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INSIDE

Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Controlled Trial

ABSTRACT & COMMENTARY

Synopsis: *The use of CEE conferred protection against fracture without an increase in breast cancer but with an increased risk of hypertension, stroke, and venous thromboembolism.*

Source: The WHI Steering Committee. *JAMA*. 2004;291:1701-1712.

THE GOAL OF THIS ARM OF THE WHI TRIAL WAS TO DETERMINE whether a standard oral 0.625 mg dose of conjugated equine estrogen (CEE) would confer cardioprotection when given to hysterectomized women with common health burdens typical for their age. A total of 10739 women were enrolled between 1993 and 1998. At the time of study termination, about half of the women in each arm (placebo or CEE) had already stopped taking their assigned medication. At enrollment, more than 80% of the women had had a hysterectomy before age 50, but only 40% of the enrollees had had a bilateral oophorectomy. About 45% of the women were in the age range 60-69 years and 25% were between 70-79 years old at the time of enrollment. The oldest women were enrolled first and thus were followed the longest. In the survival curves, the age of the cohort in the last years was most likely older than the mean age of the entire study population. The authors do not comment of how this aspect of the study design might have skewed the results. Because the data were analyzed by intention-to-treat, the survival curves also include those who were noncompliant. Interestingly, while CEE appeared to reduce cardiovascular risk in women between ages 50-59 years, this is the group with the shortest duration of follow-up and least number of events, so therefore the group for which there was the least power.

For quick reference, the overall findings are summarized in the Table. The hazard ratios for the compliant group are also included when given in the text. I have highlighted the statistically significant

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findings. The most robust finding is that CEE provided significant protection against fractures. An increase in the risk of stroke and VTE was noted. Breast cancer risk was not increased and could be interpreted as decreased.

COMMENT BY SARAH L. BERGA, MD

Those who enjoy ambiguity and complexity will certainly be rewarded by the release of the most recent WHI data. However, this ambiguity presents an additional challenge to those whose job it is to explain the results to already bewildered women. Where do these latest data leave us as practitioners?

Taking the results of the estrogen-only arm of the WHI at face value and assuming that they are generally applicable to unselected women using an oral estrogen product, one can feel confident that CEE protects against fractures. However, one will be left having to explain why the breast cancer results differed from those in the combined estrogen-progestin arm of the WHI that received so much attention when it was released about 2 years ago. One wonders if the difference is explained by the use of progestagens in general or medroxyprogesterone acetate in particular. However, it is true that the 2 populations were somewhat different in health burden and thus technically it is not proper to directly compare the results of the 2 arms. For breast cancer risk, the negative impact of progestins has been shown in other studies, including the controversial Million Woman Study published in the *Lancet* in August of 2003. Although not widely acknowledged, several studies have shown a trend for reduced breast cancer risk in estrogen-only users.

The question about the impact of progestagens upon various tissues and disease processes remains largely unanswered by the trial, although an original aim of the study was to determine if progestagens counteracted the benefits of estrogen upon cardiovascular risk. The PEPI trial attempted to determine the impact of different progestagens, including micronized progesterone delivered orally, but the trial size was much smaller and had minimal power to detect meaningful differences among progestagens. So the question about how different progestagens impact overall risk, especially for cardiovascular events and breast cancer, remains open. There is evidence to suggest that progesterone causes vasodilation whereas other progestagens cause modest vasoconstriction. One can imagine a scenario whereby small risks (such as the combination of mild hypertension, mild hypercoagulability, and mild vasoconstriction) synergistically amplify the impact of each other, especially in older women with pre-existing cardiovascular burden, but this notion has received minimal direct investigative attention.

