Are new antihypertensive agents better than old antihypertensive agents in preventing cardiovascular complications?

Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358:1305-15.

■ BACKGROUND It has not been established whether antihypertensive agents provide a benefit beyond their blood pressure lowering effects. The investigators conducted a meta-analysis to determine whether old or new antihypertensive agents are more effective in preventing cardiovascular complications.

■ POPULATION STUDIED The investigators included 9 studies enrolling 62,605 middle-aged patients (53-76 years) with a mean blood pressure at entry ranging from 145 to 194 mm Hg systolic and 83 to 106 mm Hg diastolic. The proportion of women ranged from 22% to 67%, and the proportion of patients with cardiovascular complications and diabetes varied (4% to 45% and 4% to 100%, respectively).

■ STUDY DESIGN AND VALIDITY The meta-analysis compared older antihypertensive agents (β-blockers and diuretics) with new antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors, calcium channel blockers, and (β-blockers) for the prevention of cardiovascular complications. All studies were randomized controlled trials, published in peer-reviewed journals, included an assessment of blood pressure and cardiovascular events, were at least 2 years in duration, and enrolled at least 100 patients.

■ OUTCOMES MEASURED The researchers determined cardiovascular mortality, cardiovascular events, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction (MI), fatal and nonfatal congestive heart failure (CHF) rates with old versus new antihypertensive agents.

■ RESULTS The new antihypertensive agents were as effective as the old antihypertensive agents in the prevention of cardiovascular mortality, fatal and nonfatal stroke, and fatal and nonfatal MI. Calcium channel blockers provided more reduction in the risk of stroke than the older antihypertensive agents (absolute risk reduction [ARR]=13.5%, P <.03; number needed to treat [NNT]=7) but were associated with an increase in risk of fatal and nonfatal MI (absolute risk increase [ARI]=19.2%, P <.01; number needed to harm [NNH]=5). Older antihypertensive agents were more effective in preventing cardiovascular events (ARR=11.2%, P <.001; NNT=9). Newer antihypertensive agents were less effective in preventing fatal and nonfatal CHF (ARI=52.4%, P <.001; NNH=2), but this result was attributed to the higher risk of events with the (β-blocker doxazosin compared with the diuretic, chlorthalidone, in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial.

RECOMMENDATIONS FOR CLINICAL PRACTICE

This study confirms that blood pressure control reduces the risk of cardiovascular complications in patients with hypertension. As a group, newer antihypertensive agents are as effective as the older antihypertensive agents in the prevention of cardiovascular mortality, fatal and nonfatal stroke, and fatal and nonfatal MI. However, the (β-blockers and diuretics are more effective in preventing cardiovascular events than ACE inhibitors and calcium channel blockers. Considering that (β-blockers and diuretics are much less expensive than the newer antihypertensive agents, they should remain first line in the treatment of hypertension.

Lori M. Dickerson, PharmD, BCPS
Peter J. Carek, MD, MS
Department of Family Medicine
Charleston, South Carolina

Each month, the POEMs editorial team reviews more than 90 journals of interest to primary care physicians, and identifies articles you need to know about to stay up to date. We call these articles POEMs (Patient-Oriented Evidence that Matters) because they address common primary care problems, report outcomes that matter to patients, and, if valid, require us to change the way we practice. The collected reviews are available online at **www.jfponline.com.**

How accurate is the Canadian C-spine rule for the detection of clinically significant cervical spine injuries?

Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-Spine Rule for radiography in alert and stable trauma patients. JAMA 2001; 286:1841-48.

■ BACKGROUND Current use of cervical spine (C-spine) radiography for alert and stable trauma patients is highly variable and expensive in practice. A recent clinical decision rule to identify low-risk patients was accurate in distinguishing those who would not need radiography (high sensitivity) but would result in many patients being unnecessarily imaged (low specificity).[1] The originators of the Ottawa Ankle and Knee rules have created a decision rule for use of C-spine radiography.

