Intracranial hemorrhage with combination antidepressant-NSAID therapy

A recent observational study by Shin and colleagues found that an antidepressant and non-steroidal anti-inflammatory drug (NSAID) combination increased the risk of intracranial hemorrhage (ICH) compared to antidepressant use alone. This case-control study examined over 4 million Koreans with at least 1 NSAID prescription in the first 30 days after initiating a new antidepressant. Researchers gathered data from the Korean National Health Insurance Programme (universal healthcare) database, and found about 2 million patients using this drug combination. They then identified about 2 million matched control patients who were using antidepressants alone. Patients were excluded for a new diagnosis of cerebrovascular disease within the prior year or antidepressant use within a year before the study period. Individuals using dual antidepressant therapy were also excluded. Initial differences between the study and control groups were present at baseline, but these differences disappeared after propensity-based matching. The study population was predominantly female (61%) with an average age of 52 years. The primary outcome, time to hospitalization with ICH, was more common in the combination therapy group, with an adjusted hazard ratio of 1.6 (95% confidence interval 1.32 to 1.85, p<0.001). The risk of ICH was also greater in men than women, although there was no identifiable reason. No significant differences in ICH risk were found among users of different antidepressant classes, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and others.

This study had several limitations. The specific antidepressant and NSAID agents used were not stated and no doses were provided, so it is unknown whether certain drugs or dose ranges are associated with higher ICH risk than others. It is not known whether combination antidepressant-NSAID therapy also increases the risk of ICH in higher risk ethnic groups, such as African-Americans. It is also not known whether there is an increased risk after the first 30 days of combination antidepressant-NSAID therapy. The observational nature of the study prevents making any conclusions about causality. Also, the study was limited by the quality and quantity of information in the database.

Although this study was the first to describe an increased risk of ICH with combination antidepressant-NSAID therapy, this study is not the first to examine bleeding risk with this combination. Prior studies have documented an increased risk of upper gastrointestinal (GI) bleeding with NSAIDs in combination with SSRIs, and product labeling for some antidepressants contain a warning regarding this risk.

NSAID monotherapy has consistently had no impact on ICH risk in observational studies of users compared to nonusers. However, a few observational studies have identified an increased risk of ICH with individual NSAIDs so the overall question of whether NSAIDs increase the risk of ICH remains unanswered. Studies of ICH risk with antidepressant monotherapy have not produced consistent results. Most of the observational studies focus on the use of SSRIs, and most did not observe an increased risk of ICH. However, a 2012 meta-analysis by Hackam and colleagues of 16 case-control, case-crossover, or cohort studies that included more than 500,000 people found that SSRIs significantly increased the risk of intracranial hemorrhage and intracerebral hemorrhage compared to no SSRIs. There is little data regarding the risk of ICH with other antidepressant classes.

Both NSAIDs and antidepressants are widely used; therefore, the risk of ICH associated with this drug interaction is relevant to a large patient population. This combination should be used cautiously, especially in patients with underlying risk factors for hemorrhage or ICH.
Infection risk with biologics for rheumatoid arthritis

All biologic agents that are used for rheumatoid arthritis (RA) including tumor necrosis factor (TNF)-alpha inhibitor (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), anti-B-cell agent (rituximab), anti-T-cell agent (abatacept), interleukin 1 agonist (anakinra), interleukin 6 antagonist (tocilizumab), and janus kinase inhibitor (tofacitinib) medications have a boxed warning or warning in their product labeling regarding an increased risk of serious infections. Possible serious infections include active tuberculosis or activation of latent tuberculosis, invasive fungal infections, and opportunistic bacterial or viral infections. Serious infections been observed in clinical trials and postmarketing reports with these agents, but the true incidence of serious infections with biologic agents is unknown. It is also not known if these agents have a higher risk of serious infections compared to traditional RA therapies such as disease-modifying antirheumatic drugs (DMARDs) like methotrexate.

Meta-analyses, systematic reviews, and observational studies have produced conflicting findings regarding the risk of serious infections with biologic agents in patients with RA. As a whole, these analyses and studies were limited. None included all of the currently available biologic drugs, some restricted the analysis to patients without prior DMARD exposure, some included older studies that are not likely to mimic current clinical practice, and some were focused on specific population demographics.

In an attempt to reconcile previously conflicting findings, Singh and colleagues performed a meta-analysis and systematic review to compare the risk of serious infections with biologic agents versus DMARDs in patients with RA. The analysis, which was published in the Lancet journal in July 2015, was a robust evaluation of randomized, controlled trials that the authors believed mimic today's clinical practice.

