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INSIDE

Pharmacists and Emergency Contraception

ABSTRACT & COMMENTARY

Synopsis: *Personal beliefs should not be imposed on others.*

CANTOR AND BAUM, LAWYERS FROM THE YALE UNIVERSITY School of Medicine, have written an op-ed piece in the *New England Journal of Medicine* focusing on the central role of pharmacists in providing emergency contraception. The recent decision by the Food and Drug Administration not to grant over-the-counter availability for emergency contraception has ensured that for a while there will continue to be the problem of a patient needing to obtain and fill a prescription within the narrow window of treatment associated with emergency contraception. There are now 6 states that allow pharmacists to provide emergency contraception without a prescription, but the collaboration of pharmacists is essential, and individual pharmacists do not always cooperate. Indeed, there are reports in the literature of pharmacists refusing to provide emergency contraception, even following a rape, citing personal moral grounds as a legitimate reason for this refusal. These examples are not new, but there is concern that the frequency may be increasing. There are 3 states (Arkansas, Mississippi, and South Dakota) that have legislated legal protection for pharmacists who cite "conscientious objection" as a reason to refuse to dispense emergency contraception. Similar legislation has been proposed in many other states.

They review 3 arguments supporting a pharmacist's right to object: 1) The exercise of independent judgment; 2) Employment should not require a change in personal morals; and 3) Conscientious objection is a personal right in a democracy. Independent judgment is inherent in the practice of a profession, and the courts have established that pharmacy is a profession and a part of health care services. The choice to serve a patient is a component of most, if not all, professions; and it is argued that professionals should have the right to be consistent with their morals. In addition, professionals have a right of refusal by virtue of a democracy that protects against conflicts with personal ethical, moral or religious convictions.

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There are also arguments against a pharmacist's right to object: 1) Entering a profession creates obligations; 2) Emergency contraception is not an abortifacient; 3) Pharmacists' refusals have an adverse effect on patients' health; and 4) Refusing service has no clear-cut limitations. Pharmacists themselves have argued that a patient's interests come first, and that willingly entering the profession is a choice that carried with it fiduciary obligations. Science and organizations have concluded that emergency contraception is not the same thing as an induced abortion and, therefore, this should not be a reason to refuse services to a patient. It is argued that a pharmacist's objection imposes personal religious beliefs on another, and forces an unwanted burden on the patient, especially because the timing of the treatment is an urgent consideration. Personal moral objections can be used as a reason to refuse service in other categories such as treatment for HIV infection.

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Cantor and Baum reject the alternatives of either an absolute right to object or no right to object, and believe that "state efforts to provide blanket immunity to objecting pharmacists are misguided." But they also believe that it is not appropriate for refusal to be illegal for 3 reasons: emergency contraception is not a true, absolute emergency; other options exist; and personal morals deserve consideration. At the same time, it is not appropriate to leave patients to solve the problem themselves. It is appropriate, ethically and legally, in the presence of an objection, to require referral to another resource. Cantor and Baum argue that pharmacists who object to providing emergency contraception should arrange for another pharmacist to provide this service, and that pharmacies should strive to have at least one nonobjecting pharmacist. A nonprescribing pharmacy could display a sign referring the patient to Planned Parenthood or the emergency contraception web site and hotline. These policies have been endorsed by the American Pharmacists Association. Appropriate referral maintains a standard of professional responsibility, and Cantor and Baum conclude that when pharmacists "pledge to serve the public, it is unreasonable to expect those in need of health care to acquiesce to their personal convictions." Finally, there is a need to educate pharmacists about the mechanism of action for emergency contraception and that the use of emergency contraception is safe (Cantor J, Baum K. *N Engl J Med*. 2004;2008-2012).

COMMENT BY LEON SPEROFF, MD

The mechanism of action for emergency contraception is not known with certainty, but it is believed with justification that this treatment combines delay of ovulation with a local effect on the endometrium and prevention of fertilization.[1-6] How much a postfertilization effect contributes to efficacy is not known, but it is not believed to be the primary mechanism.[4,7] Indeed, an experiment in monkeys could detect no effect of a high dose of levonorgestrel administrated post-coitally once fertilization had occurred.[8] Clinicians, pharmacists, and patients can be reassured that treatment with emergency contraception is not an abortifacient.

