duration of therapy: 31-90 days (HR 1.05, 95% CI 1.02 to 1.08); 91-180 days (HR 1.17, 95% CI 1.13 to 1.20); 181-360 days (HR 1.31, 95% CI 1.27 to 1.34); 361-720 days (HR 1.51, 95% CI 1.47 to 1.56).

The authors concluded that their evaluation pointed towards...
higher mortality risk among PPI users than groups without PPI use. The greater risk was shown in groups with and without gastrointestinal problems. It also appeared that extended PPI use was associated with a higher risk of death than shorter PPI use. They recommended limiting PPI use and duration where clinically indicated and where benefits outweigh the risks, citing that PPIs are “often overprescribed, rarely deprescribed, frequently started inappropriately during a hospital stay, and their use extended for long-term duration without medical indication.”

While this study included appropriate epidemiologic design and rigorous statistical analysis (multiple sensitivity analyses were conducted to support results), limitations to consider include the following:

- Since this is an observational study, direct causality cannot be established. The study showed only an association between PPI use and risk of death, not that PPIs caused deaths.
- The study looked at all-cause mortality only. Data sets did not include information on the cause of death. The pharmacologic mechanism by which PPIs might increase the risk of death remains unclear.
- Over-the-counter (OTC) drugs are not taken into account and non-VA meds are not identified in the secondary cohort comparisons of PPI use versus no PPI or no acid suppression therapy. This can potentially contaminate the no PPI and no acid suppression therapy groups.

Aside from this study’s findings, growing evidence associates exposure to PPIs with risks for development of other adverse outcomes, including renal harm (i.e., acute interstitial nephritis3-4; chronic kidney disease; kidney disease progression and end-stage renal disease5-7); a higher risk of incident dementia8; potentially fatal risk of hypomagnesemia9-11; increased risk of incident and recurrent *Clostridium difficile* infections12; increased risk of osteoporotic fractures (i.e., hip and spine fractures)13-14; community-acquired pneumonia15-16; and cardiovascular events17. This may have compelling implications for patients treated with this class of drugs since PPIs have a high prevalence of use and are widely available OTC.

VISNs and facilities within the VA have addressed the potential risks of inappropriate use and long-term use of PPI therapy in Veteran patients for several years. As an initiative, one VISN implemented an intervention that involved provider education at local facility meetings, patient education via handouts, and removal of refills from all PPI prescriptions without a chronic indication entered into the computerized provider order entry system. This VISN also created a datamart report to capture prescriptions with twice daily or high-dose PPI regimens for sites to review for appropriateness or dose decrease. These efforts achieved the lowest utilization of PPIs nationally within the VA system.18 In another effort, one VA facility implemented a stewardship program in March 2016 to reduce unnecessary PPI use and decrease risks of adverse events and health care associated infections.19 The PPI stewardship program targeted all internal medicine patients admitted to their medical center already on a PPI. A team of 2 pharmacists, 1 hospitalist, and 1 gastroenterologist established criteria for appropriate inpatient and outpatient continuation of PPI use based on available evidence in order to determine whether to continue or discontinue PPI use during hospitalization and after discharge.

VA PBM is working with the National Gastroenterology Program and other groups within VHA to develop interventions to help assure appropriate use of PPIs in the VA.

**REFERENCES:**

18. VISN 17 Internal data.