A total of 106 randomized trials that compared a biologic agent versus another biologic, DMARD, or placebo were included. The authors performed a traditional meta-analysis to directly compare the risk of serious infections between biologic agents when used at standard doses. They also conducted a network meta-analysis to perform indirect comparisons between biologic agents when used at low, standard, and high doses. The 42,330 patients were stratified into 3 groups: DMARD-naive (20%), prior DMARDs (69%), and prior TNF-alpha inhibitors (11%). The mean annualized baseline risk of serious infection among patients receiving DMARDs in all 3 groups was 2% (20 per 1000 patients treated per year). The risk of bias was high in 14 (13.2%) studies, low in 45 (42.5%) studies, and unclear in 47 (44.3%) studies.

The traditional meta-analysis (n=59 trials) found an increased risk of serious infections with biological drugs compared to DMARDs (odds ratio [OR] 1.27, 95% confidence interval [CI] 1.05 to 1.52, p=0.012). The increased risk of serious infection was limited to DMARD-experienced patients (OR 1.42, 95% CI 1.11 to 1.83); the DMARD-naive and TNF-alpha inhibitor experienced groups did not have an increased risk. In the subgroup analysis, an increased risk of serious infection was found for patients receiving TNF-alpha inhibitors (OR 1.34, 95% CI 1.06 to 1.69) but not non-TNF alpha inhibitors (OR 1.15, 95% CI 0.85 to 1.56), and biologic + DMARD combination therapy (OR 1.34, 95% CI 1.09 to 1.69) but not biologics alone (OR 0.89, 95% CI 0.54 to 1.48). Network meta-analysis found that low-dose biologic agents with or without DMARD therapy were not associated with an increased risk of serious infection (OR 0.93, 95% credible interval 0.65 to 1.33). However, standard and high doses with or without DMARDs were associated with an increased risk of serious infection (OR 1.31, credible interval 1.09 to 1.58 and OR 1.90, 95% credible interval 1.50 to 2.39, respectively). Overall, the absolute increase in the number of serious infections compared to DMARDs was 6 per 1000 patients treated per year with standard-dose biologics and 17 per 1000 patients treated per year with high-dose biologics.

The authors concluded that the risk of serious infections in patients with RA is increased in patients receiving standard and high doses, but not in patients receiving low doses, compared to traditional DMARD therapy. This analysis had many strengths. It was the largest meta-analysis to date (the largest prior analysis had 18 trials and 8808 patients) and numerous variations of the network meta-analysis and several confirmatory analyses were performed. Some limitations include that the definition of serious infection varied among studies, and only 22 studies included low-dose biologic arms. It is also not clear how commonly low doses are used in clinical practice. All biologic agents were evaluated together, despite their differing mechanisms of action. Patient and disease characteristics differed among studies and over time due to the likely practice changes that occurred over the 15-year time period represented by the included studies. Studies with tofacitinib were not included in the primary analysis even though tofacitinib has been approved in the United States for RA since 2012; the authors did not provide compelling reasons for exclusion of these studies from the analysis.

In summary, the latest meta-analysis by Singh and colleagues found that the risk of serious infection with biologic medications for rheumatoid arthritis may be dose-related, with an increased risk with standard and high doses. Clinicians should continue to be aware of this risk and monitor patients for serious infections, especially among patients receiving high biologic doses or with other risk factors for serious infection.
Iron is an important component of hemoglobin that helps carry oxygen in the body. Iron-deficiency anemia can occur when the iron content in the body is insufficient for erythropoiesis. Iron supplementation can be given in 2 forms: oral or parenteral. Intravenous (IV) iron therapy is indicated for the treatment of iron-deficiency anemia in adults with intolerance to oral iron or an unsatisfactory response to oral iron, as well as treatment of iron-deficiency anemia in adults with non-dialysis-dependent chronic kidney disease and those receiving chemotherapy. Currently, there are 5 parenteral iron products that are available in the United States: iron dextran, sodium ferric gluconate, iron sucrose, ferric carboxymaltose and ferumoxytol. All parenteral iron medications have the potential to cause anaphylactic reactions (most commonly seen with iron dextran) and although acute hypersensitivity reactions during iron infusions are rare, they can be life-threatening.

