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INSIDE

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A Simple Screen for Cancer?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus, Huntsville

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

Synopsis: *An elevated white blood cell count is a risk factor for several cancers in women.*

Source: Margolis KL, et al. *Arch Intern Med.* 2007;167:1837-1844.

THE NOTION THAT INFLAMMATION AND CANCER ARE LINKED, and that the relationship is possibly causal, has been with us for a long time.[1] Using the Women's Health Initiative (WHI) database, Margolis and colleagues prospectively examined the correlation of the white blood cell (WBC) count and the development of cancer of the breast, the colon and rectum, the endometrium, and the lung. After exclusion (including those with WBC < 2.5 X 109 cells/L or > 15.0 X 109 cells/L), 143,748 women were available for study. The examination of the relationship of WBC and endometrial cancer was limited to the 85,621 women who still had uteruses. Subgroup analysis for breast cancer and colorectal cancer was performed on women who had negative screening (normal mammograms or negative fecal occult blood testing, colonoscopy, or sigmoidoscopy, respectively) before admission into the study. The subjects had a single WBC drawn on enrollment and annual or semiannual follow up, when they were quizzed on any new diagnosis of cancer (other than non-melanoma skin cancer). Any new diagnosis was confirmed by medical record review. The WBC counts were divided into quartiles, 2.50-4.79, 4.80-5.69, 5.70-6.79, and 6.80-15.00 X 10^9 cells/L. The women were on average 63 years old, white (82%), and overweight (35%) or obese (30%). Twenty percent used aspirin regularly. In multivariate analysis, using the first (lowest) quartile as the reference (hazard ratio [HR] = 1), elevated WBC counts (fourth quartile) were statistically significantly associated with invasive (but not *in situ*) breast cancer, colorectal cancer, endometrial cancer, and lung cancer. This data is summarized in the table on the next page.

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Cancer	Hazard Ratios (Confidence Intervals)
Breast	1.15 (1.04-1.26)
Colorectal	1.19 (1.00-1.41)
Endometrial	1.42 (1.12-1.79)
Lung	1.63 (1.35-1.97)

To parry the concern that the cancers were subclinical (ie, they were present, but undetectable, at the start of the study, the author recalculated the rates after excluding cancers that were discovered within the first two years of the study. The results were unchanged. When they looked at individuals who had negative screening for breast or colorectal cancer at baseline, there were statistically insignificant trends for increased risk.

COMMENTARY

That an elevated WBC count is associated with cancer incidence and mortality is not a novel concept.[2] The authors speculate about the plausibility of their results and present interesting intermediate data that link inflammation to the initiation and promulgation of cancer. This involves the cellular production of cytokines and chemotactic molecules and their involvement with cell growth, migration, and differentiation. The topic was reviewed in 2002.[3]

Certainly, the prospect of an ordinary blood test that can screen for four cancers is appealing. However, there are some problems with this study. One of the things that bothered me was the selection of the WBC quartiles. The authors did not provide a rationale for having different-sized intervals. The fourth quartile's range overlaps the "normal" range for my hospital's laboratory (4.8-10.8 X 10^9 cells/L). The hazard ratios were not huge (at best, a 63% increased risk for lung cancer) and for colorectal cancer, barely significant, since the confidence interval included 1.00.

How can we put the results of this study to good use? In their accompanying editorial, Roy and Khadekar remark, "While this association was statistically significant, the magnitude of the difference was somewhat unimpressive … Moreover, because there are obviously numerous factors that can affect the WBC count, the authors' suggestion of possible future clinical value seems somewhat unrealistic."[4] I agree. The WBC is too blunt an instrument to use as a screening test. On the other hand, if your female patient presents with an elevated WBC and you cannot reasonably account for the elevation, consider recommending follow-up testing (mammography, endometrial biopsy, colonoscopy, chest x-ray), based on her risk factors and any previous testing. ■

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Duration of Immunity to Common Viral and Vaccine Antigens

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California
Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *Serum analysis of 45 subjects for antibodies and humoral immunity over a median of 15 years showed antiviral responses ranging from 11-19 years for tetanus-diphtheria, 50 years for varicella-zoster, and up to 200 years for measles and mumps.*

Source: Amanna IJ, et al. *N Engl J Med.* 2007;357:1903-1915.

A MATHEMATICAL MODEL WAS USED TO CALCULate antibody half-life and rates of decay using

630 serum samples collected from 45 individuals over a median of 15.2 years (range 5 to 26 years), with an average of 14 samples per subject. Samples were collected as part of annual screening of laboratory workers with additional samples after any injury; a smaller group had weekly samples after vaccinia vaccinations.

