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Obesity and Oral Contraceptive Efficacy

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman is a consultant to Schering-Plough and receives grant/research support from the Society for Family Planning.

Synopsis: *Oral contraceptives with a less than 30 mcg ethinyl estradiol component may be less effective in obese women.*

Source: Burkman RT, et al. Association between efficacy and body weight or body mass index for two low-dose oral contraceptives. *Contraception* 2009;79:424-427.

A LARGE PROSPECTIVE RANDOMIZED TRIAL (N = 2812 WOMEN) WAS retrospectively analyzed to look at contraceptive efficacy and weight/BMI. This study compared oral contraceptives containing 25 µg ethinyl estradiol/180/215/250 norgestimate vs 20 µg ethinyl estradiol/1 mg norethindrone. Weight and BMI were dichotomized to either < or ≥ 70 kg or < or ≥ 25 mg/kg^2. The median baseline weight was 62.5 kg (range, 39.9-108.9 kg) and median BMI was 23 kg/m^2 (range, 15.9-47.6 kg/m^2). In total, 37 pregnancies occurred. A slight but not statistically significant increase in the relative risk (RR) of pregnancy was found in the ≥ 70 kg and ≥ 25 kg/m^2 groups (RR, 1.25; confidence interval [CI], 0.63-2.46; and RR, 1.85; CI, 0.98-3.45, respectively).

COMMENTARY

Concern regarding how obesity impacts contraceptive efficacy has been a focus of recent debates, but there is a significant paucity of data upon which to base any clinical recommendations. Prior contraceptive efficacy trials have excluded women greater than 130% of ideal body weight and recent cohort studies have been conflicted in their findings — some have demonstrated an adverse effect of

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weight on contraceptive efficacy and others have not.[1-5] Burkman and colleagues have retrospectively analyzed data from their randomized clinical trial of 2 different oral contraceptives. They found a small effect of obesity on oral contraceptive efficacy but this finding was not statistically significant. This is one of the only studies to have prospectively followed pregnancy rates in obese women using oral contraceptives.

However, there are several significant limitations to this study. Although these data were obtained from a randomized trial, the outcome (how weight/BMI affects efficacy) was not originally planned; thus, the analysis may contain unknown bias. In addition, this study excluded women of > 32 kg/m^2. A BMI of 30 kg/m^2 is the starting definition of obesity,[6] so in actuality this study mainly included a population of overweight and not obese women (even though it does appear that they had a protocol breach and enrolled some women over their set BMI cut off of 32 kg/m^2).

So unfortunately, we still don't have a good answer to our question — does obesity affect oral contraceptive efficacy? Nevertheless, should we move to change our contraceptive prescribing practices in obese women based on some of these concerns? Currently, there is not enough information to recommend avoiding the use of oral contraceptives in obese women. But there is enough information even in normal BMI women that birth control methods like the intrauterine device and the implant are more effective than oral contraceptive pills and we should be promoting these to women of any weight.[7] ■

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The Raloxifene RUTH Trial Subgroup Analysis

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *In women younger than age 60 who were at increased risk of coronary events, raloxifene reduced the incidence of coronary events.*

Source: Collins P, et al. Effects of the selective estrogen receptor modulator raloxifene on coronary outcomes in the Raloxifene Use for The Heart trial. Results of subgroup analyses by age and other factors. *Circulation* 2009;119: 922-930.

THE RALOXIFENE USE FOR THE HEART (RUTH) TRIAL WAS an international randomized, placebo-controlled trial that enrolled 10,101 postmenopausal women in two groups, one at high risk for coronary heart disease, and one with established coronary heart disease. The women in each group were randomized to raloxifene, 60 mg/day, or placebo. In the initial report from the RUTH trial, no overall effect on coronary events was detected and there was an increase in strokes.[1] Because the Women's Health Initiative (WHI) and Nurses'

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Questions & Comments
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Health Study reported a reduction in coronary events associated with estrogen therapy administered to young postmenopausal women, the RUTH trial performed a post-hoc analysis of the impact of raloxifene according to age of the women at entry to the study as well as subgroups such as the use of medications, including statins.[2] Overall, raloxifene did not increase or decrease coronary events in either of the treated groups. The only category demonstrating a significant difference, a 40% reduction in coronary events, consisted of women younger than 60 years of age.

