Pharmacology Watch

Evidence-based updates in clinical pharmacology

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New PPI Mortality Data: Is There a Risk?

Are proton pump inhibitors (PPIs) associated with excess risk of mortality? That is the finding of a highly publicized study. Among the most popular medications worldwide, PPIs are available by prescription and over the counter. Known side effects include stroke, cardiovascular disease, interstitial nephritis, chronic kidney disease, osteoporosis, pneumonia, *Clostridium difficile* infections, and dementia. Researchers set out to look at whether PPIs also affect all-cause mortality. Using the Veterans Administration database, PPI users were compared to histamine 2 (H2) blocker users in a longitudinal, observational cohort study. Additional cohorts included PPI vs. no PPI, and PPI vs. no PPI and no H2 blocker. The cohorts were followed for almost six years. PPI use was associated with a 25% increased risk of death compared with H2 blockers use (adjusted hazard ratio [HR], 1.25; confidence interval [CI], 1.23-1.28). The risk also was higher when comparing PPI use to no PPI use (HR, 1.15; CI, 1.14-1.15) and PPI use to no PPI and no H2 blockers (HR, 1.23; CI, 1.22-1.24). Even factoring patients with gastrointestinal conditions, PPIs still increased the risk compared to H2 blockers (HR, 1.24; CI, 1.21-1.27). Among new PPI users, there was an increased risk of death with longer duration of treatment. The authors concluded that there is an excess risk of death among PPI users and that "limiting PPI use and duration to instances where it is medically indicated may be warranted." Although these findings sound ominous, the absolute change in death rate was small. (*BMJ Open* 2017 July 4;7:e015735. doi: 10.1136/bmjopen-2016-015735)

Antibiotics for Upper Respiratory Infections in Elderly Patients

Canadian researchers recently studied physician characteristics associated with inappropriate prescribing of antibiotics to elderly patients with acute upper respiratory tract infections. The data were drawn retrospectively from Canadian administrative healthcare files. The cohort included nearly 9,000 physicians and some 185,000 patients > 65 years of age who presented with common colds, acute bronchitis, acute sinusitis, or acute laryngitis. Almost half these patients received an antibiotic, with 70% of the prescriptions written for broad spectrum agents. Physicians who were more likely to prescribe an antibiotic for an acute upper respiratory tract infection included mid- and late-career physicians, physicians trained outside of Canada or the United States, and high-volume physicians, including those who saw between 25-44 patients a day, and especially those who saw ≥ 45 patients a day. Physician rationale for prescribing was not studied. (*Ann Intern Med* 2017;166:765-774) An accompanying editorial noted that "antibiotic prescribing seems to be more refractory to evidence-based medicine efforts than other low-value treatments, and the question is why." The authors suggested outpatient antibiotic stewardship programs, which focus on the cognitive and motivational factors driving antibiotic prescribing. (*Ann Intern Med* 2017;166:844-845)

Investigators Tackle Antimicrobial Resistance

In a related story, researchers from the National Institutes of Health have published a special communication about antimicrobial resistance (AMR). Resistant organisms cause more than 2 million infections per year in the United States, resulting in more than 23,000 deaths. The authors sought to identify factors associated with AMR and possible remedies. The authors reviewed more than 100 relevant articles, databases, and reports. They concluded that AMR represents significant risks to human health and that a diverse set of factors causes AMR. These factors include inappropriate antibiotic prescribing, use of antibiotics outside healthcare (including agriculture), and genetic factors intrinsic to

bacteria. They also cited inadequate economic incentives for the development of new antimicrobial agents. They suggested that "modified use of antimicrobial agents and public health interventions, coupled with novel antimicrobial strategies, may help mitigate the effect of multidrug-resistant organisms in the future." (*JAMA* 2016;316:1193-1204)