Levonorgestrel in a dose of 0.75 mg given twice, 12 hours apart, is more successful and better tolerated than the combination oral contraceptive method.[9,10] In many countries, special packages of 0.75 mg levonorgestrel (Plan B, Norlevo, Vikela) are available for emergency contraception. Greater efficacy and fewer side effects make low-dose levonorgestrel the treatment of choice.

Clinicians have an important role to play in this

problem. There are 2 recommended procedures: 1) To identify local pharmacies that will provide emergency contraception; and 2) To directly provide treatment as well as education about this method before it is needed.

Clinicians should consider providing emergency contraceptive kits to patients (a kit can be a simple envelope containing instructions and the appropriate number of oral contraceptives) to be taken when needed. It would be a major contribution to our efforts to avoid unwanted pregnancies for all patients without contraindications to oral contraceptives to have emergency contraception available for use when needed. This would be much more effective in reducing the need for abortion than waiting for patients to call. In studies of advanced provision and self-administration, adult women in Scotland and Hong Kong and younger women in San Francisco, Pittsburgh, and Mexico increased the use of emergency contraception without adverse effects such as increasing unprotected sex or changing the use of other contraceptive methods.[11-17]

Information for patients and clinicians, including the latest available products and clinicians who provide emergency contraception, can be obtained from the web site and hot line maintained by the Office of Population Research at Princeton University: http://ec.princeton.edu

Telephone hotline: 1-888-NOT-2-LATE or (1-888-668-2528) ■

References

1. Young DC, et al. *Obstet Gynecol*. 1994;84:266.
2. Swahn ML, et al. *Acta Obstet Gynecol Scand*. 1996;75: 738-744.
3. Trussell J, Raymond EG. *Obstet Gynecol.* 1999;93: 872-876.
4. Marions L, et al. *Obstet Gynecol*. 2002;100:65-71.
5. Croxatto HB, et al. *Contraception*. 2002;65:121-128.
6. Durand M, et al. *Contraception*. 2001;64:227-234.
7. Trussell J, et al. *Contraception*. 2003;67:167-171.
8. Ortiz M, et al. *Hum Reprod*. 2004;19:1352-1356.
9. Ho P, et al. *Hum Reprod*. 1993;8:389-392.
10. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet*. 1998;352:428-433.
11. Glasier A, et al. *N Engl J Med*. 1998;339:1-4.
12. Raine T, et al. *Obstet Gynecol*. 2000;96:1-7.
13. Jackson R, et al. *Obstet Gynecol*. 2003;102:8-16.
14. Gold M, et al. *J Pediatr Adolesc Gynecol*. 2004;17: 87-96.
15. Walker DM, et al. *J Adolesc Health*. 2004;35:329-334.
16. Lo SS, et al. *Hum Reprod*. 2004;19:2404-2410.
17. Raine T, et al. *JAMA*. 2004;in press.

Effect of DHEA on Abdominal Fat and Insulin Action in Elderly Women and Men

ABSTRACT & COMMENTARY

Synopsis: *Administration of 50 mg of DHEA to elderly men and women for 6 months improved insulin action and decreased abdominal fat.*

Source: Villareal DT, Holloszy JO. *JAMA*. 2004;292: 2243-2248.

Abdominal fat increases with advancing age and has been linked to increased risk for diabetes and cardiovascular disease. While insufficient exercise and overeating certainly contribute to age-related acquisition of abdominal fat, hormonal and metabolic factors also have been implicated. Even thin individuals who exercise regularly display increased abdominal fat as they age. This study aimed to determine whether the age-related decline in the adrenal hormone dehydroepiandrosteroine (DHEA) was one of the hormonal factors linked to increased abdominal adiposity and insulin resistance.

Elderly men (n = 28) and women (n = 28) between the ages of 65 to 78 years were enrolled and randomly assigned to receive either placebo or 50 mg of DHEA orally each day for 6 months. The mean body mass index of the men was 28 kg/m^2 and that of the women was 27 kg/m^2. Those using other hormones and having serious illnesses were excluded. Primary outcome variables were visceral and subcutaneous abdominal fat measured by magnetic resonance imaging and glucose and insulin responses to an oral glucose tolerance test. Ancillary outcome variables included food intake and levels of IGF-1, PSA, estradiol, and testosterone.

