Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Is Ibuprofen Plus Acetaminophen as Effective as Opioids?

Ibuprofen plus acetaminophen is as effective as an opioid plus acetaminophen in relieving acute extremity pain, according to a new study conducted across two EDs in the Bronx, New York. Researchers studied 411 ED patients admitted with acute extremity pain (mean score, 8.7 on the 11-point numerical rating scale). A little more than 400 patients were randomized to one of four treatments: 400 mg of ibuprofen and 1,000 mg of acetaminophen; 5 mg of oxycodone and 325 mg of acetaminophen; 5 mg of hydrocodone and 300 mg of acetaminophen; or 30 mg of codeine and 300 mg of acetaminophen. At two hours, the mean pain score decreased by 4.3 points (95% confidence interval [CI], 3.6-4.9) in the ibuprofen/acetaminophen group; by 4.4 (95% CI, 3.7-5.0) in the oxycodone/acetaminophen group; by 3.5 (95% CI, 2.9-4.2) in the hydrocodone/acetaminophen group; and by 3.9 (95% CI, 3.2-4.5) in the codeine/acetaminophen group ($P = 0.053$). The authors concluded that for patients presenting to the ED with acute extremity pain, there were no statistically significant or clinically important differences in pain reduction at two hours among single-dose treatment with ibuprofen and acetaminophen or three different opioid/acetaminophen combinations (*JAMA* 2017;318:1661-1667).

An accompanying editorial noted that opioid abuse and addiction often begins with treatment of acute pain with prescription opioid medications. Often, patients receive their first opioid prescription in an ED. This study shows that the rarely used combination of ibuprofen plus acetaminophen may be an effective pain-relieving combination that avoids initiating opioids for selected patients. Whether the combination is effective for longer-term treatment is unclear (*JAMA* 2017;318:1661-1667).

Direct-acting Oral Anticoagulants vs. Warfarin in Atrial Fibrillation

Direct-acting oral anticoagulants (DOACs) are superior to warfarin for stroke prevention in atrial fibrillation (AF), according to a new review. Of the DOACs, apixaban may be the best of the bunch. The DOACs, which include edoxaban, rivaroxaban, apixaban, and dabigatran, were compared to warfarin regarding efficacy, safety, and cost effectiveness in patients with AF. Researchers studied 23 randomized trials that included some 95,000 patients in a "network meta-analysis" in which 13 studies compared a DOAC to warfarin. All DOACs were superior to warfarin in reducing stroke or systemic embolism. The risk of all-cause mortality was lower with DOACs than warfarin as was the risk of major bleeding. The risk of intracranial bleeding also was lower with DOACs compared to warfarin, but the risk of gastrointestinal bleeding was lower with warfarin. Apixaban 5 mg twice daily was ranked highest for almost all outcomes and was favorably cost effective compared to warfarin. The authors acknowledged that this was an indirect comparison and that direct comparisons are needed (*BMJ* 2017 Nov 28;359:j5058. doi: 10.1136/bmj.j5058).

Does Warfarin Prevent Cancer?

Warfarin may produce one surprising benefit: protection against cancer. Researchers from Norway

studied this issue in a population cohort of more than 1.25 million persons. The cohort was divided into warfarin users and nonusers. Warfarin users were divided into those taking it for AF or other reasons. To be counted in the cohort, warfarin had to be taken for six consecutive months. Those taking warfarin were older and predominately men. The results showed that warfarin users demonstrated significantly lower age- and sex-adjusted incidences of cancer in all sites (incidence rate ratio [IRR], 0.84; 95% CI, 0.82-0.86). In warfarin users, the IRR for the most common cancers compared to nonusers were: 0.80 lung cancer, 0.69 prostate cancer, and 0.90 breast cancer. However, warfarin did not lower the incidence of colon cancer. Those taking warfarin for AF exhibited even lower rates of cancer. The finding that warfarin lowers the risk of cancer is plausible because warfarin inhibits AXL receptor tyrosine kinase-dependent tumorigenesis and enhances antitumor immune responses, even at doses below anticoagulation levels. The authors suggested that "warfarin use may have broad anticancer potential in a large, population-based cohort of persons older than 50 years." This finding may have implications for selection of an anticoagulant for certain patients (*JAMA Intern Med* 2017 Nov 6. doi: 10.1001/jamainternmed.2017.5512).

FDA Actions

The FDA has approved a once-a-month buprenorphine injection for the treatment of opioid use disorder. The injection is approved for adult patients with moderate-to-severe opioid use disorder and who have initiated treatment with a buprenorphine-containing product and are on a stable dose for at least one week. It is injected subcutaneously by a healthcare professional as part of a comprehensive approach. Safety and efficacy were evaluated in two studies, including one randomized, controlled trial of 848 adults with opioid use disorder, which showed that treated patients experienced more weeks without positive urine tests or self-reports of opioid use. Additionally, a higher proportion of patients demonstrated no evidence of illicit opioid use throughout the treatment period compared to the placebo group. Buprenorphine injection was granted priority review and fast-track designation. It is marketed as Sublocade.

The FDA has approved evolocumab (Repatha) to prevent cardiovascular events. The PCSK9 inhibitor previously was approved for familial hypercholesterolemia or adjunct treatment of atherosclerotic cardiovascular disease. The new indication was based on results from the FOURIER trial in which more than 27,000 patients with atherosclerotic cardiovascular disease on statins were randomized to receive evolocumab injections every two weeks or a matching placebo. After a little more than two years of follow-up, evolocumab reduced the absolute risk of cardiovascular disease by 1.5% (9.8% vs. 11.3%; hazard ratio, 0.85; 95% CI, 0.79-0.92; $P < 0.001$) (doi: 10.1056/NEJMoa1615664). Repatha has been slow to gain traction in the United States, in part because of its price tag: more than $14,000 per year.

The FDA has approved the eighth biosimilar in the United States: trastuzumab-dkst as a biosimilar to trastuzumab (Herceptin). The drug is approved for the treatment of patients with breast or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors overexpress the HER2 gene (HER2+). It represents the second biosimilar approved for the treatment of cancer, after bevacizumab-awwb (biosimilar to bevacizumab/Avastin). Approval of trastuzumab-dkst was based on extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data, which demonstrated that trastuzumab-dkst is biosimilar to trastuzumab. While the new product features the same indications as the originator drug, they are not considered interchangeable. Trastuzumab-dkst carries the same warnings, including boxed warnings, as trastuzumab. Trastuzumab-dkst is marketed as Ogivri.

The FDA has approved the first two-drug regimen for the treatment of HIV in certain adults. Previously, standard HIV treatment included three or more drugs. The new fixed-dose tablet contains two previously approved drugs: dolutegravir and rilpivirine. It is approved for adults with HIV-1 whose virus currently is suppressed on a stable regimen for at least six months with no history of treatment failure and no known substitutions associated with resistance to either dolutegravir or rilpivirine. Safety and efficacy of the two-drug regimen were evaluated in two clinical trials that contained more than 1,000 stable patients who were randomized to continue their current therapy or change to dolutegravir/rilpivirine. The results showed that the new two-drug combination was effective in keeping the virus suppressed and comparable to those who continued their current anti-HIV drugs. Dolutegravir/rilpivirine is marketed as Juluca. ■

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