■ POPULATION STUDIED The study enrolled patients 16 years and older who sustained acute blunt trauma to the head or neck and presented to an emergency department (ED) of 10 large Canadian hospitals. Patients had to be completely alert with normal vital signs. They either had to report neck pain or be nonambulatory with visible injury above the clavicles after a dangerous mechanism of injury. Patients were not studied if they were injured more than 48 hours before presentation, were returning for reassessment of the same injury, were pregnant, or had penetrating trauma, acute paralysis, or known vertebral disease.

■ STUDY DESIGN AND VALIDITY This was a prospective cohort study in which physicians determined 20 standardized clinical findings from the history and physical examination. The physician would then decide whether to obtain C-spine radiography; if no X-ray was obtained, a structured telephone interview 14 days later determined whether a clinically important C-spine injury had taken place. Clinical findings were then analyzed for their association with significant C-spine injuries. Although the study attempted to enroll consecutive patients, 3281 of 12,782 eligible patients were not enrolled for unclear reasons, and 577 patients could not be contacted by telephone for follow-up.

■ OUTCOMES MEASURED The primary outcome measure was clinically important C-spine injury, defined as a fracture, dislocation, or ligamentous instability demonstrated by diagnostic imaging.

■ RESULTS Approximately 69% of patients underwent C-spine radiography, and 31% underwent the 14-day follow-up phone interview. A total of 151 (1.7%) were determined to have a clinically important C-spine injury. No patients who did not undergo radiography were found to have important injuries 14 days later.

The researchers then developed the Canadian C-Spine rule from the collection of the clinical findings that consists of 3 main questions: (1) Is there any high risk factor present that mandates radiography? High-risk factors include age 65 or older, paresthesias in the extremities, or a dangerous injury mechanism (fall from 1 meter or greater, axial load to head, motorized recreational vehicles, bicycle collision, or motor vehicle collision (MVC) with high speed, rollover or ejection). (2) Is there any low-risk factor that allows safe assessment of range of motion, including simple rear-end MVC, sitting position in ED, ambulatory at any time, delayed onset of neck pain, or absence of midline C-spine tenderness? (3) Is the patient able to actively rotate the neck 45 degrees to the left and right? An answer of "yes" to the first question or "no" to the second or third question required radiography.

This rule had a sensitivity of 100% (95% confidence interval [CI], 98%-100%) and a specificity of 42.5% (95% CI, 40%-44%). The estimated C-spine radiography rate using this rule would have been 58.2%, compared with the actual rate of 68.9% in this Canadian sample and an even higher rate in the United States.

RECOMMENDATIONS FOR CLINICAL PRACTICE

The Canadian C-Spine rule shows promise as an aid to decide whether to use C-spine radiography in alert stable patients with head or neck injuries. It demonstrates high sensitivity and reasonable specificity. However, the rule needs to be validated in other populations before accepting it as the standard of care.

Michael T. Kinkade, MD
Erik J. Lindbloom, MD, MSPH
Department of Family and Community Medicine
Columbia, Missouri
E-mail: lindbloome@health.missouri.edu

REFERENCE

1. Hoffman JR, Mower WR, Wolfson AB, Todd KH, Zucker MI. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. N Engl J Med 2000; 343:94-99.

How effective are weekly antenatal steroids for decreasing the risks associated with preterm delivery?

Guinn DA, Atkinson MW, Sullivan L, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. JAMA 2001; 286:1581-87.

■ BACKGROUND For women at high risk of preterm delivery, it is the standard of care to administer an initial course of corticosteroids to promote lung maturity. Uncertainty remains, however, about the value of continuing treatments on a regular (weekly) schedule. This randomized controlled trial compared the efficacy of single versus weekly corticosteroids in reducing neonatal morbidity in women at high risk of preterm delivery.

■ POPULATION STUDIED A total of 502 women between 24 weeks' and 32 weeks and 6 days' gestation at high risk for preterm delivery were recruited from 13 US academic centers. High risk was defined as preterm labor, preterm rupture of membranes, maternal medical illness, or suspected intrauterine growth restriction. Women were excluded if they needed immediate delivery, had active tuberculosis or human immunodeficiency virus infection, or if their fetuses had mature lungs or severe anomalies. Approximately equal proportions of subjects were white, Hispanic, and African American, and 67% were receiving government assistance. Also, 33% were nulliparous; 54% had preterm labor; and 14.5% had multiple gestations.