DHEA administration raised participants' serum DHEA-sulfate (DHEAS) into the young physiological range. In women, DHEA use increased testosterone and estradiol, but only estradiol was raised in men. Both groups showed increased IGF-1. SHBG did not change. Those who used DHEA lost about 2 pounds over the 6 months. Weight loss was similar in men and women. Recorded food intake stayed the same. Both men and women lost abdominal visceral fat, but women lost slightly more than men, 10 vs 7%. Abdominal fat declined 6% in both men and women. Insulin sensitivity improved dramatically and there was an inverse association between changes in insulin sensitivity and visceral fat. There were

no adverse events and PSA did not change appreciably in men. Villareal and associates point out that the long-term safety of DHEA use remains unknown. However, based on the outcome variables followed in the study, short-term use appears to positively effect metabolism.

COMMENT BY SARAH L. BERGA, MD

Many physiological functions change with age. Adrenal function shows a dramatic ontological pattern that includes both adrenarche during childhood and adrenopause during the senescent years. There can be no doubt that adrenarche causes phenotypic changes. These include growth of axillary and other body hair, increased sebaceous gland secretion, altered body odor, and thickening and pigmentation of the skin. The phenotypic features of adrenopause are less well chronicled, possibly because adrenopause occurs over decades (starting at age 25 years) whereas adrenarche happens over a few years (typically from ages 7-9 years). The results of this study suggest that the increased abdominal adiposity so typical of advancing age is at least partly caused by a decline in the adrenal secretion of the androgenic hormone, DHEA. The exact mechanisms by which DHEA exerts its impact is still a subject of conjecture, although Villareal et al suggest that DHEA activates the peroxisome proliferator-activated receptor alpha (PPAR), a transcription factor that regulates fatty acid transport proteins that facilitate fatty acid entry into cells and enzymes involved in the oxidation of fatty acids. In other words, DHEA modifies fundamental metabolic pathways in a way that favors fat oxidation and reduces fat deposition.

When these changes occur as part of the tightly orchestrated ontological script that gates the aging process, they are deemed physiological, but that does not necessarily mean they are always desirable. Perhaps we should think of adrenopause as hastening what could be viewed as the "metabolic syndrome of aging." And just as we have medicalized many processes associated with aging, such as osteoporosis, cognitive decline, and menopause, we are now looking to retard other aspects of the aging process by safe and feasible means. I should point out that the "we" in the above sentence does not refer to the medical or pharmaceutical industries, but to the American public. DHEA, a powerful hormone, is classified as a food supplement for FDA purposes and is sold over the counter. Given that it is a biological agent, it cannot be patented, so there is little pharmaceutical house interest in it.

The study does not describe in detail the phenotypic or cosmetic side effects found with DHEA use in this population, but previous studies by other groups have shown that chronic DHEA use can cause androgenic side effects in women, including acne, accelerated balding, or facial hair growth in women. Other studies have suggested that DHEA improves libido, muscle mass, and energy level in those older than age 70 years, but not in perimenopausal women. DHEA can be obtained from many sources, including compounding pharmacies. I would strongly caution against using dessicated bovine adrenal as the source, as this preparation carries the risk of biological contaminants, including prion disease. Of course, medications sold as food supplements are not held to good manufacturing practices, so the quality and uniformity of over-the-counter preparations cannot be guaranteed.

Compounding pharmacies also can prepare a topical preparation. If one administers DHEA, it is best to monitor serum DHEAS levels before and after to ensure that levels are low before instituting therapy and that the levels do not rise above physiological levels after chronic use. Testosterone and estradiol circulate in nanogram and picogram quantities, but DHEAS circulates in the milligram range, so the assays available to monitor levels are robust and reliable. DHEAS has a long half-life and therefore lacks a circadian pattern and can be measured at any time of day.

In summary, DHEA is yet another of the many agents being studied for use in retarding the physiological consequences of aging. Patent opportunities notwithstanding, as the American public grays, there will be increasing demand for nutraceuticals that have promise and appear safe. We can only hope that the hype will be constrained by proactive clinical investigation.