Antibody titers were measured for 6 viral antigens (vaccinia, measles, mumps, rubella, varicella-zoster virus, and Epstein-Barr virus) and 2 nonreplicating antigens (tetanus and diphtheria). Elevations of antibody levels were seen after booster vaccinations, and the natural decline of antibodies were identical for persons exposed though actual disease vs vaccination, although the absolute level was higher for actual disease exposure.

Varicella-zoster viral immunity showed the most fluctuations. All 45 study subjects were initially seropositive, and the majority of 10 who experienced spikes in antibody level had no known exposures or viral outbreaks. Immunity decreased slowly, with an estimated half-life of 50 years. Tetanus-specific antibodies decreased the most rapidly, with estimated half-life of 11 years; diphtheria-specific antibodies had an estimated half-life of 19 years.

Memory B cells for the 8 specific antigens were also measured with limiting-dilution analysis, and their frequencies compared to corresponding serum antibody levels. B cell levels rose quickly after antigen exposures and persisted. A significant correlation to antibody levels was found after acute infection with measles, mumps, and rubella, but not vaccinia, varicella-zoster or Epstein-Barr viruses, or for the tetanus-diphtheria vaccine antigens.

To test the theory of "nonspecific bystander activation" of humoral immunity being triggered by unrelated infections, 4 subjects were followed for over 25 years for their antibody response to the 8 antigens after unrelated infection or immunization. Little or no effect on antibody levels to these antigens was seen.

COMMENTARY

This longitudinal research both supports and refutes some current theories of how longstanding immunity is maintained. For measles, mumps and rubella, antibody responses were correlated with rises in memory B cells after antigen exposure, which supports the theory that B cell activation into plasma cells is necessary for antibody maintenance. However this association was not present for the other viruses and tetanus-diphtheria antigens, although levels of immunity for both antibodies and B cells were independently maintained.

The authors suggest that a model of independent regulation of antibody levels and memory B cells is the most likely, with multiple re-exposures affecting the levels in different ways. They also note that the shorter duration of antibody levels to the protein antigens for tetanus-diphtheria immunization suggests that antibody maintenance is influenced by the nature of the antigen.

Although this research is an important contribution to the knowledge needed for vaccine design and timing of booster vaccinations, it is not enough to change clinical practice at this point. However, it does appear that our current schedule for immunizations and boosters was sufficient to maintain immunity to these common antigens over a long period of time, even if we're still not exactly sure how it all works. ■

Cereals and the Risk for Heart Failure: Is There a Link?

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

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

Synopsis: *When whole grain cereal (WGC) is consumed regularly, there is a lower risk of developing heart failure (HF). This association is likely to be linked to the beneficial effects of WGC on risk factors (ie, hypertension, obesity, hyperlipidemia) rather than HF itself.*

Source: Djoussé L, Gaziano M. *Arch Intern Med.* 2007;167: 2080-2085.

THIS PROSPECTIVE STUDY WAS AIMED AT evaluating the effect of breakfast cereals on the development of HF using data from the Physicians' Health Study I (PHSI) in which 261,248 male physicians participated in 1981. In this study, more than 22,000 participants were randomized to receive a daily low-dose aspirin, beta-carotene, both agents or

daily placebo. A total of 21,376 participants were enrolled in this trial that included specific information regarding the consumption of breakfast cereals. Self-reporting of the consumption was utilized using a survey instrument. The participants received a simple questionnaire every six months for the first year and every 12 months thereafter to obtain information regarding the occurrence of newly diagnosed HF. The total number of breakfast cereals was utilized as the main exposure. A stratified analysis followed to separate WGC from refined cereals.

The mean age at randomization was 53.7 ± 9.5 years. A higher number of elderly participants consumed breakfast cereals. The average follow up of participants was 19.8 years, during which 1018 new cases of HF were self reported. Fewer cases of HF were observed when breakfast cereal was consumed. The higher number of weekly servings also influenced the development of HF. When updated cereal consumptions was analyzed at 24, 48, 72, 96 and 120 months, an inverse association to HF was found. In further statistical analysis of the type of cereal consumed, these investigators found an inverse association between WGC and HF that was not found with refined cereals.