■ COMMENTARY

Raloxifene was expected to exert a preventive reduction in coronary heart disease because it lowered total cholesterol and LDL-cholesterol and induces coronary artery relaxation. In a 2-year randomized trial in monkeys, raloxifene exerted no protection against coronary artery atherosclerosis despite changes in circulating lipids similar to those achieved in women (increases in HDL-cholesterol and decreases in LDL-cholesterol).[3]

Despite the statistically significant reduction in coronary events in women younger than age 60, there was no relationship in any subgroup according to years since menopause, even in the group less than 10 years postmenopausal. The women who were younger than 60 years of age were an average of 9.9 years since menopause, compared with 19.4 years for the overall study population. The finding of a beneficial effect of raloxifene in the youngest postmenopausal women in the RUTH trial does not jibe with the failure to find a relationship with years since menopause.

The RUTH investigators pointed out that no evidence for coronary harm was found with raloxifene in the oldest age groups, contrary to the increase observed in the WHI when estrogen was administered to women older than age 70 (a similar age analysis of stroke in the RUTH trial would be of interest). They speculate that this may be because raloxifene does not stimulate a proinflammatory response as does estrogen, citing the lack of raloxifene effect on C-reactive protein (CRP) levels. However, CRP is a protein synthesized in the liver and atherosclerotic arteries. An estrogen-induced increase in CRP levels may be due to estrogen's well-known effect to stimulate the hepatic synthesis of proteins, especially because of the first-pass phenomenon with oral administration. Studies with multiple inflammatory markers report that oral estrogen therapy increases only CRP, the only marker synthesized in the liver. In fact, while increasing CRP, oral hormone therapy reduces the circulating levels of other inflammatory markers with inconsistent effects on interleukin-6. Most importantly, we don't know if the decrease in CRP levels with statins and the increase with estrogen (if this is indeed the case) are instrumental in clinical outcomes or reflect other effects. Thus, raising or lowering CRP levels will not necessarily increase and decrease the risk of clinical disease. A study from the Women's Health Initiative confirmed the correlation between baseline levels of CRP and an elevated risk of coronary heart disease, but the increase in CRP induced by oral hormone therapy did not further increase the risk.[4]

Two-thirds of the women in the RUTH trial were being treated with statins. It is possible that a harmful effect of raloxifene was masked by statin treatment. We should not rely on the RUTH trial to convince us that raloxifene treatment is safe for older postmenopausal women, free of an adverse effect on arterial thrombosis.

The well-written editorial that accompanies the RUTH report was written by Janet Wittes, PhD, a statistician.[5] She addressed the likelihood that if enough subgroups are analyzed, some mathematical finding will emerge that appears to be fact. The first problem is the difficulty in achieving sufficient numbers in each subgroup. Of the 10,101 women, there were only 360-460 women (14%-18%) in each of the patient groups who were younger than age 60, and only 134 women younger than age 60 experienced a coronary event. This one subgroup demonstrated a statistically significantly different conclusion than the overall finding, of 51 analyzed subgroups.

