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In-Home HIV Test Empowers Patients

ABSTRACT & COMMENTARY

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Synopsis: *The OraQuick in-home HIV-1/2 antibody test was granted market clearance by FDA on 15 May 2012. Data presented included a <0.1% false positive rate and 91.7% sensitivity to correctly detect HIV infection compared to conventional ELISA performed on blood.*

Source: http://ow.ly/ckHuF

On 15 May the FDA Center for Biologics Evaluation and Research/Office of Blood Research and Review (CBER/OBRR) granted market clearance to the OraQuick in-home HIV-1/2 antibody test based on the recommendation of the Blood Products Advisory Committee. The in-home assay is a rapid, CLIA-waived immunoassay using synthetic peptides as antigens formatted in a test strip format to be used on saliva. The in-home assay is similar to the OraQuick assay previously approved by FDA for rapid HIV testing of venous or fingerstick whole blood or plasma. Data submitted to the FDA included a study of 4999 individuals of unknown HIV status. Results obtained with OraQuick were compared to "gold standard" testing with a laboratory-based ELISA performed on serum or plasma.

Bottom line results from this performance trial showed that 4902/4903 HIV-negative patients were correctly identified (i.e. 1 false positive was seen). 88/96 (91.7%) of ELISA-positive patients were correctly identified (i.e. 8 false negatives were seen). 56/5055 (1.1%) failed to obtain a test result.

COMMENTARY

The FDA market clearance of this in-home, rapid assay to detect HIV-1/2 antibodies demonstrated fairly robust performance and seemed easy to use by most patients. The assay as performed by untrained personnel on saliva does appear to be somewhat less sensitive than the comparator laboratory-based serum or plasma HIV antibody assay. The product pack-

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age insert is careful to point out the limitations of the test in laymen's terms and emphasizes that individuals should wait at least 3 months after a suspected exposure event to test themselves with OraQuick.

The impact of confidential in-home testing may or may not be significant in interrupting transmission of HIV on a large scale in the US or Western Europe. However, it is hard for me to imagine a scenario (other than acute HIV infection where the test may be negative yet the patient highly contagious) where harm could be done. I am a firm believer in empowering patients to take responsibility for their health and for transmission of sexually-transmitted infections to others. This is a step in the right direction and will be a useful development even if only a few new cases of HIV are prevented each year in North America and Western Europe. Hopefully the OraQuick test will be priced low enough in the developing world where its impact could potentially be very large. ■

Risk of Sudden Cardiac Death with Azithromycin

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Source: Ray WA, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-1890.

In this paper, the authors performed a pharmacoepidemiologic study on the relationship between azithromycin, a frequently used broad-spectrum macrolide antibiotic, and cardiovascular death. The authors analyzed data from the Tennessee Medicaid program. This database provides information on medical care encounters and dates and causes of death and is linked to death certificates and hospital discharge data. Data on antibiotic use were taken from Medicaid pharmacy files. The cohort included patients who had been prescribed azithromycin between 1992 and 2006. Patients who had a concomitant life-threatening non-cardiovascular illness, had a diagnosis of drug abuse, resided in a nursing home, or had been hospitalized within the prior 30 days were excluded. Several control groups were analyzed. These included patients who had received no antibiotics and patients who had received courses of therapy with three other commonly used antibiotics: amoxicillin, ciprofloxacin, and levofloxacin. The study outcomes were cardiovascular death, death from any cause, and sudden cardiac death. Deaths during the typical 5-day course of azithromycin therapy and the succeeding 5 days were compared to deaths during the usual 10-day course of the other study antibiotics. Each study comparison was adjusted for an extensive set of covariates using a propensity score that also included a risk for cardiovascular disease.

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The study cohort included 348,000 patients with prescriptions for azithromycin who were compared to 1.4 million patients with no antibiotic prescriptions, and to 1.35 million, 265,000, and 194,000 patients with prescriptions for amoxicillin, ciprofloxacin, and levofloxacin, respectively. The mean ages for the groups were between 48 and 51 years of age. Approximately 75% in each group were female. The prevalence of heart failure, chronic obstructive pulmonary disease, diabetes, and measures of disability were roughly similar between groups. The most common indications for use of azithromycin and amoxicillin were respiratory tract infections. The most common indication for ciprofloxacin was genitourinary tract infection. Levofloxacin was used for a variety of infections, including both respiratory and genitourinary tract infections.

The cardiovascular death rate during a 5-day course of treatment for azithromycin was 85.2 per 1 million courses with an estimated 64.6 sudden cardiac deaths per 1 million courses. For patients who did not take antibiotics, there were 29.8 cardiovascular and 24.0 sudden cardiac deaths per 1 million matched 5-day intervals. For amoxicillin, the cardiovascular death rate was 31.5 and 29 sudden deaths per 1 million courses of therapy. The hazard ratio for death during a 5-day course of azithromycin therapy compared to no antibiotic treatment was 2.88. Amoxicillin use was not associated with an increased risk of death. Patients who took ciprofloxacin did not have an increased risk of either cardiovascular death or death from any cause, but there was a nonsignificant trend toward increased risk of cardiovascular death with the use of levofloxacin (hazard ratio 1.50). The absolute excess risk of cardiovascular death among patients who took azithromycin was related to the baseline risk for cardiovascular disease. In patients with the highest risk score, there were an estimated 245 additional cardiovascular deaths per 1 million 5-day courses of azithromycin therapy.