A finding from the present study that has not received much attention is that systolic blood pressure at 1 year was higher by a mean of 1.1 mg Hg in women taking CEE and remained similarly elevated throughout follow-up. Diastolic blood pressure did not differ between the two groups. The authors note in the discussion that the small but persistent increase in systolic blood pressure is one possible contributor to the increased risk of stroke and lack of cardiovascular benefit in the older age groups. The risk of stroke would have likely been further increased by the pro-coagulant effect of oral CEE, which is amply demonstrated by the increased risks of deep-vein thrombosis (DVT) and pulmonary embolism (PE). One is tempted to conclude that the present study design reveals the worst case scenario, that is, what happens when an oral estrogen is given without titration to women regardless of age, years since menopause, symptomatology, or overall health burden.

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Table

Results of CEE in Postmenopausal Women with Hysterectomy arm of the WHI

Outcome	Hazard Ratio Overall	UnadjustedConfidence Interval	Adjusted Confidence Interval	Cases	Hazard Ratio for Compliers
CHD	0.91	0.75-1.12	0.72-1.15	376	0.89
Stroke	1.39	***1.10-1.77***	0.97-1.99	276	1.74
VTE	1.33	0.99-1.79	0.86-2.08	179	—
DVT	1.47	***1.04-2.08***	0.87-2.47	131	—
PE	1.34	0.87-2.06	0.70-2.55	85	1.99
Breast Ca	0.77	0.59-1.01	0.57-1.06	218	0.65
Colorectal Ca	1.08	0.75-1.55	0.63-1.86	119	0.92
Hip Fracture	0.61	***0.41-0.91***	0.33-1.11	102	0.48
Vertebral Fx	0.62	*0.42-0.93*	0.34-1.13	103	—
Total Fx	0.70	*0.63-0.79*	*0.59-0.83*	1227	—
Total CVD	1.12	1.01-1.24	0.97-1.30	1557	—
Total Ca	0.93	0.81-1.07	0.75-1.15	780	—
Total Mortality	1.04	0.88-1.22	0.79-1.46	378	1.26
Global Index	1.01	0.91-1.12	0.89-1.14	1397	1.06

Like all good studies, this one raises more questions than it answers. Such is the piecemeal pace of progress. One cannot help wonder what would happen if the VTE risk were eliminated or reduced by using a transdermal approach (Scarabin P, et al. *Lancet*. 2003;362:428-32) and titrating the dose to the lowest level needed to control symptoms. A nonoral route would also be less likely to raise systolic blood pressure. Might the benefits be preserved and the risks ameliorated or eliminated to move the overall global index in favor of benefit by use of a low dose of estradiol delivered nonorally? Total mortality was similar in the placebo and CEE arms in the present study. Is there a way to improve mortality by reducing untoward consequences, such as eliminating stroke and VTE events? Are there particular women who might especially benefit from the use of estrogens postmenopausally and, if so, what are their characteristics?

The hypothesis that estrogen use would synergize with a healthy lifestyle to confer long-term health benefits has not been directly tested in this or any other randomized trial, although earlier observational studies suggested that this might be the case. While the question about neuroprotective effects of exogenous estrogen and progestagens remains open, one would predict that any preparation that causes hypercoagulability and increases the rate of stroke would lead to increased rates of dementia. As noted recently, it is practically impossible to separate vascular and other forms of dementia (Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet*. 2004;363:1139-1146). Given these considerations, one would predict that neuroprotection most likely might be seen with a nonoral delivery of estradiol.

Thoughts About the WHI

Leon Speroff, MD, adds additional commentary.

The published results of the Women's Health Initiative agree with more than 20 years of case-control and cohort data with the exception of the cardiovascular results. Clinicians and patients should regard this as good news. With the exception of breast cancer, the results from the estrogen-only arm of the clinical trial are essentially identical to those in the estrogen-progestin arm.