So, which conclusion is more important and more reliable: that raloxifene has no overall effect on preventing coronary events, or that raloxifene reduces the risk of coronary events in the youngest postmenopausal women? The statisticians say that the overall conclusion, the primary objective of the designed trial, is the most reliable. But the beneficial finding in young postmenopausal women is consistent with the analyses of the WHI and the Nurses' Health Study, lending credibility to the age subgroup analysis. Wittes pointed out that in the age groups defined by the original study design, there were no differences by age. Only in this post-hoc analysis, stimulated by the desire to match the recent age reports from the WHI, did a single subgroup benefit appear. Furthermore, Wittes agrees with my point about the failure to demonstrate a difference according to years since menopause, making the single subgroup conclusion either a chance finding or an effect smaller than applied mathematics in the report suggest. Wittes argues that analyses of subgroups that consist of less than 30% of the study population are not reliable (in the RUTH trial, the younger than age 60 years subgroups were 14%-18% of the total number).

In conclusion, a decision to use raloxifene should not be influenced by its effects on the cardiovascular system. This is a bone and breast decision. ■

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Use of Magnesium Sulfate as a Neuroprotector

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Although still controversial, pooling of data from randomized trials suggests the neuroprotective benefit of magnesium sulfate in patients in preterm labor prior to 34 weeks of gestation.*

JUNE SEEMS TO HAVE BEEN MAGNESIUM SULFATE MONTH in both the *Obstetrics & Gynecology* and *American Journal of Obstetrics & Gynecology* journals. There were two reviews of the literature (with meta-analyses), one clinical opinion, and one editorial in the *American Journal of Obstetrics & Gynecology*, all on its neuroprotective effect. In addition, there was another review on the same subject and a current commentary on magnesium sulfate as a tocolytic in the June issue of *Obstetrics & Gynecology*. For the most part, magnesium sulfate came off reasonably well as the protector against cerebral palsy (CP).[1-5]

I will summarize the five studies that provided the bulk of the data that were analyzed in the meta-analyses and discussed in the commentaries.

1. Magnesium and Neurological Endpoints Trial (MAGNET).[6] This study had two arms, which were applied to patients who entered the hospital with singletons or twins at less than 34 weeks in preterm labor (PTL) or with premature rupture of membranes (pPROM). Ninety-two were randomized to magnesium sulfate or placebo to stop labor, and 52 were randomized to having magnesium sulfate or placebo for neuroprophylaxis. In the tocolysis arm, 29% (16/55) had adverse outcomes (intraventricular hemorrhage, neonatal morbidity, periventricular leukomalacia, or CP), compared with 18% (9/51) who had placebo. In the neuroprophylaxis arm, 27% (11/30) of those having magnesium sulfate had adverse outcomes, compared with 21% (6/29) in the placebo arm. Although the differences were not statistically significant, the trend in this study was worrisome for increased risk with magnesium sulfate.

2. Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO$_4$).[7] This was a multicenter study designed to test the neuroprotective capacity of 24 hours worth of magnesium sulfate in patients in labor with advanced cervical dilatation at less than 34 weeks. Only 70 of the 535 patients in the placebo group and 70 of 527 patients in the magnesium sulfate group were undelivered after 24 hours. In this select cohort, 24% of neonates in the placebo group and 19.8% of the neonates in the magnesium sulfate group died or had CP. Also, gross motor function was impaired in children by 2 years of age in 17% of the magnesium sulfate group vs 22.7% in the placebo group. This study suggested a beneficial effect of magnesium sulfate, although not a dramatic one.

3. Magnesium Sulfate for Prevention of Preeclampsia (Magpie) trial.[8] One hundred seventy-five hospitals in 33 countries participated in this study to see if magnesium sulfate prevented seizures (which it did in 58% fewer patients). In a subset of 2895 infants studied later, there were no significant differences in death rates or neurosensory disabilities between children exposed in utero to magnesium sulfate compared with placebo.

4. PREMAG Study.[9] Follow-up data were presented in a letter to the editor of the journal *Pediatrics*, involving a multicenter study in France in which 508 patients about to deliver prior to 34 weeks were randomized to a loading dose of magnesium sulfate or placebo. The peri-

natal mortality rate in the magnesium sulfate group was similar to the placebo group (9.4% vs 10.4%), but the incidence of moderate-to-severe CP was significantly lower in the magnesium sulfate group (1.9% vs 3.5%; relative risk [RR], 0.55; confidence interval [CI], 0.32-0.95). This represented a check in the good column for magnesium sulfate.

