POEMs

Third-Generation Oral Contraceptives Associated with Greater Risk of PE, Stroke, and MI

Clinical Question

Which oral contraceptive combinations have the highest risk of cardiovascular effects?

Bottom Line

Although there is risk with any current oral contraceptive combination, those that contain lower doses of estrogen, and levonorgestrel instead of desogestrel or gestodene, are associated with the least risk of ischemic stroke, myocardial infarction (MI), or pulmonary embolism (PE). These safer products are older so are often less expensive. This is not the first study to show this difference, but its enrollment of 5 million women may make it the largest. (Level of Evidence = 2b)

Synopsis

This study, conducted in France, used the national health insurance database to identify all women who filled at least one prescription for an oral contraceptive between July 2010 and September 2012. The authors compared these data with the hospital discharge database to identify whether any of these women experienced an admission for PE, cancer, ischemic stroke, or MI over the same period. They identified almost 5 million women with a total of 5,443,916 woman-years of oral contraceptive use.

The risk of cardiovascular effects was very low: roughly six events per 10,000 woman-years, which is similar to other reports. However, the authors found some differences among products: After adjustment for progestogen and risk factors, stroke, PE, and MI risk were all statistically lower with lower-dose estrogen (20 mcg vs. 30 to 40 mcg). They also found, after adjustment, that progestogen mattered: desogestrel (in Desogen, Mircette) and gestodene (Gynera, Femoden, and many others) were associated with higher risk of PE than levonorgestrel. Norethisterone (in Loestrin, Microgestin, and others) was associated with lower PE risk. The combination of estrogen, 20 mcg, and levonorgestrel is associated with the lowest risk. These risks are still small (numbers needed to treat to harm are in the thousands). This study does not tell us about products that contain other estrogens or progestogens because these are the only combinations covered by French national health insurance. Also, the database does not allow for analysis by smoking status.

Study design: Cohort (retrospective)

Funding source: Foundation

Setting: Population-based

Reference: *Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study.* BMJ. *2016;353:i2002.*

ALLEN F. SHAUGHNESSY, PharmD, MMedEd
Professor of Family Medicine
Tufts University
Boston, Mass.

Procalcitonin Guidance Safely Decreases Antibiotic Use in Critically Ill Patients

Clinical Question

Can the use of procalcitonin levels to determine when to discontinue antibiotic therapy safely reduce the duration of antibiotic use in critically ill patients?

Bottom Line

For patients in the intensive care unit (ICU) who receive antibiotics for presumed or proven bacterial infections, the use of procalcitonin levels to determine when to stop antibiotic therapy results in decreased duration and consumption of antibiotics without increasing mortality. (Level of Evidence = 1b)

Synopsis

To test the effectiveness and safety of procalcitonin-guided antibiotic therapy, these investigators recruited patients in the ICU who had received their first doses of antibiotics for a presumed or proven bacterial infection within 24 hours of enrollment. Patients who were severely immunosuppressed and patients requiring prolonged courses of antibiotics (such as those with endocarditis) were excluded. Using concealed allocation, patients were assigned to procalcitonin-guided treatment (n = 761) or to usual care (n = 785). The usual care group did not have procalcitonin levels drawn. In the procalcitonin group, patients had a procalcitonin level drawn close to the start of antibiotic therapy and daily thereafter until discharge from the ICU or three days after stopping antibiotic use. These levels were provided to the attending physician who could then decide whether to stop giving antibiotics.

Although the study protocol recommended that antibiotics be discontinued if the procalcitonin level had decreased by more than 80% of its peak value or reached a level of 0.5 mcg per L, the ultimate decision to do so was at the discretion of the attending physician. Overall, fewer than one-half the physicians actually discontinued antibiotics within 24 hours of reaching either of these goals. Despite this, the procalcitonin group had decreased number of days of antibiotic treatment (five vs. seven days; between group absolute difference = 1.22; 95% confidence interval [CI], 0.65 to 1.78; $P < .0001$) and decreased consumption of antibiotics (7.5 vs. 9.3 daily defined doses; between group absolute difference = 2.69; 95% CI, 1.26 to 4.12; $P < .0001$). Additionally, when examining 28-day mortality rates, the procalcitonin group was noninferior to the standard group, and ultimately had fewer deaths than the standard group (20% vs. 25%; between group absolute difference = 5.4%; 95% CI, 1.2 to 9.5; $P = .012$). This mortality benefit persisted at one year.

Study design: Randomized controlled trial (nonblinded)

Funding source: Industry

Allocation: Concealed

Setting: Inpatient (ICU only)

Reference: *de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial.* Lancet Infect Dis. *2016;16(7):819-827.*

NITA SHRIKANT KULKARNI, MD
Assistant Professor in Hospital Medicine
Northwestern University
Chicago, Ill.