The mechanisms of iron-induced adverse reactions may vary with the iron formulation as well as with the pre-existing morbidity of the patient. Two proposed causes of anaphylactic reactions with IV iron are immunological IgE-mediated responses or complement activation-related pseudo-allergy (CARPA). While IgE-mediated responses are generally a common cause of anaphylaxis, there is no strong evidence to support its role in hypersensitivity to more current formulations of IV iron such as ferumoxytol. There is, however, some indirect evidence suggesting that CARPA may play a role in IV-iron hypersensitivity reactions. A family history of atopy, older age, autoimmune disease, cardiovascular disease, and concurrent infection are proposed risk factors for hypersensitivity reactions to IV iron.

Additionally, there is suggestion that the greater amount of free iron that is released from the iron complex, the higher the incidence of adverse reactions. A slower infusion rate is believed to be needed for products that release more free iron. Of the available preparations, ferumoxytol has been shown to have the lowest amount of free iron release.

Ferumoxytol is a semi-synthetic, superparamagnetic iron oxide with a carbohydrate coating indicated for the treatment of iron deficiency anemia in adults with chronic kidney disease. Due to the fact that little free iron is released from the preparation, ferumoxytol was initially approved to be administered via rapid administration. Ferumoxytol does not require a test dose and is also 1 of only 2 IV iron products (along with ferric carboxymaltose) that requires as little as 2 administration doses. The adverse effect profile of ferumoxytol is slightly more favorable compared to the other products as hypotension and dizziness are still present, but there is a lower frequency of diarrhea, nausea, constipation, and edema. There are several trials that support the safety of use of ferumoxytol in patients.

In March 2015, the US Food and Drug Administration (FDA) strengthened existing warnings for ferumoxytol to a boxed warning. Ferumoxytol had previously carried the same warning as other intravenous iron replacement medications of the occurrence of serious and potentially fatal anaphylactic reactions. However, the new stricter warning comes in the wake of postmarketing reports of anaphylactic reactions submitted to the FDA Adverse Event Reporting System. The FDA found 79 anaphylactic reactions associated with ferumoxytol from its approval in June 30, 2009 up to June 30, 2014. Reported symptoms included nausea, vomiting, flushing, hypotension, and cardiac arrest. Of the 79 reported cases, 60 of the patients (75%) reported that their reaction began during the infusion or within 5 minutes of administration completion. Thirty-four of the 79 patients (43%) previously had a medical history of drug allergy and 24% of patients reported multiple drug allergies. Although 50% of cases occurred in patients who received ferumoxytol for the first time, hypersensitivity reactions did occur in patients in whom a ferumoxytol dose was previously tolerated.

Providers and patients should monitor for symptoms including hypotension, syncope, unresponsiveness, and cardiac or cardiorespiratory arrest with or without the appearance of rash. Due to the potential for serious hypersensitivity reactions, ferumoxytol should not be administered to patients with a history of an allergic reaction to ferumoxytol or any other IV iron products. Before using ferumoxytol, its risks and benefits should be thoroughly evaluated in patients with a history of multiple drug allergies and in older patients with multiple comorbidities due to their greater susceptibility to and severity of hypersensitivity reactions with use of IV iron products.

In addition to the boxed warning regarding anaphylactic reactions, the recommendations for administration of ferumoxytol have changed. Previously, the labeling stated that the drug could be given undiluted at a rate of up to 30 mg/sec (1 mL/sec). The revised product labeling now states that ferumoxytol should be administered as an infusion of a diluted solution. The drug should be diluted in 50 to 200 mL of 0.9% sodium chloride or 5% dextrose and administered over a period of at least 15 minutes. Patients should be observed for at least 30 minutes after completion of administration of ferumoxytol. Additionally, providers should wait at least 30 minutes before administering other medications that have a high incidence of hypersensitivity. Although the mechanism of hypersensitivity to parenteral iron products is not yet fully understood, it has been suggested that hypersensitivity may be a result of a reaction to the crystalline core and carbohydrate shell of the iron complexes rather than the amount of free iron released. In order to maintain a lower concentration and therefore, potential reaction to these substances, a lower infusion rate for IV iron products may be beneficial.
Adverse events involving ferumoxytol should be reported to the FDA MedWatch program which can be found and accessed in the “Contact FDA” section of the FDA website.

Authors: Wendy Zhang, PharmD Candidate
Heather Ipema, PharmD, BPCS
David Chong, PharmD Candidate

Editors: Heather Ipema, PharmD, BCPS
Rita Soni, PharmD, BCPS