5. Beneficial Effects of Antenatal Magnesium (BEAM) trial.[10] This was a large study conducted by the NICHD perinatal network in 2241 patients at risk for delivering prior to 32 weeks of gestation. The perinatal mortality was roughly the same between magnesium sulfate and placebo groups (9.4% magnesium sulfate vs 8.5% in the control group), but the rate of moderate-to-severe CP was significantly higher in the control group (1.9% vs 3.5%; RR, 0.55; CI, 0.32-0.95). This represented a strong check in the good column for magnesium sulfate, but, as we will see, not two checks.

Two meta-analyses were published in June, one by Doyle et al[4] and another by Conde-Agudelo and Romero.[2] After breaking down and combining the best available data, the authors of both studies concluded that magnesium sulfate had a protective effect against moderate-to-severe CP (RR = 0.61 and 0.64, respectively) and one meta-analysis showed a lessening of gross motor dysfunction (RR = 0.60). Neither showed any significant difference in pediatric mortality.

■ COMMENTARY

The authors of the meta-analyses came down rather strongly for the benefit of magnesium sulfate and Rouse,[3] the lead author of the BEAM study, in an opinion piece in the same issue of the *American Journal of Obstetrics & Gynecology*, calculated that by treating 63 women threatening to deliver prior to 32 weeks, one case of moderate-to-severe CP would be prevented. Despite this tilt toward the virtues of magnesium sulfate, the above study should not represent a slam dunk endorsement for its ability to protect against CP. Actually, of the five studies, only two showed a benefit and it was the meta-analysis that made the major difference.

The benefit of meta-analysis is to pool data when the individual studies do not have the statistical clout to show a difference between groups. However, as is often the case, the above study designs were not identical, as well as the criteria for inclusion and the heterogeneity of patients. For example, 8% of the ACTOMgSO_4 patients had pPROM, while 86% in the BEAM study had this complication of pregnancy. Also, perhaps the most important factor, as pointed out by Cahill and Caughey in a companion review,[1] was that the study that tipped the scale with regard to CP was the BEAM trial.[4] In this study, the death rate was higher (but not statistically significantly so) in the magnesium sulfate group. Since many of the neonatal deaths represented CP cases waiting to happen, the authors calculated that of the 99 deaths in the magnesium sulfate arm, just two more cases of CP in infants that might have survived would have rendered the results statistically insignificant.

Last, magnesium sulfate is certainly not devoid of side effects — just ask any women who has had it. For example, Elliott et al in the same issue of *Obstetrics & Gynecology*, made a pitch for resurrecting magnesium sulfate as a tocolytic.[5] In their commentary, the authors enumerate the well-known side effects that clinicians observed in patients who have had magnesium sulfate: loss of reflexes, blurred vision, lethargy, muscles weakness, as well as the more dangerous complication of fluid overload and pulmonary edema (occurring in one study in 4 of 455 patients). Also, there is always the risk of inadvertent drug overdose.

The point is that, despite the suggestion of its worth in two meta-analyses above, some feel that there still is not enough evidence from randomized trials with uniform protocols to endorse giving every patient at risk for preterm delivery prior to 32 weeks a drug that is expensive (by being labor intensive to administer) and has many side effects. In fact, as calculated above, it may be ineffective or unnecessary in 62 of the 63 patients being treated in a best case scenario. I do wish we were better at predicting true preterm labor so that only a small proportion of those with preterm contractions would need to be treated.

In the meantime, every clinician will have to make his/her decision based on the total clinical picture. ■

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Emergence of True "Individualized" Therapy: The PARP Inhibitors

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is a retained consultant to GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer; and serves on the speakers bureaus for GlaxoSmithKline, Eli Lilly Co., and OrthoBiotech.