The report of neither a beneficial effect nor an adverse effect on coronary heart disease gives the impression that the estrogen-only arm represents an improvement over the estrogen-progestin arm. However, the updated results, after central adjudication of diagnoses, indicating an increased risk of coronary heart disease from the canceled estrogen-progestin arm of the WHI did not achieve statistical significance.[1] Indeed, only the first year results were statistically significant in the year-by-year analysis, a conclusion based on a difference of only 19 cases. In the subgroup analysis, only the women who were 20 or more years distant from menopause when they started treatment had a statistically significant increased risk of coronary heart disease (1.71; 95% CI, 1.20-2.50). Subtracting this group from the rest of the participants, coronary heart disease now was observed in an identical prevalence comparing the treated and placebo groups.

In both clinical arms of the WHI, there was an indication that younger postmenopausal women treated with hormones had a decreasing risk of coronary heart dis-

ease over time. The test for trend was significant in both the estrogen-progestin and estrogen-only arms. However, the high dropout rate of about 50% in both arms hampered this analysis because of decreasing numbers over time.

Therefore the 2 arms of the WHI are not so dissimilar in regard to coronary heart disease. Like coronary heart disease, it is reasonable to expect the stroke and vascular dementia (not Alzheimer's disease) data to reflect the effect of hormone therapy given to an older group of women many years distant from menopause. In the canceled estrogen-progestin arm, the only increase in dementia was in the women who were 75 years and older when they started treatment. It is not appropriate to conclude that hormone therapy increases the risk of coronary heart disease, and perhaps stroke, in all postmenopausal women; this conclusion applies only to a specific older group of women.

The WHI concluded (as did many individuals and organizations) that postmenopausal hormone therapy is not a viable intervention for primary prevention of coronary heart disease. We cannot quarrel with the uniform conclusions in a series of secondary prevention trials that hormone therapy does not reduce or slow the progression of established coronary heart disease. The results provide a reasonably solid basis not to recommend postmenopausal hormone therapy for women with existing atherosclerosis in the anticipation of preventing future cardiovascular events. The results also indicate that there is no need to avoid the use of medroxyprogesterone acetate, because there is no clinical difference observed comparing women treated only with estrogen to those treated with estrogen and progestin. Certainly the case for primary prevention of coronary heart disease merits controversy; however, at the same time, the issue is not settled. In my view, there continues to be good reason to believe that hormone therapy can have a beneficial role in the primary prevention of coronary heart disease.

The most important unanswered question in regard to breast cancer is whether postmenopausal hormone therapy initiates the growth of new breast cancers or whether the epidemiologic results reflect an impact on preexisting tumors. Observations that favor an impact on preexisting tumors include: 1) in the studies reporting an increase in risk, the evidence is apparent relatively rapidly, within a few years; 2) the return of the risk ratio in the WHI estrogen-progestin arm almost to 1.0 in year 6, and in the observational data, a return to baseline immediately after discontinuing therapy; 3) no difference in noninvasive breast cancers in the WHI; and 4) the large body of literature documenting lower grade and stage disease in hormone users, resulting in better survival rates.

In contrast, the WHI results in the estrogen-progestin arm indicated an earlier appearance of worse tumors than previously reported in case-control and cohort studies. And of course, the estrogen-only arm of the WHI indicated a reduced risk of breast cancer, although it failed to reach statistical significance. It is important to keep in mind that the participants in the 2 arms of the WHI were not identical.[2] In regard to risk factors for breast cancer, the women in the estrogen-only arm experienced more births and bilateral oophorectomy and more and longer duration of previous hormone therapy. It is possible that earlier and greater use of hormone therapy before participation in the study identified those individuals with preexisting tumors who were then excluded from participation, accounting for the lower incidence of breast cancer in the treated group. Postmenopausal hormone therapy is either associated with a small increase in the risk of breast cancer or it affects preexisting tumors. The different results reported by the WHI in regard to tumor characteristics are a puzzle and may reflect the older age of the participants or variations in diagnosis and management.