COMMENTARY

This study showed a strong association between the consumption of WGC and the incidence of HF. Several studies have previously demonstrated beneficial effects of fiber consumption on hypertension, atherosclerotic cardiovascular disease and obesity.[1,2] In a previous study, utilizing this same population, an inverse association between WGC consumption and cardiovascular mortality was found.[3]

The specific mechanism by which WGC are protective remain to be determined. However, these cereals contain potassium, which is known to lower blood pressure.[4] In addition, they have antioxidant properties, and have an effect on lipid metabolism.[5] With the findings of the present study, intervention studies should follow in attempts to prospectively diminish the incidence of HF. ■

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Pharmacology Update

Ciclesonide Nasal Spray (Omnaris™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

THE FDA HAS APPROVED A NON-HALOGENATED nasal steroid for use in pediatric patients aged 6 to 12 years and adults. Ciclesonide is a prodrug that was previously approved for adults and adolescents but was not marketed. It's to be marketed by Nycomed US Inc. as Omnaris.

Indications

Ciclesonide nasal spray is indicated for the treatment of seasonal allergic rhinitis in patients 6 years of age and older and for perennial allergic rhinitis in patients 12 years of age and older.[1]

Dosage

The recommended dose is 200 mcg (2 sprays [2 x 50 mcg]) in each nostril twice daily. The dose should not exceed 200 mcg daily. The pump must be primed (eight actuations) prior to initial use. If the bottle has not been used for 4 consecutive days, it should be re-primed with one spray or enough sprays to make a fine mist appear.[1]

Ciclesonide is available as a 12.5 g unit with 50 mcg per actuation and 120 sprays.

Potential Advantages

Ciclesonide is formulated in a hypotonic solution without benzalkonium chloride as a preservative. This may enhance drug uptake into the nasal mucosa and reduce the bitter taste.[2]

Potential Disadvantages

Ciclesonide is not indicated for use in children

under the age of 6 years. Controlled studies have shown that intranasal steroids may cause reduction in growth velocity in pediatric patients even in the absence of hypothalamic-pituitary-adrenal axis suppression.[1]

Comments

Ciclesonide is a nonfluorinated corticosteroid that is the prodrug for C21-desisobutyryl-ciclesonide. It is activated by esterases in the nasal mucosa. Dose ranging studies demonstrate that the optimal dose of the drug is 200 mcg daily.[1,3] This dose was shown to be statistically more efficacious than placebo in one 4-week study in adolescent and adult patients with seasonal allergic rhinitis (n = 324) and a 6-week study in patients with perennial allergic rhinitis (n = 461).[1,4] The primary endpoint was the difference from placebo of the average of morning and evening nasal symptom scores. This is the sum of 4 nasal symptoms (runny nose, itchy nose, sneezing, and nasal congestion).

Ciclesonide reduced baseline symptoms scores by 27% compared to 17% for placebo in seasonal allergic rhinitis over the first 2 weeks and 33% and 24% respectively in perennial allergic rhinitis over 6 weeks. Onset of action was seen within 24 to 48 hours with improvement over 1 to 2 weeks for seasonal allergic rhinitis and 5 weeks in perennial allergic rhinitis. In pediatric patients (6-11 years, n = 219), ciclesonide was significantly more effective than placebo in seasonal allergic rhinitis with a 30% reduction in baseline score compared to 25% for placebo over 2 weeks. Ciclesonide was not effective in perennial allergic rhinitis in this population.[1] In a long-term study in adolescents and adults, ciclesonide was shown to be safe and effective for up to 52 weeks (n = 663).[5]

Patients with greater impairment in quality of life (related to activities, nasal symptoms, eye symptoms, and emotional factors) at baseline showed greater improvement with ciclesonide. A slightly higher incidence of epistaxis (10% vs 7.2%), sinusitis (9.3% vs 7.2%), and pharyngolaryngeal pain (9.3% vs 4.5%) was associated with ciclesonide compared to placebo. No clinically relevant differences were observed in morning or 24-hours urinary free cortisol levels and no tachyphylaxis was observed. Similar results were observed in pediatric patients in a 12-week study.[1] There are currently no published comparative studies with other intranasal steroids. The cost was not available at the time of this review.

Clinical Implications

Intransal steroids are the mainstays in the treatment of allergic rhinitis. There are currently 7 intranasal steroid products on the market. Ciclesonide does not appear to offer any clear advantages or disadvantage over existing products. Whether the unique formulation differences (ie, hypotonic solution) offers any advantage remains to be determined. ■

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CME Questions

1. **In an analysis of data from the Women's Health Initiative, women with an elevated white blood cell count were at risk for:**
   a. endometrial cancer
   b. lung cancer
   c. invasive breast cancer
   d. colorectal cancer
   e. all of the above

2. **Which of the following antigens would be expected to trigger the shortest duration of protective antibody levels?**
   a. Epstein-Barr virus
   b. varicella-zoster
   c. tetanus-diphtheria
   d. vaccinia
   e. measles-mumps