Synopsis: *The BRCA genes function as tumor suppressors and perform an important role in DNA repair. Women and men who harbor germline mutations in these genes are at increased lifetime risk for a number of cancers, including breast, ovarian, and prostate cancers. The recently identified susceptibility of tumors to inhibition of PARP, a single-strand DNA repair enzyme, opens a new chapter in cancer therapeutics. This phase I trial provides the first "proof-of-principle" of this strategy in the clinic.*

Source: Fong PC, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009 Jun 24; Epub ahead of print.

PRECLINICAL DATA RECENTLY DEMONSTRATED THE extreme sensitivity of BRCA-deficient cells to inhibition of the single-strand repair enzyme poly(ADP-ribose) polymerase (PARP). Inhibition of the PARPs leads to an accumulation of single-strand DNA breaks, which can lead to double-strand breaks at replication forks. Normally, these breaks are repaired through homologous recombination of which the BRCA genes play a major role. However, "synthetic lethality" occurs when these genes themselves improperly function due to mutation or silencing. This prompted the clinical development of a new class of novel therapeutic, the PARP inhibitor, which theoretically holds promise in patients whose tumors rely on this pathway for continued cell growth.

To test this hypothesis and to evaluate the safety of the first drug in this class, olaparib, a phase I, dose-escalation clinical trial was conducted to examine the pharmacokinetic and pharmacodynamic effects in patients with cancers refractory to standard therapy. Given the mechanism of action of olaparib, the population was enriched for patients with BRCA1 or BRCA2 mutations. Overall, 60 patients were recruited to the trial, including 22 who carried a BRCA1 or BRCA2 mutation and one with a strong family history of BRCA-related cancer. The dose of olaparib ranged from 10 mg daily, administered 2 of 3 weeks to 600 mg twice daily, continuously. At the two highest dose levels, dose-limiting toxicities were observed. This led to a compromised dose of 200 mg twice daily, which was studied in a second cohort of BRCA1 and BRCA2 patients only. In general, the agent was well tolerated with primary toxicities of somnolence, mood alteration, and fatigue. The toxicity profile was not increased in the BRCA subpopulation. Analysis of PARP function by pharmacodynamic studies demonstrated rapid and high level inhibition within the recommended dosing levels. In support of the hypothesis, objective antitumor activity (63% complete or partial response plus stable disease) was seen only in BRCA mutation carriers. Olaparib has few side effects relative to conventional chemotherapy, inhibits PARP, and has antitumor activity only in patients with BRCA germline mutation.

■ COMMENTARY

Conceptually, the idea of identifying the right patient for the right treatment that has the best chance to impact an individual tumor is easy to understand and certainly appealing from both an efficacy and toxicity point of view. However, as the complexity of carcinogenesis becomes clearer, individualized therapy in this regard looms as a light at the end of the tunnel that never seems

to brighten. The current report is certainly one clear exception — on many levels. First, it follows from a significant preclinical discovery and leverages the very genetic defect that predisposes to cancer in the first place, for a highly specific anticancer therapy. Second, the presence of a functioning BRCA gene in normal tissues affords a heightened therapeutic index, promoting tumor selectivity and low toxicity. Third, the level of "target engagement" or PARP inhibition, is high with rapid onset, even at low doses. Elimination is also rapid and predictable, making the agent clinically savvy. Based on these observations and findings, a new crop of PARP inhibitors is being introduced into the clinic in hopes of extending the beneficiary population. Indeed, it has been identified that somatic (or acquired) mutation in tumors may behave with a certain BRCA-ness, which could make them vulnerable to this type of intervention. Further, combination therapy of PARP inhibitors with chemotherapy was recently reported to be more beneficial than chemotherapy alone in unselected patients with metastatic, triple-negative breast cancer. While these latter two strategies may not prove clinically viable in the long run, it is clear that for the 10-15% of ovarian cancer patients who carry a BRCA mutation, truly individualized therapy is closer than ever imagined. ■