It is tempting to compare the results obtained in the two arms of the WHI. But there are important differences.[2] The estrogen-only arm had 5859 fewer participants, making it more susceptible to a loss of statistical power with the increasing dropout rate that reached 53.8% over time. In addition to the differences in breast cancer risk factors already mentioned, the women in the estrogen-only arm were more obese, less active, and had more preexisting cardiovascular disease. Therefore, these were 2 different trials with two different populations and treatments, making direct comparisons inappropriate.

The overall news from the WHI has been presented in many forums and in the media in a pessimistic, exaggerated fashion. There are critical questions still unanswered, explanations for adverse results that disagree with previous reports, and impressive good news (protection against fractures and colorectal cancer). In my view, the results of the WHI do not preclude clinicians and patients from making individualized decisions that support postmenopausal hormone therapy. ■

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Special Feature

Adjuvant Radiation Determined for Intermediate Risk Endometrial Cancer! Or has it?

By Robert L. Coleman, MD

The strength of a clinician's recommendation for patient care is greatest in data generated through carefully conducted experimental studies. In many cases, this quality of data is generated from randomized clinical trials where a novel intervention is compared against some standard of care. When properly designed and conducted, positive or negative results will generally provide convincing evidence to support a change in that standard or refute one, particularly if the outcomes are independently confirmed. The US Preventative Services Task Force recognized the confusion of interpreting clinical studies generated a rating system which categorizes both the quality of evidence into 1 of 3 levels and the strength of recommendation into 5 levels.[1] In general, the best quality data (Level 1) and strongest recommendations (Level A) are assigned to data generated through randomized, controlled trials. In the gynecologic cancer business, therapeutic intervention trials, for example, have methodically, albeit slowly, refined the care of affected women, in many cases to the improvement of survival or the reduction of toxicity. With the "muscle" of an international cooperative group research network and expanded collaboration, confirmatory trials have been increasingly contemporaneously launched or provided important data in a timely fashion to help solidify important issues in the care of our patients.

And so it is in the care of women with early, but intermediate risk, endometrial cancer. This disease site will account for approximately 40,320 new cases this year and be responsible for about 7090 cancer-related deaths.[2] Fortunately, many new cases of this disease are early stage, low grade and cured with surgery. However, an important and sizeable fraction of patients are diagnosed either at an older age, with some element of myometrial invasion, or with a higher grade or atypical histology that increases the risk for recurrence. These features we have known for many years and have been well documented through careful surgical staging studies reported more than 20 years ago.[3-6] In addition, 3 randomized controlled clinical trials involving more than 1600 patients and spanning almost 4 decades have been completed (*see Table 1*).[7-9] So it may come as somewhat a surprise that we still don't have a clear answer to the question, "What's the best treatment for women with intermediate risk uterine cancer?"

The latest and likely most anticipated results were recently published and represented the efforts of 40 member Gynecologic Oncology Group institutions and 8 years of accrual.[7] In this trial, "intermediate risk" was defined as any grade non-clear cell or papillary serous adenocarcinoma with any degree of myometrial invasion (FIGO Stage IB, IC), confined to the uterus (FIGO Stage IIA & B [occult]) with negative lymph nodes and cytology. The source for this broad entry criteria was historical and rooted in a prior GOG trial (GOG #33) where patients included in this cohort would have a risk for disease recurrence of 20 to 25% at 5 years with nearly all recurrences occurring within the first 2 years.[4] Surgical staging was required for entry and while adequacy was left to the discretion of the primary surgeon, it included hysterectomy, bilateral salpingo-oophorectomy and nodal sampling from key nodal basins unless enlarged nodes were identified. In the latter case, these were to be biopsied, but if negative, the patient could be enrolled. Eligible patients were randomized to either standard pelvic radiation after surgery or no additional treatment. The primary end point was a variable termed recurrence-free interval (RFI) which was defined as "the time from study entry to clinical, histologic or radiographic evidence of disease recurrence." This is different from the traditional progression-free interval (which was also evaluated in the trial) in that patients who died of intercurrent disease were censored in survival statistics. Ordinarily, these events would be captured as "events." Over the long accrual period, 448 patients were randomized, of which, 392 (88% of total) were included in the final analysis (202 to surgery alone, 190 to surgery + radiation). In regard to the primary endpoint, disease recurrence was reduced by 58% (hazard ratio [HR], 0.42; 90% confidence interval [CI], 0.25-0.73; $P = 0.007$). At 2 years, the recurrence rate was 12% vs 3% in the adjuvant radiation cohort. In fact, the 2 women with vaginal recurrences randomized to radiation actually never received the therapy but are included in the intent-to-treat analysis. Most of this difference was in isolated local vaginal recurrences where the risk at 2 years was significantly reduced from 7.4% to 1.6%. So far, so good, right?