■ STUDY DESIGN AND VALIDITY This was a randomized placebo-controlled double-blinded trial. Women at high risk for preterm delivery who received an initial course of corticosteroids and had not delivered in 1 week were randomized to receive either betamethasone 12 mg twice in 24 hours every week until 34 weeks or similarly administered placebo. Analysis was by intention to treat, using chi-square tests and t tests with assessment of study site as a potential confounder. The study was halted after 502 of a planned 1000 patients were recruited, due to emerging evidence that weekly corticosteroids might produce long-term neurologic sequelae. The methodology of this study was strong. The major weakness was lack of statistical power.

■ OUTCOMES MEASURED The primary outcome was composite neonatal morbidity (including severe RDS, BPD and IVH, periventricular leukomalacia, sepsis, NEC, or death). Secondary outcomes included each individual outcome, maternal side effects, and clinical course. Utilization, cost, and patient satisfaction were not addressed.

■ RESULTS The groups were similar at baseline and follow up was 97%. There was no significant difference in composite morbidity between the weekly course group and the single-course group. Exploratory analysis showed that weekly corticosteroids decreased severe RDS (15.3% vs 24.1%; *P*=.01), but there also a trend toward an increased risk of severe IVH in the weekly course group (7.6% vs 2.0%; *P*=.06). The weekly course group had shorter time to delivery (5.0 vs 5.8 weeks; *P*=.02) and a trend towards more chorioamnionitis (24.1% vs 17.8%; *P*=.09). There was no significant difference between the 2 treatment regimens in endometritis, wound infections, hemorrhage, or length of stay.

RECOMMENDATIONS FOR CLINICAL PRACTICE

This study provides fair evidence that there is no significant benefit and possibly an increased risk of morbidity in giving weekly corticosteroids to mothers at risk for preterm labor. In the context of studies that have suggested adverse behavior[1] and delayed psychomotor development[2] in children of mothers treated with repeated corticosteroids, clinicians should administer only a single course of corticosteroids and avoid weekly treatment. The burden of proof is on advocates of weekly treatments to demonstrate that benefits clearly exceed risks.

Woodward Burgert III, MD
Warren P. Newton, MD, MPH
The University of North Carolina at Chapel Hill
E-mail: warren_newton@med.unc.edu

REFERENCES

1. French N, Hagan R, Evans S, Godfrey M, Newnham J. Repeated antenatal corticosteroids: size at birth and subsequent development. Am J Obstet Gynecol 1999; 180:114-21.
2. Esplin M, Fausett M, Smith S, et al. Multiple courses of antenatal steroids are associated with a delay in long-term psychomotor development in children with birth weights ≤1500 grams. Am J Obstet Gynecol 2000; 182:S24.

What is the most effective regimen for eradication of *Helicobacter pylori* in patients who have failed a first eradication attempt?

Hojo M, Miwa H, Nagahara A, Sato N. Pooled analysis on the efficacy of the second-line treatment regimens for *Helicobacter pylori* infection. Scand J Gastroenterol. 2001; 36:690-700.

■ BACKGROUND Based on randomized clinical trials (RCTs), the most effective first-line eradication therapy for *Helicobacter pylori* is a combination of proton pump inhibitor (PPI) and 2 antimicrobial agents.[1] Yet there remains a significant treatment failure rate of 5% to 25%. Antibiotic resistance is the major impediment of cure.[2] Using a pooled analysis approach, the authors determined the second-line treatment strategy resulting in the greatest percentage of *H pylori* eradication.

■ POPULATION STUDIED Studies of *H pylori* re-eradication in adults were retrieved from MEDLINE database, reference lists of retrieved research papers, and major congress abstract lists. All studies were performed between 1994 and 1999, were conducted prospectively (or without information on study design), contained detailed information on eradication agents, and included subjects with only one treatment failure. Eighteen articles and 47 abstracts were identified; 16 articles and 24 abstracts met the inclusion criteria.