Suggested Readings

1. De Soto JA, Deng CX. PARP-1 inhibitors: Are they the long-sought genetically specific drugs for BRCA1/2-associated breast cancers? *Int J Med Sci* 2006;3:117-123.
2. Edwards SL, et al. Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 2008;451: 1111-1115.
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Special Feature

A Warm Thank You

By Leon Speroff, MD, Editor

ABOUT 30 YEARS AGO (SO LONG AGO THAT I CAN'T remember the exact year), I began to edit a monthly newsletter devoted to reproductive medicine. The newsletter went through several titles and publishers until it became *OB/GYN Clinical Alert*, but in each of those nearly 400 newsletters, there has been one guiding principle: Express a clinically meaningful opinion.

There are and have been other newsletters. However, the commentary that follows an abstract almost always concludes: This finding will require more study, or the meaning of this report awaits the results of a randomized, clinical trial. My requirement from each contributing editorial board member over the years has been not only to interpret a current important article, but also to give clinicians your judgement regarding the impact of the article on clinical practice. It takes a little chutzpah to stick your neck out, especially in the recent years of "evidence-based medicine." But the newsletter has served to remind us all that we know more than what we read in the literature, that our clinical decisions are based not only on a foundation of knowledge gained through our journals, but also our continuing education and our experience, the knowledge gained from every clinical encounter.

It is the task of an epidemiologist to derive study conclusions based on study data. It is the obligation of a clinician to make a judgment whether the epidemiologist's conclusions have clinical meaning. For example, an epidemiologist can conclude that estrogen reduces coronary artery calcification and point out that a randomized clinical trial has not proved that such a reduction lowers the risk of coronary heart disease. But it is appropriate for a clinician, knowing the correlation between coronary artery calcification and coronary heart disease, to conclude that estrogen reduction of coronary calcification will translate into less coronary heart disease. Medical judgments require more than absolute evidence from randomized trials; medical judgments frequently do not have the luxury of postponing clinically meaningful decisions until data are conclusive. I am proud that the contributors to the newsletters over the years have consistently shared their medical judgement in comments that were aimed to help clinicians and patients.

But it hasn't been a one-way path. The newsletters forced us to analyze current reports and think about them in depth, searching for flaws and for pearls. Many of my newsletter sentences found their way into my textbook. And a "hot" newsletter commentary often served as material for my weekly resident seminars. I am sure it has been the same for my editorial colleagues. We are thankful for the added motivation provided by writing for the newsletters. The best way to learn something is to teach it!

Now the time has come to pass the torch. Jeff Jensen, MD, my colleague in Oregon, will be the new chief editor. This is not nepotism; Jeff has acquired a national and international reputation in the area of family planning.

He will continue to enforce the guiding practical, clinical principle of the newsletter, and his sense of humor is better than mine.

My heart-felt thanks to my editorial board members over the years, and especially to our readers. Now I am a professor emeritus, happy and thankfully well, writing nonmedical books, playing softball, fly-fishing, and riding my tractor. My best wishes to all for good health and a happy, rewarding life. ■

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

CME Questions

14. Obese women should not use oral contraceptives.
a. True
b. False

15. An intrauterine device has higher contraceptive efficacy than an oral contraceptive for a woman of any weight.
a. True
b. False

16. The following statements are true regarding raloxifene and the cardiovascular system *except*:
a. The use of raloxifene has a small increase in stroke risk, similar to estrogen.
b. Raloxifene modifies the lipid profile in a pattern similar to estrogen.
c. Raloxifene exerts a primary prevention effect for coronary heart disease.
d. Raloxifene increases the risk of stroke.

17. Which of the following does *not* fit regarding the neuroprotective effect of magnesium sulfate?
a. Both meta-analyses mentioned above show a benefit.
b. Four of the 5 studies analyzed show benefit.
c. The 5 randomized trials came from different countries.
d. The studies did not show a statistically significant increase or decrease in perinatal mortality with magnesium sulfate.