Efficacy of a Bivalent L1 Virus-Like Particle Vaccine in Prevention of Infection with Human Papillomavirus Types 16 and 18 in Young Women

ABSTRACT & COMMENTARY

Synopsis: *The bivalent HPV vaccine was efficacious in prevention of incident and persistent cervical infections with HPV-16 and HPV-18, and associated cytological abnormalities and lesions. Vaccination against such infections could substantially reduce incidence of cervical cancer.*

Source: Harper D, et al. *Lancet*. 2004;364:1757-1765.

The most important clinical manifestation of persistent human papillomavirus (HPV) infection is

development of uterine cervix cancer. Worldwide this preventable cancer continues to be a dominant killer and a significant contributor to years of life lost in women. Two years ago efficacy of a monovalent vaccination program was demonstrated against the most common oncogenic HPV type, HPV-16. In the current report, Harper and colleagues report efficacy, safety, and immunogenicity of a bivalent HPV-16/18 L1 virus-like particle (VLP) vaccine. Outcome measures were the prevention of incident and persistent infection with these 2 virus types, associated cervical cytological abnormalities, and development of precancerous lesions. In this study, 1113 women between 15 and 25 years of age participated in this randomized, double-blind, placebo-controlled trial. All were required to be negative for HPV infection at enrollment.

The primary outcome measure was HPV-16/18 infection between 6 and 18 months after enrollment. Participants received 3 doses of either the vaccine formulated with AS04 adjuvant or placebo on a 0 month, 1 month, and 6 month schedule in North America and Brazil. Women were assessed for HPV infection by cervical cytology and self-obtained cervicovaginal samples for up to 27 months. Vaccine safety and immunogenicity were also evaluated. Among women who received all 3 doses, vaccine was 92% effective against incident infection and 100% effective against persistent infection with HPV-16/18. In the intention-to-treat analyses, vaccine efficacy was 95% against persistent cervical infection with HPV-16/18 and 93% against cytological abnormalities associated with HPV-16/18 infection. The vaccine was safe, generally well tolerated, and highly immunogenic. Harper et al concluded that the bivalent HPV vaccine can prevent incident and persistent cervical infections with HPV-16 and HPV-18, and their associated cytological abnormalities and lesions. Widespread vaccination programs against these infections could substantially reduce incidence of cervical cancer.

COMMENT BY ROBERT L. COLEMAN, MD

The causal link between HPV infection and development of uterine cervix cancer is now well established and represents an important association underlying developmental therapeutics directed at reducing incident disease. In countries with well-established screening programs for HPV and its associated cervical precancerous pathologies, impressive reductions in disease-specific mortality are the fruit of these initiatives. However, most of the world's incident cancers are located in countries with little capacity for national screening efforts and affected women experience greater reductions in life expectancy from cervix cancer than complications associated with HIV, pregnancy, and tuberculosis. Even in countries where limited screening does exist, follow-up care, whether it be for treatment or repeat cytology, is even more limited and efforts to gain greater compliance are unlikely to make a measurable difference in incident disease. Clearly the cliché, "An ounce of prevention is worth a pound of cure. . ." is relevant and such an effort would be particularly life saving.

In a 2002 landmark article in the *New England Journal of Medicine*, Koutsky and colleagues demonstrated the merits of a vaccination program against HPV-16 with a monovalent L1 virus-like particle vaccine.[1] Given the association of this viral subtype in more than 60% of cervical cancers, this target was valid. The highly anticipated results demonstrated a clear benefit for 768 vaccinated women against persistent infection and associated cervical dysplasia. In the current well-conducted trial, a bivalent vaccine was used in a similar manner, targeting both HPV-16 and HPV-18. While the addition of HPV-18 represents only about an additional 10-15% of cancers, it is an important addition, as this viral subtype is associated with adenocarcinoma and its precursor lesions. Typically, these are more difficult to screen by Pap smear and represent and important increasingly recognized cohort.