Studies were categorized based on the following 6 second-line therapies: (1) PPI-based dual therapy, a PPI and a antimicrobial; (2) PPI-triple therapy, a PPI and 2 antimicrobials; (3) bismuth-based triple therapy with 2 antimicrobials; (4) ranitidine bismuth-based triple therapy with 2 antimicrobials; (5) PPI-bismuth based triple therapy with a antimicrobial agent; and (6) quadruple therapy, an antisecretory agent (PPI or H2-blocker), bismuth compound, and 2 antimicrobials. As a result of the various combinations of different antibiotics and antisecretory agents, a total of 75 treatment arms were evaluated.

■ STUDY DESIGN AND VALIDITY The authors performed a pooled efficacy analysis of re-treatment regimens for *H pylori* eradication in adults. They included all prospective studies–randomized and nonrandomized–that reported eradication rates in patients previously treated with antibiotic therapy. The inclusion criteria were appropriate, and the search for relevant articles was complete in that the authors included abstracts from international gastroenterology meetings. An analysis strategy of simple pooling was used (total number of patients successfully treated divided by all those enrolled in given treatment category), which is appropriate since the primary outcome was the eradication rate.

■ OUTCOMES MEASURED The authors calculated a pooled eradication rate with 95% confidence intervals for each of the 6 general treatment categories. They also determined the eradication rate of each second treatment, accounting for differences in initial treatment therapy regimen. Finally, they ascertained if the effectiveness of second-line therapy regimens improved when distinct antimicrobials not used in the first attempt at treatment were used.

■ RESULTS The most effective second-line therapies for eradication of *H pylori* were quadruple therapy, either ranitidine-bismuth-based triple therapy (ranitidine-bismuth product plus 2 antimicrobials) at 80.2% (95% confidence interval [CI], 75%-85%) or H2-blocker or PPI, bismuth compound, and 2 antimicrobials) at 75.8% (95% CI, 73%-79%). The second-line treatment eradication rate was lower when the initial therapy was a PPI with 2 antimicrobials versus a PPI with one antimicrobial. Re-treatment was more difficult with an increased number of antimicrobials used in initial therapy. The re-treatment eradication rate was greater when 2 new antimicrobials were included in the regimen than when a single new antimicrobial was added (P=.0064).

RECOMMENDATIONS FOR CLINICAL PRACTICE

If initial attempts fail at eradication of *H pylori* then quadruple therapy (an antisecretory agent, a bismuth compound, and 2 antimicrobials) or ranitidine-bismuth (Tritec) plus 2 antimicrobials is the most effective follow-up treatment. The latter approach is fairly expensive ($150). For patients whose first course included only one antimicrobial, using 2 new antimicrobials is just as effective as quadruple or ranitidine bismuth-based therapy. These approaches will achieve eradication in 75% to 80% of resistant cases.

Tsveti Markova, MD
Kendra Schwartz, MD, MSPH
Wayne Sate University
Detroit, Michigan
E-mail: tmatkova@med.wayne.edu

REFERENCES

1. Unge P. Antimicrobial treatment of *H pylori* infection--a pooled efficacy analysis of eradication therapies. Eur J Surg Suppl 1998; 582:16-26.
2. Nakajima S, Graham DY, Hattori T, Bamba T. Strategy for treatment of *Helicobacter pylori* infection in adults. II. Practical policy in 2000. Curr Pharm Des 2000; 6:1515-29.

CONTINUED ON PAGE 82

Continued from page 14

Are once-daily iron drops as effective as thrice-daily therapy in children with iron deficiency anemia?

Zlotkin S, Arthur P, Antwi KY, Yeung G. Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia. Pediatrics 2001; 108:613-16.

■ BACKGROUND The standard treatment for iron-deficiency anemia in preschool children has been 4.5 to 6.0 mg per kg per day of ferrous sulfate divided into 3 daily doses. Given the difficulty of giving medicine 3 times per day to young children, less frequent dosing should improve compliance.