The authors conclude that azithromycin results in a small absolute increase in cardiovascular deaths that is particularly noted in patients with the highest cardiovascular risk.

■ COMMENTARY

Azithromycin is a macrolide antibiotic. Two other agents in the same class, erythromycin and clarithromycin, have been shown to block IKr and prolong the QT interval, and have been associated with reports of drug-induced polymorphic ventricular tachycardia (torsades de pointes). Limited animal data have suggested that azithromycin has a much lower proarrhythmic potential.[1] The current report, however, suggests that the risk for proarrhythmia with azithromycin, although low, can be quantitated.

Azithromycin was developed and released before the current rigorous protocols for testing new drugs for QT prolongation were standardized. Recently, the FDA revised the azithromycin product label to include a warning about a low risk for proarrhythmia. They did not add a black-box warning since the risk is felt to be low.

Most proarrhythmia associated with antibiotics involve the combination of more than one factor that favor development of the problem. These might possibly include genetic factors, electrolyte imbalance, cardiac status, bradycardia, and other drug therapy. Physicians should be aware of how these factors might interact in a given patient and consider the use of alternative therapy when several risk factors are present.

Reference

1. Milberg P, et al. Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: Fast phase 3 repolarization prevents early afterdepolarizations and torsade de pointes. *J Pharmacol Exp Ther* 2002;303:218-225. ■

Coffee Consumption and Mortality

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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Source: Freedman ND, et al. Association of coffee drinking with total and cause-specific mortality. *N Engl J Med* 2012;366:1891-1904.

Coffee is widely consumed throughout the United States. Some prior studies have associated coffee consumption with increased rates of heart disease, whereas other studies have shown less heart disease in coffee drinkers. The data associating coffee consumption and total mortality have also been conflicting. In the *New England Journal of Medicine*, Freedman and colleagues examined the association of coffee drinking with subsequent total and cause-specific mortality among 229,119 men and 173,141 women in the National Institutes of Health–AARP Diet and Health Study.

This very large cohort study enrolled subjects (AARP members) who were 50 to 71 years of age, and assessed dietary and lifestyle factors. Coffee consumption was assessed once at baseline. Participants with cancer, heart disease, and stroke were excluded. The subjects were followed for 14 years (5,148,760 person-years of follow-up) and the data were linked to the Social Security Administration Death Master File to assess mortality. In age-adjusted models, the risk of death was increased among coffee drinkers. However, coffee drinkers were also more likely to smoke, and after adjustment for smoking status and other potential confounders, there was a significant inverse association between coffee consumption and mortality. Adjusted hazard ratios for death among men who drank coffee as compared with those who did not were: 0.99 for drinking less than 1 cup per day, 0.94 for 1 cup, 0.90 for 2 or 3 cups, 0.88 for 4 or 5 cups, and 0.90 for 6 or more cups of coffee per day ($P < 0.001$). The respective hazard ratios among women were 1.01, 0.95, 0.87, 0.84, and 0.85 ($P < 0.001$). Reduced mortality was observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections. However, cancer-related deaths were not reduced, and there was a trend toward higher mortality from cancer in men who drank more than 6 cups per day. Interestingly, both caffeinated and decaffeinated coffee were associated with similar reductions in mortality. The authors conclude that coffee consumption was inversely associated with total and cause-specific mortality, but whether this was a causal or associational finding cannot be determined from these data.

■ COMMENTARY

This study is welcome news for coffee drinkers. However, several aspects of this study need to be taken into account. First, this was an observational study, and therefore cause and effect cannot be concluded from these data. Second, coffee consumption was ascertained at baseline and never again throughout 14 years of follow-up. Patterns of consumption may well have changed during that long follow-up period. Third, participants resided in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta and Detroit). Thus, the cohort may not be truly representative of the entire country. Fourth, the distinction between persons who drank caffeinated coffee and those who drank decaffeinated coffee was subject to misclassification, since these categories were defined on the basis of consumption of either beverage more than half the time. Fifth, there were no data about how coffee was prepared (espresso, boiled, or filtered) and the constituents of coffee may differ according to the method of preparation.

Despite the limitations to observational studies like this one, this is a very large study, and its sheer size strengthens the associations that it demonstrates. If indeed coffee were to cause this reduction in mortality, what could be the potential mechanism? Coffee is a rich source of antioxidants and other bioactive compounds. Some prior studies have shown inverse associations between coffee consumption and serum biomarkers of inflammation, as well as reductions in insulin resistance, diabetes, inflammatory diseases, and stroke. Although other antioxidants have not reduced cardiovascular events in clinical trials, perhaps the particular constituents in coffee succeed where others have failed. Or perhaps a combination of antioxidants and anti-inflammatory actions combine to have salubrious effects.

Importantly, this study does not tell us about other potentially deleterious effects of coffee, such as effects on blood pressure, lipids, or arrhythmias. These should all be taken into account before advocating our patients increase coffee consumption. Although this study does not prove cause and effect of coffee reducing mortality, I feel comfortable continuing my morning coffee ritual. ■

PHARMACOLOGY WATCH

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

Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■