Drug Monitor

Pneumonia After Acid-Suppressing Drugs

Several studies have suggested that acid-suppressing drugs (proton pump inhibitors [PPIs] and histamine 2-receptor antagonists [H2s]) can increase the risk of recurrent community-acquired pneumonia in some elderly patients. Researchers from University of Alberta, Edmonton, Alberta, Canada tested this hypothesis and found current PPI/H2 users had a 51% increased risk of recurrent pneumonia compared to nonusers. Significantly, new users had the highest risk.

Between 2000 and 2002, a total of 1,950 patients over 65 years of age were admitted to six hospitals in Edmonton, Alberta, Canada for community-acquired pneumonia. Researchers conducted five years of follow-up for 1,797 of these patients to determine how many were readmitted to the hospital for recurrent community-acquired pneumonia ≥ 30 days after their initial hospitalization. They found that 248 (14%) had recurrent pneumonia during follow-up.

After matching the 248 cases to 2,476 controls, researchers found that 71 of 608 current PPI/H2 users (12%) were readmitted to the hospital for pneumonia, compared with 130 of 1,617 nonusers (8%) (P = .008). In contrast, there was no association between past PPI/H2 use and recurrent community-acquired pneumonia.

The researchers stratified the current users according to when the PPI/H2 was started and found "incident" current users bore the highest risk: 15% developed pneumonia versus 8% of nonusers (P < .001). There was no observed risk associated with "prevalent" current PPI/H2 use compared with nonuse (8% versus 8%, P = .66).

Speculating about the mechanism, they suggest that PPIs (and H2s, to a lesser extent), by suppressing acid within 24 to 48 hours of ingestion, could permit rapid bacterial recolonization and overgrowth. Gastric acid plays an important role in protecting against infection and "elevation of gastric pH…promotes proliferation of bacteria, particularly Gram-positive organisms commonly found in the mouth and oropharynx." Patients who are vulnerable (such as the elderly) especially are at risk for developing infection. The researchers say they could not find any literature to support or refute that premise, but in a previous observational study, PPI use increased the risk of pneumonia associated with gastric pathogens, but not airborne pathogens.

Their findings are consistent with those of previous studies, the researchers say, which suggest incident new users are at highest risk for community-acquired pneumonia but that the risk may diminish over time with continued PPI/H2 therapy. Because the risk seems to be restricted to new users (a more than two-fold relative risk and a 7% absolute risk), physicians should practice caution when prescribing acid-suppressive therapy in patients who have been hospitalized recently for pneumonia.

The strength of their study, they note, is its five-year observation period—longer than that of previous studies. Moreover, they selected a population at very high and relatively uniform risk of pneumonia, in contrast to previous studies where the overall risk of community-acquired pneumonia was considerably lower.

Source: *Am J Med.* 2010;123(1):47–53.
doi:10.1016/j.amjmed.2009.05.032.

Fenofibrate's Effects on Renal Function

Studies have shown fenofibrate therapy to be associated with reducing the progression of microalbuminuria in patients with type 2 diabetes. Plasma creatinine levels seem to increase with the use of fibrates, however, and the available data are unclear whether the increase is or is not detrimental. Researchers for the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Helsinki study suggest that, in fact, fenofibrate may not have any beneficial effects on albuminuria, combined with deleterious effects on renal function.

Researchers randomized 228 patients with type 2 diabetes to receive either placebo or micronized fenofibrate 200 mg/day for five years. After excluding patients who had a statin added to their medication during the study, 170 patients were eligible for analysis, which included measurement of several markers of albumin excretion and renal function.

After five years, plasma creatinine increased by a mean of 14 µmol/l for those in the fenofibrate group compared with an increase of 2 µmol/l for the placebo group (P < .001). Cystatin C levels also increased significantly in the fenofibrate group compared with the placebo group (14.1% versus 3.6%, respectively, P < .001). Urine creatinine levels remained comparable for both groups, however, resulting in a decrease in creatinine clearance and estimated glomerular filtration rate (eGFR). There was no difference in albumin excretion rate (AER), albumin-to-creatinine ratio (ACR), and 24-hour urine protein excretion between the groups during the study.

The researchers conclude that "fenofibrate reduces several measures of renal function to a greater extent than placebo." In addition, fenofibrate showed no beneficial effect on AER or ACR. The 14% increase in cystatin C levels—often considered the best marker of renal function—indicates impairment of renal function in the fenofibrate therapy group.

The researchers say their study results don't allow them to conclude whether the increase in creatinine and cystatin C are relevant for the prognoses of these patients, but add that "obviously the changes in the estimates of eGFR impair the follow-up of renal function in clinical practice." Currently, they advise the use of fenofibrate for cardiovascular protection in the context of the creatinine and cystatin C increases.

Source: *Diabetes Care.* 2010;33(2):215–220. doi:10.2337/dc09-0621.

Does Vancomycin Deserve the Bad Raps?