■ POPULATION STUDIED Infants aged between 6 and 18 months with a hemoglobin concentration between 7.0 and 9.9 g per dL were enrolled in the study. The study was conducted in Ghana, a malaria-endemic area, with an 83% prevalence of anemia in young children (compared with a 3%-5% prevalence in the United States).

■ STUDY DESIGN AND VALIDITY The investigators of this randomized controlled trial screened 880 infants to find 557 who were eligible. These children were divided by concealed allocation to standard dose (5 mg per kg per day of elemental iron, rounded to a total of 40 mg of elemental iron given in 3 equal daily doses) or single-dose (40 mg of elemental iron as a single bolus dose) ferrous sulfate drops. Children had blood samples analyzed for hemoglobin concentration and serum ferritin at entry and after 2 months of therapy. Also, a peripheral blood smear was obtained at entry to look for malaria parasites.

The strengths of this study include an adequate number of study subjects and biweekly field visits to assess compliance and side effects.

Of the 557 eligible infants, 57 (10.2%) were not available at the end of the study, leaving 247 in the once-daily group and 253 in the thrice-daily group. Those lost to follow-up were equally distributed between the groups and had similar baseline characteristics. There were no significant baseline differences between the once-daily and thrice-daily groups with respect to mean age (13 months vs 12.8 months, P=.75), mean hemoglobin (8.8 g/dL vs 8.7 g/dL, P=.23), mean ferritin (34.8 µg/L vs 40.0 µg/L; P=.87), sex, or presence of malaria parasites on the peripheral blood smear (66.9% vs 66.7%; P=.95). None of the children in the study required treatment of the malaria parasitemia as evaluated by World Health Organization criteria.

■ OUTCOMES MEASURED The primary outcome was percentage of children whose anemia resolved (hemoglobin concentration > 10.0 g/dL). Ferritin levels, compliance, and side effects were also measured and reported.

■ RESULTS Anemia resolved in 59% of the infants after 2 months of therapy. There was no significant difference in the response rate between the once-daily group and the thrice-daily group (61% vs 56%; P=.51). Final mean hemoglobin (10.2 g/dL vs 10.0 g/dL; P=.25) and ferritin (101 µg/L vs 107 µg/L; P=0.1) values (in the once-daily and thrice-daily groups respectively) were all significantly increased from baseline but not significantly different between groups.

Compliance was similar between the groups, with 81% of the once-daily group receiving all of the prescribed doses compared with 80% of the thrice-daily group. Side effects were uncommon and mild, consisting mainly of diarrhea. There was no significant difference in the rates of diarrhea between the once-daily and thrice-daily groups.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Once-daily iron therapy (5 mg/kg/day of elemental iron) is as effective as 3 times per day dosing in the treatment of infants with iron deficiency anemia without an increase in side effects. The Centers for Disease Control recommends a single dose of 3 mg per kg per day.[1] Most parents (and probably their children as well) should prefer once-a-day dosing of medicine, which is supported by this study. Though there was no difference in compliance noted in this study, many other studies have shown that compliance increases as dosing frequency decreases. Although the overall response rate was only 59%, the response may have been blunted due to other comorbid factors that are common in this population (malaria parasitemia, *Helicobacter pylori* and other gastrointestinal infectious diseases, and hemoglobinopathies such as sickle cell disease or thalassemia).

Scott Kinkade, MD
MAJ, MC, US Army
Darnall Family Practice Residency Program
Ft Hood, Texas
E-mail: scott.kinkade@amedd.army.mil

REFERENCES
1. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. MMWR 1998; 47:1-30. www.cdc.gov/mmwr/PDF/RR/RR4703.pdf.

What is the diagnostic accuracy of the clinical examination for meniscus or ligamentous knee injuries?

Solomon DH, Simel DL, Bates DW, Katz JN. Schaffer JL. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. JAMA 2001; 286:1610-20

■ BACKGROUND An accurate physical examination of knee pain can aid in determining the need for further diagnostic testing, specialist referral, and surgical intervention.