Well, yes and no. While a reduction in cancer recurrence is always a good thing, unfortunately, the reduction didn't translate into a survival benefit (HR, 0.86; 90% CI, 0.57-1.29). This is largely the result of effective salvage radiation in cases of local vault recurrence.

Table 1

Comparison of the Randomized Trials of Adjuvant Radiotherapy in Stage I Endometrial Cancer

Trial	Patients & Eligibility	Surgery	Randomization	Age (mean)	Locoregional recurrence	Survival	Severe Complications
Norwegian[9] 1968-1974	540 Stage I	TAH-BSO	Brachytherapy vs Brachytherapy and Pelvic RT	60	7% vs 2% at 5 yrs $P < 0.01$	89% vs 91% at 5 years; P = NS	N/A
PORTEC[8] 1990-1997	714 IB Grade 2-3 IC Grade 1-2	TAH-BSO	NAT vs Pelvic RT	66	14% vs 4% at 5 years; $P < .001$	85% vs 81% at 5 years $P = 0.31$	3% GI at 5 years (actuarial)
GOG-99[7] 1987-1995	392 Stage IB, IC Stage II	TAH-BSO, lympha-denectomy	NAT vs Pelvic RT	~61	12% vs 3% at 2 years $P < 0.01$	86% vs 92% at 4 years $P = 0.56$	8% GI at 2 years (occult)

TAH-BSO: Total Abdominal Hysterectomy Bilateral Salpingoophorectomy

GI: Gastrointestinal Toxicity (Grade 3/4)

NAT: No Additional Therapy

RT: Radiotherapy

Adapted from: Creutzberg C, et al. Gynecol Oncol. 2004;92:740-743.

Four-year survival estimates were 86% for surgery and 92% for surgery and radiation. And, as anticipated, intercurrent disease was a significant contributor to mortality with nearly one-half of the patients dying from causes not related to their primary cancer. In addition, the study grossly overestimated recurrence risks. It was determined that the current sample size could detect with 80% power a 58% decrease in recurrence and a 56% decrease in death with its initial recurrence estimates. However, recurrence was far less than anticipated. This prompted a post hoc creation of a high intermediate risk group (HIR) and a low intermediate risk group (LIR). Criteria used for this new determination are listed in Table 2. Under the new allocation, 132 patients (one-third of total) were determined HIR (70: surgery alone, 62: surgery + radiation) and had a 2-year recurrence of 27%; 260 were LIR with a 2-year recurrence of 6%. Analysis of the primary end point, RFI, again demonstrated a significant reduction of recurrence (HR, 0.42; 90% CI, 0.21-0.83) for those treated adjuvantly with radiation, but only among the HIR cohort. However, even with this secondary cohort allocation, survival was not significantly different with radiation (HR, 0.73; 90% CI, 0.43-1.26), although the authors state the benefit is somewhat lower.

The purported benefits of radiation do come at a premium though. In this trial, the combination of surgical staging and postoperative pelvic radiation produced more frequent and higher-grade gastrointestinal toxicity with the only 2 treatment-related deaths occurring in the radiation arm from intestinal injury. In summary, radiation given in adjuvant-to-surgical staging produces lower isolated local recurrences, without a clear improvement in survival and with more toxicity compared to surgery alone in patients with early stage endometrial cancer.