The efficacy of the vaccine in preventing incident disease, reducing persistence of HPV infection (a recognized necessary component in the pathogenesis of cancer) and preventing cytological abnormalities is proof-of-principle and a critically important advance in this regard. Indeed, the one cytological abnormality identified in the vaccinated cohort was judged a result of a viral subtype (HPV-51) not vaccinated against. The measured acute immunogenicity brought about by the vaccine was hundreds of fold higher than that produced by a native infection and persisted as several folds higher for the duration of the trial.[2,3]

These latter 2 points represent some of the important questions that must be addressed as these products undergo further development. For instance, how many different HPV subtypes should be included? What effect will HPV infections with subtypes not immunized against have on clinical outcomes? How long will the immunity last? When should a booster be given? Will vaccination be efficacious in the treatment of known disease? When should first immunization be undertaken? Should both men and women be vaccinated? How do you roll out a national vaccination program? Answers to these questions will likely be answered in the years to come. Our distinct hope is that a global effort will be extended in eradicating this "preventable" cancer. ■

References

1. Koutsky LA, et al. *N Engl J Med*. 2002;347:1645-1651.
2. Pinto L, et al. *J Infect Dis*. 2003;188:327-338
3. Munoz N, et al. *Int J Cancer*. 2004;111:278-285.

Non-Invasive Prenatal Diagnosis Screening

ABSTRACT & COMMENTARY

Synopsis: *This study demonstrates that a sequential screening program that provides patients with first-trimester results and offers the option for early invasive testing or additional serum screening in the second trimester can detect 98% of trisomy 21-affected pregnancies. However, such an approach will result in 17% of patients being considered at risk and, hence, potentially having an invasive test.*

Source: Platt LD, et al. *Obstet Gynecol*. 2004;104(4): 661-666.

NON-INVASIVE PRENATAL DIAGNOSTIC SCREENING has become a hot topic of late. Large studies from England, Europe, and now 2 from the United States have borne out the efficacy of first trimester ultrasound determined nuchal translucency (NT) testing, with or without additional information provided by first trimester biochemical analysis (beta-hCG and PAPP-A). Now the data from one of these NICHD-funded studies (First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening [BUN]) have been published regarding the usefulness of adding a second trimester triple screen to the diagnostic mix.

Platt and colleagues tracked 4325 patients of the original 7392 patients having first trimester NT and biochemical screening who elected to have second trimester testing through triple screening (total hCG, unconjugated estriol, and alpha-fetoprotein). In this study, 4145 patients had a negative first-trimester screen and 180 had a positive first-trimester screen (> 1:270).

In the 4325 first-trimester screen-negative sample, there were seven fetuses with trisomy 21, 6 of whom were picked up by the second trimester biochemistry. All 7 cases of trisomy 21 that were in the screen positive group were also identified with the second trimester biochemistry, but there was a screen positive rate of 38% in this group. Platt et al found that by using both first and second trimester testing together in this way (the sequential method) a sensitivity of 98% could be attained with a cut-off for trisomy 21 of 1:270 at an overall false-positive rate of 17%.

COMMENT BY JOHN C. HOBBINS, MD

Over the past 5 years various combinations of prenatal testing for Down syndrome have emerged: 1) ultrasound assessment of NT alone (with or without evaluation of the fetal nasal bone); 2) combined—NT and first trimester biochemistry; 3) integrated—NT, first trimester biochemistry and second trimester quad screen (hCG, E3, MSAFP, and Inhibin-A); and now 4) sequential—as described above. The difference between the integrated method and the sequential method is simply that with the former only one risk figure is generated which is only available to the patient after the results of the second trimester biochemistry are in. With the sequential approach each patient will get 2 sets of results: one at the end of the first trimester and another a short time after the second trimester blood is drawn. The advantage of the sequential method is that the patient can weigh her options at least 2½ weeks earlier than the patient enrolling in the integrated program. The theoretical advantage of the integrated screen is that it is more sensitive than the sequential while generating fewer false positives.

It is interesting that some individuals initially challenged the ethics of the soon to be published First and Second Trimester Evaluation of Risk Trial (FASTER) trial in which information about the thickness of the NT and the biochemistry was withheld until the second trimester data had been folded into the results. In fairness, however, if cystic hygromas or large NT's were found in the FASTER study, the patient was immediately notified at the time of the ultrasound scan. Also, when the study was initiated the compelling data from Britain was not matched by results from the only United States study at the time which had a sensitivity of 33%, compared with the NT data from the Landmark British Trial, suggesting a sensitivity > 75%. The FASTER study represented a way to independently assess in an American population the true sensitivity of NT testing with well-trained operators using compulsively standardized methods. Fortunately, this study and the BUN investigation have yielded information that is very similar to the British group's data.