■ POPULATION STUDIED The authors of this systematic review conducted searches of MEDLINE, HealthSTAR, and bibliographies of retrieved articles. They identified 88 articles of which 23 compared physical examination techniques to a reference standard (arthroscopy, arthrotomy, or magnetic resonance imaging).

■ STUDY DESIGN AND VALIDITY Two of the authors graded the methodologic quality of the included studies using a standardized scoring system. The authors abstracted data from individual studies to calculate the sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) for specific examination techniques.

The included studies were quite heterogeneous, and the summary likelihood ratios (LRs), therefore, were appropriately estimated using a random effects model.

The LRs are likely overstated and should be applied to the primary care population with caution for 2 reasons. First, the included studies were quite heterogeneous as evidenced by their wide CIs. Second, in all of the included studies, the examiners were experienced orthopedic specialists; there were no studies using nonspecialist physicians as examiners. This may indicate a referral bias in the data and, therefore, a skewed population (which the authors refer to as a "spectrum bias").

■ OUTCOMES MEASURED The sensitivity, specificity, LR+, and LR- were calculated for examination of anterior cruciate ligament (ACL) injuries ("composite" examination and Lachman, anterior drawer, and lateral pivot shift maneuvers), posterior cruciate ligament (PCL) injuries ("general" examination and posterior drawer and abduction stress test maneuvers), and for meniscus injuries (joint line tenderness, presence of joint effusion, and the McMurray and medial-lateral grind tests). No articles were found that examined the diagnostic accuracy of physical examination techniques for medial collateral ligament (MCL) or lateral collateral ligament (LCL) injuries. The review includes detailed descriptions of the examination techniques.

■ RESULTS The results for all of the diagnostic tests are in the form of LRs. An LR greater than 10 provides strong evidence that the disorder is present; an LR less than 0.1 provides strong evidence that the disorder is not present. Scores between 0.5 and 2.0 are neutral. Summary LRs with 95% confidence intervals (95% CI) for examinations of ACL injuries were as follows: composite examination (specific maneuvers not delineated): LR+ = 25.0 (95% CI, 2.1-306.2), LR- = 0.04 (95% CI, 0.01-0.48); the Lachman test: LR+ = 25.0 (95% CI, 2.7 - 651), LR - = 0.1 (95% CI, 0.0 - 0.4); anterior drawer test: LR+ = 3.8 (95% CI, 0.7 - 22.0), LR- = 0.3 (95% CI, 0.05 - 1.50); and pivot shift stress test: LR+ = 42 (95% CI, 2.7-651.0) and LR- = 0.1 (95% CI, 0.0-0.4).

For PCL examination: composite examination (specific maneuvers not delineated), LR+ = 21.0 (95% CI, 2.1-205.0) and LR- = 0.05 (95% CI, 0.01-0.50). LRs could not be calculated for the posterior drawer test, and only one small study examined the abduction stress test: LR+ = 94 (95% CI, 6-1487) and LR- = 0.1 (95% CI, 0.0-0.4).

For the determination of meniscus lesions: LRs for joint line tenderness, examining for joint effusion, and the medial-lateral grind test were nonsignificant (CIs included 1). For the McMurray test: LR+ = 1.3 (95% CI, 0.9-1.7) and LR- = 0.8 (95% CI, 0.6-1.1).

RECOMMENDATIONS FOR CLINICAL PRACTICE

The anterior drawer, pivot shift, and Lachman maneuvers are useful for evaluating ACL injuries. The abduction stress test may be useful for evaluating PCL injuries but the posterior drawer test has not been evaluated. A "composite" examination has good test properties for ruling in or out either ACL or PCL tears; however, the specific maneuvers that constitute the "composite" are not defined. As also shown in a recent meta-analysis,[1] no test including examining for joint line tenderness or for joint effusion, the medial-lateral grind test, or McMurray test is of value for determining meniscal tears. No data exist for the examination of MCL or LCL lesions.

John R McConaghy, MD
The Toledo Hospital Family Practice Residency
Ohio
E-mail: john.mcconaghy.md@promedica.org

REFERENCE

1. Scholten RJ, Deville WL, Opstelten W, Bijl D, van der Plas CG, Bouter LM. The accuracy of physical diagnostic tests for assessing meniscal lesions of the knee: a meta-analysis. J Fam Pract 2001; 50:938-44.

