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INSIDE

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¿Qué Pasa, Acetaminophen?

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

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

Synopsis: *Acetaminophen, taken at the maximum recommended dose for 14 days by healthy adults, can elevate liver enzymes far above the upper limit of normal.*

Source: Watkins PB, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA*. 2006;296:87-93.

Watkins, Kaplowitz, and Slattery (all paid consultants of Purdue Pharma, LP) made the serendipitous discovery of elevated serum alanine aminotransferase (ALT, previously known as serum glutamic pyruvate transferase [SGPT]) levels in participants in a clinical trial that they were conducting of a hydrocodone and acetaminophen (APAP) combination medication. Since APAP is generally considered safe and effective and is available over-the-counter (OTC), they set out to study this matter more closely. One concern they had was that the combination of APAP and the opioid caused the elevation. Could other opioids do the same? The study randomized healthy adults to one of five groups: placebo+placebo, placebo+APAP, oxycodone+APAP, hydromorphone+APAP, or morphine+APAP.

Each group received medication every six hours in the form of four tablets for 14 days (56 doses). The groups receiving APAP got 500 mg tablets (8 tablets/day), for a total daily dose of 4000 mg, the recommended maximum dose. The inclusion criteria were age 18 to 45 years and "non-childbearing potential." Health was determined by history and physical, electrocardiogram, and clinical laboratory. Patients were excluded for positive results on hepatitis B surface antigen, hepatitis C antibody, or urine drug screen. No subjects were taking any other medication and their diet was strictly controlled (read, "no alcohol allowed"). After appropriate exclusions, 145 subjects were randomized. They were mostly Hispanic (57%) males (78%) in

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their mid-thirties with an average Body Mass Index (BMI) of 25.7. Demographically, the groups were similar. Once in the study, bilirubin, aspartate aminotransferase (AST, previously known as serum transferase [SGOT]), ALT, alkaline phosphatase, and α glutathione S-transferase (αGST) were measured daily through Day 8 and then, if there were no elevations, every other day. Daily APAP levels were obtained; and on Day 3 they were drawn every six hours.

ALT levels were recorded as multiples of the upper level of normal (ULN). Only 1 of 39 subjects taking placebo+placebo had an ALT value > 2× ULN during the entire study; the level peaked at < 3× ULN. In contrast, in the other four groups, ALT peaked at > 5× ULN in 19-37% of subjects and > 8× ULN in 4-15%. Elevations of ALT > 3× ULN did not occur until at least Day 3 in the APAP groups. Per protocol, when ALT rose to > 3× ULN, APAP was discontinued. The ALT levels continued to rise for a median of another 2 days post-discontinuation. The highest ALT in an opioid+APAP group was 16× ULN; the highest in the APAP group was 14× ULN. AST and αGST levels followed ALT levels. Bilirubin and alkaline phosphatase levels were normal. There was no difference in APAP levels or area-under-the-curve APAP concentrations between subjects with elevated ALT values and those with not. No subject was symptomatic. Except for one subject who was lost to follow up, ALT levels returned to normal after treatment was stopped. On linear regression analysis, being Hispanic conferred a 1.9 relative risk of having an ALT > 3× ULN (95% confidence interval, 1.1-3.3).

COMMENTARY

These subjects obviously had no needle phobia! I usually avoid reviewing articles that deal with intermediate, non-patient-oriented-evidence outcomes (like elevated ALT levels), but this study generated considerable news coverage,[1] and your patients may ask you about it. Acetaminophen (known as paracetamol in the rest of the world) is the most commonly used analgesic/antipyretic. Most people take APAP for shorter durations and lower dosages than the subjects in this study. However, there are populations who take it chronically and at the maximum recommended dosage (think chronic pain from osteoarthritis or cancer). It is frequently recommended as a first-line drug for pain, especially in patients who cannot tolerate NSAIDs and as an add-on to avoid larger doses of opioids.[2,3] A single dose of 150 to 200 mg/kg, or about 7 to 10 g in adults, is considered toxic, and alcoholics are especially at risk because of depleted hepatic glutathione stores.[4]