Now patients have a variety of options available to them, which, hopefully, can be laid out in a way that is reasonably easy to understand (despite the nuances involved). We have not even touched upon the role a genetic sonogram might play as either an additional diagnostic adjunct or as a substitute for, let's say, second trimester biochemistry. The obvious benefit would be to

identify non-chromosomal anomalies and those forms of aneuploidy, such as trisomy 13, which might not be screened in by the above testing regimens. Data from patients in the FASTER trial suggest that the genetic sonogram also will pick up the remaining trisomy 21's not screened in with NT and first and second trimester biochemistry testing.

The goal of all non-invasive testing, which seems to be close to being met, is to limit the need for chorionic villus sampling and amniocentesis to a minimum while re-assuring with reasonable accuracy the overwhelming majority of patients that their risk of having a fetus with trisomy 21 is substantially lower than the risk of invasive testing. ■

Additional Reading

- Wapner R, et al. *N Engl J Med*. 2003;349:1405-1413.
- Snijders RJ, et al. *Lancet*. 1998;352:343-346.
- Pandya PP, et al. *Br J Obstet Gynaceol*. 1995;102: 957-962.
- Krantz DA, et al. *Am J Obstet Gynecol*. 1996;174: 612-616.
- Wald NJ, et al. *Lancet*. 2003;361:835-836.
- Hobbins JC, et al. *J Ultrasound Med*. 2003;22:33-38.

Raloxifene and Breast Cancer: The CORE Study

ABSTRACT & COMMENTARY

Synopsis: *Raloxifene treatment of postmenopausal women with osteoporosis is associated with a lower incidence of estrogen receptor-positive invasive breast cancer.*

Source: Martino S, et al. *J Natl Cancer Inst*. 2004;96: 1751-1761.

Martino and colleagues report the results of the Continuing Outcomes Relevant to Evista (CORE) trial, on the incidence of breast cancer. The MORE trial, the Multiple Outcomes of Raloxifene Evaluation trial, was a randomized, double-blind, multicenter clinical study of postmenopausal women with osteoporosis that reported a 72% reduction in estrogen receptor-positive invasive breast cancer in the treatment group after 4 years compared to placebo. The CORE study was designed to measure the impact of 4 additional years of raloxifene (60 mg/d), to begin during the fourth year of the MORE trial. Of the 7705 participants initially randomized in the MORE trial, 3510 women elected to continue raloxifene treatment (2336 completed the CORE trial) and 1703 continued on placebo (1106 completed the trial). During the 4-year CORE study, raloxifene treatment was associated with a 66% (HR = 0.34; CI = 0.18-0.66) reduction of estrogen receptor-positive invasive breast cancer in the treated group. There was no difference in estrogen receptor-negative tumors. Over the entire 8-year period, the reduction in estrogen receptor-positive cancers reached 76%. In the 8-year period, there was no difference in the number of deaths in the 2 groups.

■ COMMENT BY LEON SPEROFF, MD

Overall, these results support a preventive effect of raloxifene treatment on the incidence of estrogen receptor-positive invasive breast cancer. The strength of this observation, however, can be questioned because of some problems within the study. One concern is the fact that the beginning of the CORE trial did not exactly coincide with the end of the MORE trial. From the end of the first 4-year study to the beginning of the next 4-year study, participants were not involved in study regulation for a time period that ranged from 2.6 to 62 months. During this interval, some participants experienced a long period without exposure to raloxifene, others used a standard regimen of hormone therapy, and those who experienced an adverse event, including breast cancer during this interval were excluded from the study. The characteristics of this interval and the impact on the results are issues essentially not addressed in this report.

The reduction in breast cancer observed in the 4 years of the MORE trial continued during the 4 years of the CORE study, and it is possible that the results in the second 4-year period reflect the effect of the initial 4 years. At the same time, the results are compatible with an ongoing impact beyond 4 years. Although the percentage of reduction is impressive, keep in mind that the actual numbers are not large: 21 cases of estrogen receptor-positive cancers in the placebo group and 15 in the treated group. In the entire 8-year period, the numbers added up to 58 in the placebo group and 40 in the treated group.