Are oral contraceptives (OCPs) with anti-androgenic progestins preferred over other OCPs in patients with acne?

Worret I, Arp W, Zahradnik HP, Andreas JO, Binder N. Acne resolution rates: results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (Belara) and EE/LNG (Microgynon). Dermatology 2001; 203:38-44.

■ BACKGROUND Some women with acne may suffer from a hypersensitivity of the sebaceous glands to androgens. The use of OCPs with anti-androgenic properties may therefore be a useful approach to treating these patients.

■ POPULATION STUDIED The population studied included 199 women 18 to 40 years of age (smokers up to age 30 years), with mild to moderate papulopustular acne of the face and acne-related disorders. Patients were recruited from 32 office-based gynecology centers in Germany.

■ STUDY DESIGN AND VALIDITY Patients were randomized in an investigator blinded-only fashion (nonconcealed allocation assignment) to 12 treatment cycles with one of 2 OCPs--either Belara, a monophasic OCP containing 0.3 mg of ethinylestradiol and 2 mg of chlormadinone acetate (EE/CMA), a progestogen derivative with anti-androgenic properties or Microgynon, an OCP containing an equal dose of estrogen and a more commonly used progestin, levonorgestrel (EE/LNG). Blinded observers performed regular skin exams after cycles 4, 7, 10 and 12. Women were not allowed to use any other treatments for acne.

The 2 groups studied were similar in baseline characteristics. Subjects were analyzed in the groups that they were assigned (intention-to-treat analysis). Dropouts were defined as nonresponders in the intention-to-treat analysis. A total of 75% of women completed the entire study protocol; dropout rates and reasons for doing so were equal in the 2 groups. The main limitation of this study is the single blind format (nonconcealed allocation assignment), which can exaggerate benefits, making it seem that the treatment is more efficacious than it actually is.

■ OUTCOMES MEASURED The primary endpoint was the number of papules/pustules per half of the face decreasing by 50% in the 12th medication cycle. Secondary endpoints were the assessment of comedomal acne of the face, acne of the décolleté and back, further signs of adrogenization, such as seborrhea, alopecia, and hirsuitism. Blood levels of androgens, SHBG, cycle stability and incidence of adverse events were also examined.

■ RESULTS A total of 59% of patients on EE/CMA compared with 46% on EE/LNG showed a 50% reduction in the number of papules/pustules after 12 treatment cycles (P=.02; number needed to treat=8). The number of women with complete resolution reached 16.5% by cycle 12 in those taking EE/CMA compared with 4.3% by cycle 12 in the EE/LNG group (difference nonsignificant). Similar nonsignificant trends were seen for a reduction in comedonal acne favoring the EE/CMA group. Equal improvements were seen in each group for seborrhea, alopecia, and hirsuitism. There was no difference in the incidence and intensity of break-through bleeding or amenorrhea between the 2 groups. Adverse events were similar between the 2 groups.

RECOMMENDATIONS FOR CLINICAL PRACTICE

OCPs with an anti-androgenic progestin derivative may be slightly more effective than other OCPs in improving mild to moderate acne. However, nearly half of the women in this study treated with either OCP had a significant reduction in their acne after 12 cycles of treatment.

The progestin in this phase III trial (chlormadinone) is currently not used in any OCP available in the United States. Other combination pills have been shown in randomized controlled trials to be effective for treating acne.[1-3] For now it makes sense to prescribe cheaper OCPs in women with acne and switch to more expensive "designer" brands only in the case of a nonresponse.

Kenneth H. Johnson, DO
Eastern Maine Medical Center
Bangor
E-mail: Kjohhnson@emh.ort

REFERENCES

1. Thiboutot D, Archer DF, Lemay A, et al. A randomized trial of low-dose contraceptive containing 20 ug of ethinyl estradiol and 100 ug of levonorgestrel for acne. Fertility Sterility 2001; 76:461-68.
2. Redmond GP, Olson WH, Lippman JS, Kafrissen ME, Jones TM, Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet Gynecol 1997; 89:615-22.
3. Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer LJ. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. J Am Acad Dermatol 1997; 37:746-54.