The results seem cogent, so what's the confusion? Three critical elements continue to keep the controversy vibrant. First, surgical staging, while the mantra of contemporary care in the United States, is not universally accepted among investigators and, even among its advocates, comprises a range of procedural intents. Results from the large PORTEC trial concluded that adjuvant pelvic radiation produced a similar reduction in isolated vaginal recurrences among a slightly differently defined intermediate risk cohort compared with surgery alone.[8] Patients in this trial did not undergo any formal surgical staging and as such had approximately one-third the bowel complications as the GOG trial (*see Table 1*). These authors opined (in a subsequent editorial) that surgical staging added little more than toxicity and should be avoided in many patients with early endometrial cancer.[10] In their view, in the absence of surgical staging procedures, radiation was associated with a better therapeutic ratio and should be administered in all such patients. On the other hand, surgical staging when performed as a complete lymphadenectomy identifies with precision patients who are at risk for pelvic and distant recurrence, and as such, call into question the merits of pelvic radiation if the at-risk nodal tissues are resected.

Table 2

Criteria For HIR Patient Allocation

Variable	Definition 1	Definition 2	Definition 3
Age (yrs)	≥ 70	≥ 50	Any age
Grade 2/3	Any 1	Any 2	Yes
LVSI*	Any 1	Any 2	Yes
Over 2/3 invasion†	Any 1	Any 2	Yes

* LVSI: Lympho-vascular Invasion

† Invasion is myometrial

Indeed, several advocates of therapeutic lymphadenectomy have reported rare pelvic recurrences in these patients not treated with radiation.[11-13] As isolated local failures are frequently salvaged, these authors opine that surgical staging, if complete, can reduce toxicity and cost from radiation without affecting survival—as similarly presented in the GOG trial. Although there is no consensus on the issue of surgical staging between the two camps, trials are underway to evaluate whether radiation can be modified (PORTEC-II) and what information is gained by formal surgical staging in stage I endometrial cancer (MRC-ASTEC).[10]

The second element obstructing a consensus on the issue of adjuvant therapy is whether vaginal brachytherapy can be substituted for pelvic radiotherapy, regardless of whether surgical staging is done. In the only other randomized trial of clinically staged, intermediate-risk patients, loco-regional recurrences were significantly higher in women treated with adjuvant vaginal brachytherapy compared to adjuvant pelvic radiation and vaginal brachytherapy.[9] Survival, again, was not adversely impacted but staging data were not collected and presumably, some of these recurrences may have represented patients with occult stage IIIC disease. A comparative trial with carefully selected, but clinically defined intermediate-risk patients is underway in the Netherlands. A similar trial among formally staged patients has also been advocated.[14]

The third, and arguably most critical, element fueling the ongoing debate is the inconsistent definition of intermediate risk. As outlined above, the GOG intended to identify a risk cohort where recurrence would be expected in approximately 25% of accrued patients. However, by their definition, both a 45 year-old woman with 10% invasion of a grade I tumor and a 75 year-old woman with 95% invasion and cervical extension of a grade III tumor could have been equally enrolled. Clearly, these represent different risk groups. In the PORTEC trial, all stage IC grade III tumors were excluded, as were stage II patients. In some respects, while the recurrence rates and survival estimates are similar between these 2 recent trials, they represent different cohorts and lack sufficient power to evaluate important subgroups. The authors of the PORTEC trial have recently reported the outcomes of this latter excluded stage I cohort who were registered in the trial but were treated with pelvic radiation.[15] Ninety-nine of 104 such patients were followed for a median 83 months. In comparison to other randomized patients in the original trial, this patient cohort was characterized by significantly higher loco-regional relapse rates (14% vs 3%), shorter 5-year survival (58% vs 83%; HR, 5.5; $P < 0.0001$), and more frequent distant recurrence (32% vs 8%). Grade III was the most important prognostic factor to cancer-specific death by multivariate analysis. Effective therapeutic strategies in this cohort will need to address both loco-regional and distant failure. These data, thus, highlight the importance of case selection in constructing randomized protocols for intermediate-risk patients.