18. The aim of a meta-analysis is to pool data to show a difference in outcome when individual studies no not have the statistical power to show a true difference.
a. True
b. False

19. Which of the following best fits the data about magnesium sulfate?
a. It has been calculated that one would have to treat 22 women in preterm labor at less than 34 weeks of gestation to prevent one case of CP.
b. No randomized trial has shown an increase in adverse neonatal events.
c. Side effects of magnesium sulfate are uncommon in the incidence of pulmonary edema is less than 1 in 500.
d. Meta-analyses suggest that magnesium sulfate can reduce the incidence of moderate-to-severe CP by 40%.

20. Which of the following is *not* true of the BRCA genes?
a. They function as a tumor suppressor genes.
b. They primarily repair single-strand DNA breaks.
c. They are crucial to homologous recombination.
d. Dysfunction may occur though genetic or epigenetic mechanisms.

Answers: 14. b, 15. a, 16. c, 17. b, 18. a, 19. d, 20. b.

In Future Issues:

Whole Blood in the Management of Hypovolemia Due to Obstetrical Hemorrhage

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Meta-analysis Compares Antihypertensive Classes

In this issue: Comparing blood pressure medications, determining optimal length of androgen-deprivation therapy, red yeast rice for LDL reduction, and FDA Actions.

Comparison of antihypertensive classes

All classes of antihypertensive drugs are equivalent in preventing CHD and stroke according to a British study. In the largest meta-analysis of randomized trials of blood pressure reduction to date, researchers reviewed the efficacy of the 5 major classes of blood pressure medications (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and calcium-channel blockers). Beta-blockers were found to have a special effect over and above that of blood pressure reduction in preventing recurrent CHD events in people with a history of CHD (29% risk reduction vs 15% with other drugs), although this affect was limited to a few years after myocardial infarction. Otherwise, the 5 main classes and blood pressure-lowering drugs were similarly effective in preventing CHD events and strokes, with the exception of calcium-channel blockers, which have a slightly higher benefit in preventing stroke (relative risk, 0.92; 95% confidence interval, 0.85-0.98). There was benefit in reducing risk of CHD and stroke with BP-lowering treatment regardless of the patient's pretreatment blood pressure, surprisingly even as low as 110 mmHg systolic and 70 mmHg diastolic. Treatment with blood pressure-lowering medications was also associated with a 13% reduction in all-cause mortality, although there was no reduction in cancer or nonvascular related deaths. The authors conclude that blood pressure lowering is important in everyone over a certain age regardless of pretreatment blood pressure and that all classes of blood pressure medications had similar effective in reducing CHD events and stroke (*BMJ* 2009;338:b1665).

Length of androgen-deprivation therapy

Men with locally invasive prostate cancer who have received external beam radiation do better with 3 years of androgen-deprivation therapy compared to 6 months of therapy according to a new study from Europe. After receiving radiation therapy, 970 men were randomly assigned to 6 months of androgen suppression (n = 483) vs 3 years of suppression (n = 487). After mean follow-up of 6.4 years, 132 patients in the short-term group and 90 patients in the long-term group had died. The number of deaths due to prostate cancer was 47 in the short-term group and 29 in the long-term group. The 5-year overall mortality was 19% vs 15.2% for short-term and long-term suppression, respectively, with an observed hazard ratio of 1.42 (P = 0.65 for non-inferiority). The authors conclude that the combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiation therapy plus 3 years of androgen suppression in men with locally advanced prostate

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cancer (*N Engl J Med* 2009;360:2516-2527). In an accompanying editorial, Peter Albertson, MD, points out the importance of determining the optimal length of androgen-deprivation therapy because of long-term side effects including weight gain, fatigue, hot flushes, osteoporosis, cardiac disease, and depression. With the high level of regular screening for prostate cancer, most men are diagnosed earlier with much lower grade disease than those addressed in this study, and it is unclear whether these findings can be applied to these men with clinically localized cancer. Radiation plus or minus androgen deprivation vs surgery, age of the patient at diagnosis, and staging of the tumor all are important in determining therapy (*N Engl J Med* 2009;360: 2572-2574).