All Analgesics Are Better Than Placebo in Patients with Knee or Hip DJD

Clinical Question

Which analgesics are most effective in treating patients with degenerative joint disease (DJD) of the hip or knee?

Bottom Line

In patients with hip or knee DJD, all analgesics are more effective than placebo in relieving pain and improving function. Although paracetamol (acetaminophen) is the least effective of all the drugs studied, it still may be the first treatment for these patients because of its safety profile. Move on to other agents, if necessary, according to the patient's response. (Level of Evidence = 1a–)

Synopsis

These authors searched the Cochrane Central Register of Controlled Trials to identify randomized trials comparing nonsteroidal anti-inflammatory drugs, paracetamol, and placebo in patients with DJD of the hips or knees. The studies had to have at least 100 patients in each group. Two researchers independently evaluated each study for inclusion and used discussion to resolve disagreements. The team assessed each study's methodologic quality and extracted data related to pain and function. They ultimately included 74 trials with nearly 59,000 patients, seven different drugs, and 23 different permutations. Across the trials, the mean age of patients ranged from 58 to 71 years, most patients were women (49% to 90%), and most studies were of short duration (median follow-up of 12 weeks; range = 1 to 52 weeks). None of the studies were at high risk of bias.

All analgesics, regardless of dose, were more effective than placebo in relieving pain. However, several agents were more likely to provide clinically important relief (diclofenac, 150 mg per day; etoricoxib, 30, 60, and 90 mg per day; and rofecoxib, 25 and 50 mg per day). Paracetamol was the least likely to provide meaningful pain relief. Although patients generally functioned better while taking medication, the data on improved function were not particularly robust and no treatment stood out as better than the rest. The authors do not directly assess the harms of treatment. Finally, rofecoxib has been withdrawn from the worldwide market, and

etoricoxib is not available in the United States because of U.S. Food and Drug Administration demands for further safety information.

Study design: Meta-analysis (randomized controlled trial)

Funding source: Foundation

Setting: Various (meta-analysis)

Reference: *da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis.* Lancet. *2016;387(10033):2093-2105.*

HENRY C. BARRY, MD, MS
Professor
Michigan State University
East Lansing, Mich.

Low-Dose Morphine Less Effective Than Diclofenac or Acetaminophen for Renal Colic

Clinical Question

Which analgesics are most effective in providing significant pain relief in patients who are passing kidney stones in the emergency department?

Bottom Line

This is a good example of how a well-done study can lead to erroneous conclusions. The comparator most likely to be effective here—titrated morphine—was used at a low dose and found to be less effective than intramuscular diclofenac or intravenous paracetamol (acetaminophen). (Level of Evidence = 1b)

Synopsis

These authors randomly assigned more than 1,600 patients who presented to an emergency department with suspected kidney stones and pain severity of at least 4 out of 10 to receive 75 mg of intramuscular diclofenac (n = 548), 1 g of intravenous paracetamol (n = 548), or 0.1 mg per kg of intravenous morphine (n = 549). All patients had intravenous lines started and received intravenous or intramuscular placebo (each patient received one active injection and two placebo injections). They did not give any intravenous fluids until 30 minutes after the initial treatment and then only at the discretion of the treating physician. Approximately 80% of the patients in each group had a confirmed stone, and approximately 3% had no imaging performed.

After 30 minutes, nearly two-thirds of the patients in each group experienced at least a 50% reduction in their pain intensity (68%, 66%, and 61%, respectively; $P = .04$). The authors report that 3% of morphine-treated patients experienced adverse events compared with 1% with each of the other treatments. What happened after the first 30 minutes? The median pain score for each group at 90 minutes was 0. The median time to a pain score of less than 2 out of 10 was 60 minutes, regardless of treatment. Approximately 10% of patients who received diclofenac required rescue analgesia compared with approximately 20% of patients who received the other analgesics. The authors report that two weeks after treatment, no additional adverse events occurred. The study was too small to identify potentially serious adverse events, such as kidney failure, gastrointestinal bleeding, and so forth. Regarding the morphine dose, it was probably too low to be a realistic comparator. The benefit with morphine is that you can rapidly titrate up the dose to get nearly 100% pain relief quickly.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Emergency department

Reference: *Pathan SA, Mitra B, Straney LD, et al. Delivering safe and effective analgesia for management of renal colic in the emergency department: a double-blind, multigroup, randomised controlled trial.* Lancet. *2016;387(10032):1999-2007.*

HENRY C. BARRY, MD, MS
Professor
Michigan State University
East Lansing, Mich. ■