Fortunately, the quest for truth is embraced heartily in every generation. To this end, randomized trials of not only surgery but also radiation and chemotherapy are being planned and conducted in the worldwide gynecologic oncology theater. Eventually, these issues should be ironed out, but I for one am not sure if I should breathe a sigh of relief or hold my breath! ■

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CME Questions

11. Which of the following techniques is best in reducing pain associated with Pipelle biopsies?

a. Oral naproxen sodium
b. Intrauterine installation of 2% lidocaine
c. Paracervical block
d. Pudendal block
e. a and b

12. The following statements are true regarding the WHI *except*?

a. The results of the WHI indicated an increased risk of cardiovascular events in younger postmenopausal women.
b. The WHI data do not prove that hormone therapy causes breast cancer.
c. In contrast to data with bisphosphonates and raloxifene, the WHI provides evidence that hormone therapy prevents fractures in a low risk group of postmenopausal women.
d. The WHI has not provided any information regarding Alzheimer's disease.

13. For women randomized to the CEE arm of the WHI, all of the following were found *except*:

a. reduced rate of fracture.
b. increased rate of breast cancer.
c. increased risk of stroke.
d. increased risk of venous thromboembolism.
e. increased systolic blood pressure.

Answers: 11(e); 12 (a); 13 (b)

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Missing Link Between Vaccines and Diabetes

A large cohort study from Denmark suggests no link between childhood vaccines and type 1 diabetes. The potential for such a link has been of concern for years because of the association between certain infections and the development of type 1 diabetes in children. Epidemiologists also noted that the incidence of type 1 diabetes has increased in developed countries along with a widespread use of vaccines in those countries. Danish researchers studied the records of children born in Denmark between 1990 and 2000, which represented 4,720,517 person-years of follow-up. In the cohort, 681 cases of type 1 diabetes occurred. The rate ratios for developing diabetes among children who received at least 1 vaccine compared to unvaccinated children were: 0.91 for *Haemophilus influenzae* type B vaccine, 1.02 for diphtheria/tetanus/polio vaccine, 0.96 for diphtheria/tetanus/pertussis/polio vaccine, 1.06 for whole cell pertus! sis, 1.14 for measles/mumps/rubella vaccine, and 1.08 for oral polio vaccine. No clusters of diabetes cases were found at any age level. The authors conclude that the data do not support the causal relationship between childhood vaccine and type 1 diabetes (*N Engl J Med*. 2004; 350:1398-1404).

Breast Cancer and the Use of Statins

Adding to the considerable evidence regarding the safety and efficacy of statins, it now appears that statins may slightly reduce the risk of breast cancer. Published in the "Early View" online journal *Cancer*, this case-control study was designed to assess whether statins were associated with an increased risk of breast cancer. At least 1 previous study has suggested an increased risk of breast cancer with statin use. The study looked at 975 women in Washington state who were diagnosed with primary invasive breast carcinoma, and were between 65 and 79 years old at the time of diagnoses. The comparison group was 1007 randomly selected women from the same residence area. Compared with non-users, current users, or ever-users of statins were not found to be at an increased risk for breast carcinoma. And in fact, the odds ratio of statin users was 0.9 compared to non-statin users (95% CI, 0.7-1.2). Long-term statin use of > 5 years was related to an even lower odds ratio of 0.7. The authors conclude that statins are not associated with an increase risk of breast carcinoma, and may in fact impart a reduced risk among long-term users (*Cancer* April 26, 2004).