Is oral oseltamivir safe and effective for the prevention of influenza and its complications in frail elderly long-term care residents who have received influenza vaccine?

Peters PH, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc 2001; 49:1025-31.

■ BACKGROUND Significant morbidity and mortality may result after influenza infection in the elderly. Influenza vaccination is recommended for all persons older than 65 years but does not confer universal protection against disease or complications. Chemoprophylaxis against influenza with oseltamivir is effective in a younger unvaccinated population but has not been studied in an elderly vaccinated population.

■ POPULATION STUDIED The study population included residents of long-term care facilities located throughout the United States and Europe. Of the 548 subjects enrolled (272 placebo, 276 oseltamivir), 493 completed the study. Study groups were similar at baseline. Residents 65 years and older were included; the mean age was approximately 81 years. Participants had a mean of 6.1 concurrent diseases and were taking an average of 7.7 medications. Approximately 80% of participants received the influenza vaccination.

■ STUDY DESIGN AND VALIDITY This was a randomized double-blind placebo-controlled study. Participants were recruited during the 1998-1999 influenza season and performed a stratified randomization according to vaccination status and coexistence of chronic obstructive airways disease. Subjects took either oseltamivir 75 mg or placebo once daily for 6 weeks. Treatment was started when influenza infection was detected in either one resident of the center or in two individuals in the immediate community. Participants were examined at 3, 6, and 8 weeks and when influenza-like symptoms were documented on daily diary cards.

The study was performed well. Study outcomes were assessed through intention-to-treat analysis and allocation to treatment group was concealed from investigators enrolling patients into the study. Rather than sampling a group of patients, they used all persons living in many nursing homes located in several different countries. Another strength of this study is that all cases of suspected influenza were confirmed by laboratory analysis. Unfortunately, little influenza occurred during the study year, which probably results in an underestimate of the benefit of the therapy.

■ OUTCOMES MEASURED The primary outcome was incidence of laboratory-confirmed clinical influenza A or B, defined as fever, one respiratory symptom, and one constitutional symptom plus a greater than 4-fold increase in influenza antibody titer or viral replication from nasal or throat swabs. Secondary outcomes included symptomatic laboratory-confirmed influenza not meeting clinical criteria, asymptomatic laboratory-confirmed influenza, influenza-like illness, and secondary influenza complications (otitis media, sinusitis, bronchitis, or pneumonia).

■ RESULTS Thirteen cases of laboratory-confirmed clinical influenza were identified; 12 of the 13 infected patients previously had been vaccinated. No influenza occurred in 22 of the 31 participating study sites. Compared with placebo, treatment with oseltamivir significantly protected against laboratory-confirmed influenza (4.4% vs. 0.4%; *P*=.002; number needed to treat [NNT]=25) and reduced secondary influenza complications (2.6% vs 0.4%; *P*=.037; NNT=45). The difference in rates of pneumonia (1.1% vs 0.0%) is not clinically significant. Adverse events were not more likely in oseltamivir-treated patients and withdrawals due to adverse events was similar among the patients in the 2 groups. One patient died in each study group (unrelated to influenza or study medication).

RECOMMENDATIONS FOR CLINICAL PRACTICE

In this study of frail elderly residents of nursing homes, most of whom had been vaccinated, the addition of oseltamivir (Tamiflu) prophylaxis produced a reduction in episodes of influenza during the 1998-1999 season. The impact was small -- one additional episode of influenza was prevented for each 25 patients treated. At a cost of $270 per person for 6 weeks of therapy, which works out to $6750 to avoid one additional case of influenza and $12,150 to prevent one additional complication, the benefits of the addition of oseltamivir to previously vaccinated persons may not be worth the cost.

Deborah Sturpe, PharmD
Terry L. Seaton, PharmD
Mercy Family Medicine
St. Louis, Missouri
E-mail: tseaton@stlcop.edu