It is impossible to determine if there is a special high-risk group for whom this treatment is recommended. At the beginning of the CORE study, the women were assessed with the Gail breast cancer risk model. There was no difference between the treatment and placebo groups Gail predicted risk (about half were considered to be at high risk).

If medical treatment is truly preventive, one would expect to see a reduction in noninvasive breast cancer in the treated individuals. In the CORE trial there were

only 9 cases (2 in the placebo group and 7 in the treated group) and in the 8-year period only 7 cases in the placebo group and 16 in the treated group, a number too small to allow confident analysis. On the other hand, an effect only on invasive disease without an effect on noninvasive disease keeps the possibility alive that raloxifene is affecting preexisting tumors. In contrast, a reduction in noninvasive disease has been reported with the preventive use of tamoxifen.[1] One might conclude that the different results with tamoxifen and raloxifene reflect the risk level of disease in the 2 populations studied, high risk for breast cancer in the tamoxifen studies and low risk in the raloxifene osteoporosis study. However, as noted, assessment of breast cancer risk with the Gail model in the raloxifene study indicated that at least half of this population was also at high risk of breast cancer.

The evidence supports tamoxifen reduction of the risk for estrogen receptor-positive breast cancer, but at the same time, tamoxifen should not be recommended as a preventive agent, except for women at very high risk. This conclusion is based upon the degree of reduction in risk compared with the incidence of side effects. The evaluation by the National Cancer Institute is very helpful.[2,3] Because the risks associated with tamoxifen (endometrial cancer, stroke, pulmonary embolism, and deep vein thromboembolism) increase with age, balancing the risks and benefit indicates that tamoxifen is best for younger women with an elevated risk of breast cancer (an increased relative risk of approximately 1.7). A similar conclusion was reached by a working group of the American Society of Clinical Oncology.[4] This means that only a relatively small number of women qualify, about 5% of American white women and 0.6% of black women.[3]

The data are too limited to support the use of raloxifene as prophylactic treatment, and a stronger position awaits the outcome of the STAR trial comparing tamoxifen with raloxifene and the RUTH trial assessing the effect of raloxifene on both cardiovascular disease and breast cancer. The Medical Research Council of the United Kingdom and the National Cancer Institute of the United States have reached similar conclusions.

It is well-recognized that raloxifene shares with tamoxifen and estrogen about a two-fold increase in venous thrombosis. However, the increase observed in the 8 years of the combined MORE and CORE population did not achieve statistical significance, a problem of relatively small numbers because of the infrequency of this event. It is noteworthy that the 9 cases of pulmonary embolism all occurred in the raloxifene group. ■

References

1. IBIS INVESTIGATORS. *Lancet*. 2002;360:817-824.
2. Gail M, et al. J Natl Cancer Inst. 1999;91:1829-1846.
3. Freedman A, et al. *J Natl Cancer Inst*. 2003;95: 526-532.
4. Chlebowski R, et al. *J Clin Oncol*. 2002;20:3328-3343.

CME Questions

1. **The following statements regarding emergency contraception are true *except*:**
   a. Emergency contraception is available over-the-counter in some states in the United States.
   b. There is no evidence that emergency contraception is an abortifacient.
   c. All drugs used for emergency contraception have equivalent efficacy.
   d. The American Pharmacists Association is opposed to individual pharmacists obstructing access to emergency contraception.

2. **When given orally to women, DHEA use leads to an increase in which one of the following hormones:**
   a. Cortisol
   b. 17-hydroxyprogesterone
   c. Estradiol
   d. Aldosterone
   e. Adiponectin

3. **The following statements are true regarding raloxifene treatment and the risk of breast cancer *except*:**
   a. Raloxifene decreases the incidence of postmenopausal breast cancer in-situ.
   b. It is premature to recommend raloxifene for the prevention of breast cancer.
   c. The effect of raloxifene appears to be limited to postmenopausal estrogen receptor-positive, invasive breast cancer.
   d. There is no reason to believe that raloxifene, tamoxifen, and estrogen differ in their effect on the risk of venous thrombosis.

Answers: 1 (c); 2 (c); 3 (a)

PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.