3. **In the study by Djoussé and Gaziano, the consumption of whole grain cereals was:**
   a. associated with a lower incidence of seizures
   b. associated with more incidence of diarrhea
   c. inversely correlated to the presence of heart failure
   d. more common among people younger than 24 years of age
   e. directly related to the incidence of hypertension

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

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CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Resilient Medical Myths: Disproven Precepts that Refuse to Die

PROBABLY EVERY CLINICIAN HAS more than one medical "belief" to which he clings, despite the preponderance of evidence to the contrary. Sometimes, clinical thinking contrary to science persists because of conflicting bodies of evidence, or, as was the subject of this communication, because powerful initial data sets—especially when they fit comfortably with our common-sense judgment—are hard to relinquish even in the face of newer, better science. The recent shock of disillusionment subsequent to the Women's Health Initiative, which did NOT confirm the essentially "assumed" cardiovascular benefits in menopausal women, was a prime example of the disparate information obtainable from observational data (which said that HRT uniformly reduces cardiovascular risk) compared to interventional data (which said that no demonstrable CHD benefit was seen with HRT).

In the 1990s, common wisdom held that vitamin E—purportedly through its antioxidant activity—should be beneficial for reducing vascular events. Indeed, some early reports supported this concept. The HOPE trial, a large randomized interventional trial that included a vitamin E arm, not only failed to show benefit, but tended towards HARM from vitamin E. Subsequently, two meta-analyses conclude that vitamin E is associated with INCREASED mortality.

Tatsioni, et al compared the support stance of authors for utilization of vitamin E in the period immediately after publication of the initial positive trials, and compared this with publications after large data sets had essentially refuted vitamin E benefits. Even 5 years after the best data had refuted vitamin E benefits, a majority of articles addressing the topic still supported the opposite conclusion, although trends in support did decrease over time. Apparently, the progress of science is often difficult for some proponents of opposing ideas to accept. Clinicians will have to be vigilant that outdated or observational data sets not cloud their perceptions of established scientific fact. ■

Tatsioni A, et al. JAMA. 2007;298(21):2517-2526.

NSAID, Manipulation or Both for LBP

CURRENT KNOWLEDGE ON MANagement of acute low back pain (LBP) suggests that best outcomes are obtained when patients anticipate a favorable outcome, remain active, avoid bed rest, and use acetaminophen for analgesia. NSAIDs used to be considered appropriate first line therapy, but recent heightened awareness of NSAID potential toxicities (GI bleeding, electrolyte disarray, renal dysfunction, BP elevation, and CHD events) mandates that their continued utilization provide meaningful benefits that outweigh such adversity.

Hancock et al studied 240 patients who were randomized to receive—in addition to the advice/acetaminophen—either NSAID (diclofenac), spinal manipulation, both, or placebo. Diclofenac was administered 50 mg b.i.d., and spinal manipulation was provided by trained physiotherapists diplomated in manipulative therapy. All subjects were followed for 12 weeks, looking at the number of days until recovery, defined as the first pain-free day, and the first 7 consecutive 7-day period in which the patient reported pain 0-1/10 every day.

Neither diclofenac, spinal manipulation, nor the combination of both was superior to simple first-line advice. Predictable adverse effects of NSAIDs were seen (none serious). Simple first-line tools for management of LBP are not improved by the addition of diclofenac, but adverse events are increased. ■

Hancock MJ, et al. Lancet. 2007;370:1638-1643.

Pomegranate Juice for Erectile Dysfunction

POMEGRANATE JUICE (POM) HAS attributes that might benefit men with erectile dysfunction (ED), including potent antioxidant activity and enhanced endothelial nitric oxide production. Forest, et al studied the effects of POM when administered as 8 ounces of POM daily vs placebo in men with ED.

Men with mild-moderate ED (n=53) were randomly assigned in a crossover fashion to two 4-week periods of POM or placebo. The primary outcomes assessed at 10 weeks were improvements on the International Index of Erectile Function (IIEF) score and the Global Assessment Questionnaire (GAQ) for sexual dysfunction.

Although there was a trend towards improvement in both GAQ and IIEF in persons receiving POM, it did not achieve statistical significance (p= 0.58). The mean age of the subjects in this pilot study population, 46 years, was younger than usually selected in studies of ED; additionally, the overall ED severity (mild-moderate) was low. The authors consider that perhaps with a larger study population, and longer duration of evaluation, the effects of POM might achieve statistical significance. ■

Forest CP, et al. Int J Impot Res. 2007;19:564-567.