Exploring the Rising Prices of Generic Drugs

As competition among generic drugs decreases, prices go up. That is the conclusion of researchers who studied the prices of more than 1,000 generic drugs between 2008 and 2013. Generic drugs were divided into four groups: those with high levels of competition, with moderate levels of competition, a near monopoly, and monopoly. For the drugs with a high level of competition, prices dropped significantly (-31.7%), while moderate competition led to a 11.8% drop in prices. However, a near monopoly resulted in a 20.1% increase in price, while a monopoly resulted in a 47.4% price increase. The authors concluded that market competition levels are associated with a change in generic drug prices. (*Ann Intern Med* 2017 Jul 4. doi: 10.7326/M16-1432. [Epub ahead of print]) High-profile cases of companies raising generic prices include Turing's acquisition of pyrimethamine (Daraprim) in 2015, and a subsequent price increase from $13.50 per pill to about $750 per pill (a 5,000% increase). Increasingly, generic manufacturers are merging (such as Teva merging with Allergan), which may reduce levels of competition and drive generic prices higher for consumers.

Comparing Insulin Treatments for Diabetic Patients

The ultralong-acting insulin analogue insulin degludec (Tresiba) may be associated with fewer hypoglycemic episodes than insulin glargine U100 (Lantus) when used as basal insulin in type 1 and type 2 diabetics. In two industry-sponsored studies, type 1 diabetics (n = 501) and type 2 diabetics (n = 721) were randomized to insulin degludec followed by insulin glargine U100, or the reverse, for two 32-week treatment periods that included a 16-week titration and 16-week maintenance period. All patients had at least one risk factor for hypoglycemia. For the type 1 group, insulin degludec resulted in fewer hypoglycemic episodes (2,200.9 vs. 2,467.7 per person-years' exposure; $P < 0.001$ for both noninferiority and superiority). In the type 2 group, insulin degludec also resulted in fewer hypoglycemic episodes (185.6 vs. 265.4 per person-years' exposure, rate ratio 0.70; 95% confidence interval, 0.61-0.80; $P < 0.001$). A1c and fasting blood sugar levels were the same in both groups in both studies. The authors of the two studies suggested that 32 weeks' treatment with insulin degludec vs. insulin glargine U100 resulted in a reduced rate of overall symptomatic hypoglycemic episodes. (*JAMA* 2017;318:33-44 and *JAMA* 2017;318:45-56)

FDA Actions

In the face of mounting abuse concerns, Endo Pharmaceuticals voluntarily removed Opana ER, an opioid painkiller, from the market on July 6, less than a month after the FDA requested the manufacturer take such action. It was the first opioid drug the agency had ever requested be removed over abuse concerns. The drug is a long-acting formulation of the powerful opioid oxymorphone. The drug originally was approved in 2006 and reformulated in 2012, with the intention of making the drug resistant to physical and chemical manipulation for abuse by snorting or injecting. However, the new formulation produced dangerous, unintended consequences. The 2012 formulation of Opana ER caused abuse patterns to shift from nasal to injection, which led to an outbreak of HIV and hepatitis C infections, as well as thrombotic microangiopathy. In a June 13 letter, FDA Commissioner Scott Gottlieb, MD, wrote that the agency will be reviewing all abuse-deterrent opioids to make sure "these products are having their intended impact on limiting abuse and helping to curb the [opioid] epidemic." In a statement, Endo maintained the safety of the product when used effectively, but said it will work with the FDA to transition patients to safer alternatives.

Gottlieb has taken several other steps since taking over the FDA. In a recent FDA statement, the new commissioner pledged to improve the safety of compounded drugs. The FDA initially increased oversight of compounded agents in 2012, after a fungal meningitis outbreak was traced back to a contaminated compounded steroid injection made by a Massachusetts company. More than 800 people became sick, of whom 64 died. The FDA increased scrutiny of compounding pharmacies as part of the Drug Quality and Security Act of 2013, a process that Gottlieb pledges to continue by active oversight of compounders.

Finally, Gottlieb has pledged to eliminate the backlog of orphan drug designation requests by releasing "modern and risk-based tools" to assess new treatments for rare diseases. There are about 200 orphan drug designation requests that the FDA has not addressed. ■

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