Red yeast rice and LDL

Patients may be asking about red yeast rice for the treatment of hypercholesterolemia because of a recent study in the *Annals of Internal Medicine*. Patients were recruited from a cardiology practice in suburban Philadelphia who had had a history of statin-associated myalgias. Thirty-one patients were randomized to receive red yeast rice 1800 mg or placebo twice daily for 24 weeks. All patients were also enrolled in a 12-week therapeutic lifestyle program. Red yeast rice was effective in lowering LDL-cholesterol an average of 43 mg/dL from baseline at week 12 and 35 mg/dL at week 24 compared to reductions of 11 mg/dL at week 12 ($P < 0.001$) and 15 mg/dL at week 24 ($P = 0.011$) in the lifestyle-only group. Total cholesterol was also lowered in the treatment group, although there was no change in HDL-cholesterol or triglycerides. Treatment with red yeast rice was not associated with changes in liver enzymes or CPK levels and there was no difference in weight loss or pain severity scores between the two groups. The authors conclude that red yeast rice and therapeutic lifestyle change decreased LDL-cholesterol without increasing CPK or pain levels in patients with a history of statin-related myopathy (*Ann Intern Med* 2009;150:830-839).

The study is interesting because of the large number of patients who do not tolerate statins due to muscle pain and weakness. These patients frequently experience myalgias without myositis (normal CPK levels), and the majority continue to have symptoms despite dose adjustments or changing to a different statin. Red yeast rice is a Chinese supplement known to contain naturally occurring lovastatin (monocolin K) and other monocolins that inhibit HMG-CoA reductase, the same enzyme targeted by statins. It is unclear why red yeast rice is better tolerated than commercial statins, but the authors suggest it may be due to the relatively low dose of the statin, or other, yet undiscovered properties of red yeast rice. The authors also point out that since red yeast rice is a supplement, the chemical composition of different manufacturers is problematic and that patients should be monitored while taking the product. These findings beg the question whether low-dose generic lovastatin may be equally well tolerated, but future studies may help determine if red yeast rice has unique properties that make it an option for the many patients who do not tolerate statins and need to lower cholesterol. In 2007, the FDA issued a warning to consumers to avoid red yeast rice because it contains a pharmaceutical drug, though most products marketed in this country contain negligible amounts of lovastatin.

FDA Actions

The FDA has alerted consumers that 3 Zicam® products may result in long-lasting or permanent loss of smell (anosmia). Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs Kids Sized are all implicated, and the FDA is recommending that consumers stop using the products and throw them away. All 3 of these products contain zinc, which has not been shown to be effective in reducing the duration or severity of cold symptoms. Other Zicam oral tablets and lozenges have not been included in this advisory. Matrixx Initiatives, the manufacturer of Zicam, is offering refunds for the 3 products noted above. The company is also withdrawing the two adult products from the market — Cold Remedy Swabs Kids Sized had been previously withdrawn. There have been more than 130 reports of anosmia associated with intranasal Zicam product use ranging from 1 dose to long-term use.

The FDA has approved the first formulation of parenteral ibuprofen to treat fever and pain in hospitalized patients. The drug is given intravenously over 30 minutes in doses of 400-800 mg every 6 hours as needed for pain; lower doses are indicated for fever. As with all NSAIDs, caution is warranted when using injectable ibuprofen in patients with heart failure, renal dysfunction, increased risk for thrombosis, or history of ulcers or GI bleeding. Injectable ibuprofen is marketed by Cumberland Pharmaceuticals as Caldolor™. ■