Warnings Issued for IBS Drugs

Tegaserod (Zelnorm-Novartis), the heavily promoted serotonin 5-HT4 partial agonist for the treatment of irritable bowel syndrome (IBS), is the subject of new warnings by the FDA. The drug is indicated for women with IBS whose pri-

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mary symptom is constipation. The warning is the result of reports of diarrhea leading to hypovolemia, hypotension, and syncope in a small number of patients. There have also been rare cases of bowel ischemia in patients taking tegaserod, although no causal relationship has been found. Novartis has issued a "Dear Doctor" letter regarding the change in labeling dated April 26 (for more information see www.FDA.gov/medwatch). This is the second IBS drug to come under FDA scrutiny. The serotonin 5-HT3 antagonist alosetron (Lotronex-GlaxoSmithKline), for the treatment of IBS in women with severe diarrhea, was briefly withdrawn from the market in June 2002 because of over 80 cases of ischemic colitis associated with use of the drug. Alosetron became available again in December 2002 under a restricted use program.

What is the risk of a re-prescribing penicillin to penicillin allergic patient? The risk may be quite low according to a new study. Researchers looked at a database from the UK General Practice Research Database which included over 3.3 million patients who received penicillin. More than 6000 patients reported an allergy to the initial prescription, however, 48.5% of those patients were given the second prescription for penicillin at least 60 days later. Of those 3014 patients, only 57 (1.89%) had another event after the second prescription. This was much higher than the rate of reactions in patients who had not had an initial reaction (odds ratio, 11.2; [95% CI 8.6-14.6]), however, the absolute rate of reactions in patients who had an initial allergic reaction was quite small (*J Allergy Clin Immunol.*2004:113; 764-770). An accompanying editorial pointed out that even anaphylactic reaction had a low rate of recurrence with repeat exposure (1 out of 16) (*J Allergy Clin Immunol.*2004:113;605-606). And, while no one is recommending rechallenging patients with penicillin allergies, the low rate of repeat reactions is a far cry from the reported 60% rate of previous studies

FDA Actions

The FDA has removed the warning for lactic acidosis from metformin (Glucophage) and metformin extended release (Glucophage XR). Once considered the most serious side effect associated with metformin, a recent meta-analysis showed that there were no reports of lactic acidosis during more than 20,000 patient years use of the drug (*Arch Intern Med.*2003;163:2594-2602).

The FDA has approved apomorphine injection (Apokyn-Bertek) for hypomobility associated with Parkinson's disease. Hypomobility or "off periods" become more frequent with advanced Parkinson's disease and may occur at the end of a dosing interval or may occur spontaneously. A subcutaneous injection of apomorphine is effective for both types of “off periods.” However, because the drug causes severe nausea, it must be taken with an anti-emetic—although, not a 5HT3 antagonist because the combination may cause hypotension and syncope.

Aventis has received approval to market insulin glulisine (Apidra), a new rapid-acting insulin. The drug is a novel recombinant DNA human insulin analogue that is designed to be given 15 minutes before a meal or within 20 minutes after starting a meal. With a rapid onset and short duration of action, it is designed to cover mealtime blood sugar spikes. Aventis is marketing insulin glulisine to be used in combination with insulin glargine (Lantus), the company's long-acting basal insulin preparation.

The FDA has approved changes in prescribing information for finasteride (Proscar-Merck) that include concomitant use of the alpha-blocker doxazosin for the treatment of benign prostatic hyperplasia. Finasteride is a 5-alpha-reductase inhibitor. The combination was recently found to be better than either drug alone in reducing the overall clinical progression of benign prostatic hyperplasia (NEng J Med.2003;349:2387-2398).

Telithromycin (Ketek-Aventis) has been approved by the FDA for marketing for the treatment of community-acquired pneumonia including pneumonia caused by drug-resistant pneumococcus, sinusitis, and acute exacerbations of chronic bronchitis. Telithromycin represents the first of a new class of antibiotics known as ketolides. It is an oral tablet that is given once a day. ■