Vancomycin—a drug used to treat methicillin-resistant *Staphylococcus aureus* (MRSA)—often is associated with nephrotoxicity. Despite this fact, vancomycin treatment failures in patients with MRSA have led to more aggressive dosing than that approved by the FDA (1 g/12 hours). Many physicians are administering trough concentrations of 10 to 20 µg /mL as recommended by Infectious Diseases Society of America-endorsed guidelines, even though these recommendations have not been validated clinically. Therefore, researchers from Texas Tech University Health Sciences Center and University of Texas Southwestern Medical Center, both in Dallas, TX sought out to determine whether there is an association between increased vancomycin trough doses and nephrotoxicity.

Defining the risk of nephrotoxicity with higher doses of vancomycin is paramount given the availability of alternative MRSA agents that are not nephrotoxic. However, few studies exist that evaluate vancomycin above the FDA-approved 2 g/day. Researchers only found three published studies suggesting a significant association between vancomycin trough concentrations and nephrotoxicity. The increased nephrotoxicity rates are likely due to selection biases, the researchers say: Patients who received aggressive doses were more likely to receive other nephrotoxic drugs and have other risk factors for nephrotoxicity, such as changing hemodynamics.

Researchers say there is some value in the existing literature, however, because it "provides insight to patients at an increased risk of nephrotoxicity that warrant close monitoring or selection of an alternative agent." Other anti-MRSA agents, such as linezolid, daptomycin, and tigecycline do not cause nephrotoxicity, but they are associated with other adverse effects (linezolid, for example, has been shown to cause thrombocytopenia and anemia in 6% to 7% of patients). Therefore, researchers recommend using vancomycin as a first-line treatment option for those with suspected MRSA until further data become available.

Several pharmacokinetic studies have demonstrated that vancomycin should be dosed based on actual body weight, a finding that has been incorporated into clinical practice guidelines but not yet into the prescribing information, the researchers note. This "mismatch" has resulted in patients receiving doses lacking a rigorous evaluation of efficacy and safety. They suggest that providers who are uncomfortable using weight-based dosing for vancomycin due to nephrotoxicity concerns should use an alternative agent since inadequate dosing increases the likelihood of MRSA.

Source: *Am J Med.* 2010;123(2):182.e1–182.e7. doi:10.1016/j.amjmed.2009.05.031.

Triple-Strength Therapy After DES

Compared to bare metal stents (BMS), drug-eluting stents (DES) are known to reduce adverse cardiac events, including death and myocardial infarction (MI); stent thrombosis remains a significant concern, however. Previous studies have suggested using triple antiplatelet therapy—by adding cilostazol to aspirin and clopidogrel—to reduce long-term complications after BMS implantation. Researchers from the University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea conducted a study to see whether this triple therapy also is effective at reducing cardiac events after DES implantation, without increasing the risk of bleeding complications.

Researchers studied 3,099 patients with symptomatic coronary artery disease or documented myocardial ischemia who underwent DES implantation between February 2003 and June 2006. Patients were divided into two groups: a dual-therapy group (which received aspirin 200 mg/day plus clopidogrel 75 mg/day) and a triple-therapy group (which received aspirin 200 mg/day plus clopidogrel 75 mg/day plus cilostazol 200 mg /day).

During 12 months of follow-up, 47 patients died (21 in the triple-therapy group and 26 in the dual-therapy group). Five patients in the triple-therapy group developed MI versus 15 patients in the dual group. Stent thrombosis occurred in three patients in the triple group (two subacute and one late) versus 12 patients in the dual group (two

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acute, three subacute, and seven late). After using inverse probability of treatment weighting (IPTW) adjustment, 12-month mortality risk did not differ between the groups, but 12-month risks of MI and stent thrombosis were significantly lower in the triple-therapy group.

Risk of bleeding was similar between the two groups. Major bleeding was observed in 21 patients in the triple group versus 27 in the dual group (P = .9372). Minor bleeding occurred in 76 triple-therapy patients versus 82 dual-therapy patients (P = .7504).

Although it isn't known exactly how the triple therapy produces beneficial effects, much of the long-term success may be due to continuing cilostazol, the researchers say. "Cilostazol, in addition to enhanced platelet inhibition when used on top of dual antiplatelet therapy may have favorable effects on vascular bed, including inhibition of atheroma plaque formation, atheroma regression, vasodilatation, favorable change of lipid profile, and prevention of angiographic restenosis after BMS or DES implantation." It also acts on endothelial cells, improving cell function, which may partially explain the minimal risk of bleeding in the triple-therapy group. While bleeding complications were not statistically significant, patients in the triple group were more likely to have rash, gastrointestinal disturbance, and headache. Adverse effects resolved after cilostazol was discontinued, however.

Optimal duration of triple antiplatelet therapy after DES implantation has yet to be determined. Researchers say prolonged use for at least six months may be beneficial for patients at high risk for cardiac events. They admit that their study was underpowered to prove meaningful differences in ischemic events, so they suggest large, prospective trials be conducted to confirm the effects of triple therapy.

Source: *Am Heart J.* 2010;159(2):284–291.e1. doi:10.1016/j.ahj.2009.11.014.