Atypical Chest Pain and an Abnormal ECG

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*
Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

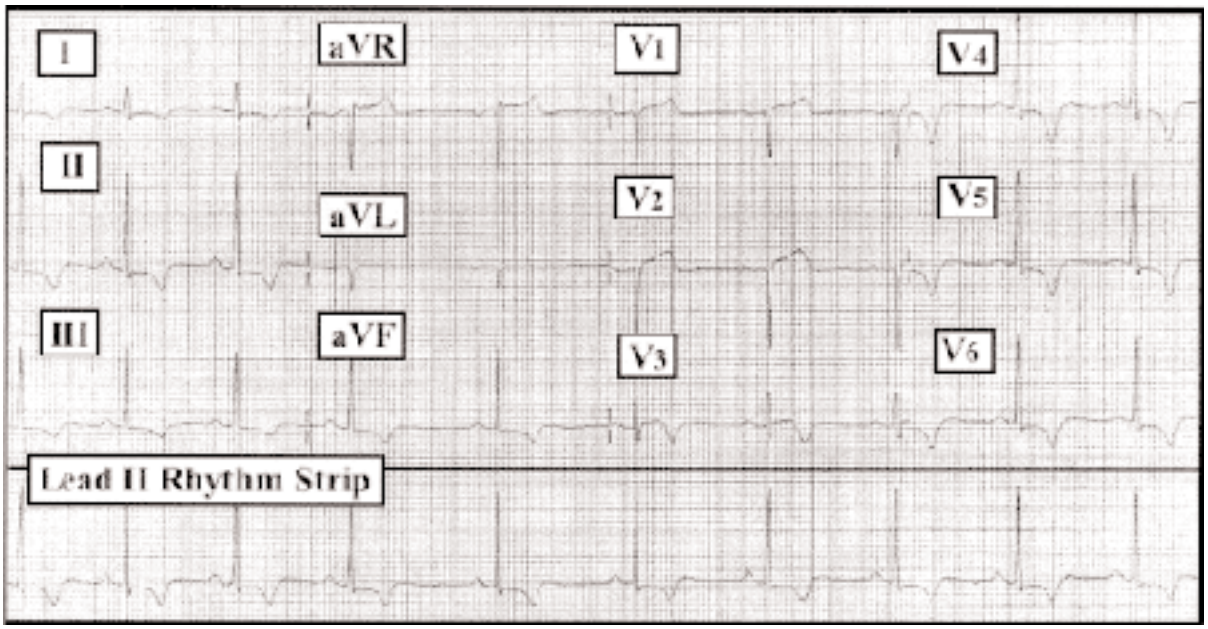

Figure: 12-lead ECG obtained from a 50-year old African American man with hypertension and chest pain.

Clinical Scenario:

The ECG in the Figure was obtained from a 50-year old African American man with hypertension who was admitted to the hospital because of chest pain. His chest pain was intermittent, and of several weeks duration. It was generally short-lived, and not regularly precipitated by activity. He was a non-smoker, and did not abuse cocaine. Blood pressure was significantly elevated. How would you interpret this patient's ECG? Does it suggest acute infarction?

Interpretation/Answer:

The ECG in the Figure is clearly abnormal. There is sinus arrhythmia and bradycardia. All intervals are normal. The mean QRS axis is +75°. There is voltage for LVH (left ventricular hypertrophy). The most remarkable finding is deep, symmetric T wave inversion in multiple leads. There is also worrisome ST segment *coving* and elevation in lead V3, and J point ST segment depression in leads II, V5, and V6. In the right clinical setting (and in the absence of a prior tracing for comparison), one would have to interpret these changes as suggestive of *acute* evolving myocardial infarction. However, the history in this case is not typical for acute infarction in that chest pain is intermittent in occurrence, of short duration, and recurring over a period of several weeks.

In the absence of a prior ECG for comparison, admission to the hospital to rule out acute myocardial infarction was prudent. Serial troponins were negative, and cardiac catheterization was completely normal. The ECG changes seen here therefore represent LVH and "strain" *and/or* ischemia in a patient with significant hypertension — but not acute infarction. Perhaps this middle-aged African American man *also* had a similar underlying repolarization variant as was shown in ECG Review #190 (see July 15, 2007 *Internal Medicine Alert*, p. 104), accounting for ST segment coving and elevation in lead V3 . . . Deep, symmetric T wave inversion as seen here is a common accompaniment of severe, longstanding hypertension. ■

In Future Issues:

Diagnosing UTI Is As Simple As 1, 2, 3

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.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5413. E-mail: iris.young@ahcmedia.com.

drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■