From these data, it would appear that the combination of an opioid and APAP is not responsible for the elevated ALT levels. What the authors had difficulty reconciling is the number of studies that have not shown elevations of ALT with APAP use. In a study earlier this year[5] of older women with osteoarthritis, no subject experienced hepatic failure, hepatic dysfunction, or aminotransferase levels > 2× ULN. Previous studies have correlated ALT elevation to diet,[6] infectious disease, toxins, and, in overdose, APAP. None of these explanations are plausible in the current study. Overdose with APAP can result in liver failure and death, but previous studies have not shown ALT elevation with therapeutic doses of APAP. The authors speculate that since their study had a much higher proportion of Hispanics than other studies and since being Hispanic was the only risk factor they identified, perhaps ethnicity may play a role.

Additional studies, that enroll enough Hispanics to power it, are needed to confirm results of this study. While we are waiting, what is a prudent physician to do? Prescribing any medication at the lowest effective dose is always good practice. If your patient has elevated ALT levels, inquire about APAP use as you pursue other sources of the elevation. Remind your patients that APAP is a constituent of many OTC medications; these may be forgotten as they try to limit the total daily dose. In my opinion, if your Hispanic patient is taking 4 grams of APAP daily, you should

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discuss the results of this study, and based on your mutual level of risk aversion, monitor ALT levels periodically. ■

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What About a Testosterone Patch for Women?

ABSTRACT & COMMENTARY

By Eileen C. West, MD

Director, Primary Care Women's Health, Clinical Assistant Professor, Internal Medicine/Obstetrics and Gynecology; University of Oklahoma Health Sciences Center, Oklahoma City

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

Synopsis: *In this Phase III drug trial, use of a testosterone patch increased desire and the frequency of satisfying sexual activity in naturally menopausal women with hypoactive sexual desire disorder.*

Source: Shifren JL, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause*. 2006;13:770-779.

Hypoactive sexual desire disorder (HSDD) refers to a persistent decrease of interest in or aversion to sexual contact which causes distress. The affected person has a low level of sexual desire that is manifested by a failure to initiate or be responsive to a partner's initiation of sexual activity. HSDD becomes a diagnosable disorder when it causes marked distress or interpersonal instability.[1] It occurs in both genders. It is the most common of female sexual disorders, affecting more than 20% of all women. Primary HSDD can be the result of early sexual trauma, repressive family attitudes about sex, or a history of painful intercourse. Acquired HSDD is associated with boredom in the relationship with a sexual partner. Depression must be ruled out before making the diagnosis. Younger, surgically postmenopausal women are at high risk. Priapism, vaginismus, hypogonadism, antidepressant use, substance abuse, prolactinoma, genital infections, diabetes mellitus, and chronic renal disease may all be associated with HSDD.

Treatment thus far has focused on the source of the disorder, using medical therapy or behavioral psychotherapy. Women exhibit falling androgen levels as they age and total testosterone concentrations of women older than age 50 are half that of women in their 20s.[2] What's more, menopausal hormone therapy with oral estrogen increases sex hormone binding globulin (SHBG) levels, decreases luteinizing hormone secretion, and lowers testosterone production and availability.[3] In cases where insufficient testosterone is suspected as a possible cause, serum androgen levels are tested. However, low libido and serum testosterone levels do not correlate well.

Dr. Shifren, assistant professor of obstetrics and gynecology at Harvard Medical School, and colleagues have now published a randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of a testosterone patch for the treatment of women with HSDD after natural menopause. Although no androgen product is approved in the United States for the treatment of female sexual dysfunction, many women use compounded products and products intended for men. There is keen interest in testosterone testing and treatment. Androgen therapy seems to have most benefit in patients who have undergone early surgical menopause, and this study attempts to extend that use to naturally menopausal women.

This Phase III trial is the first large study of testosterone therapy among naturally menopausal women with HSDD on estrogen or combined hormone therapy.

In 549 menopausal patients taking estrogen (+ progesterone where indicated) application of a twice-weekly 300 microgram testosterone patch for 24 weeks increased the total number of satisfying sexual encoun-

ters and orgasms by one to two per month and lowered personal distress by 20%. It also improved circulating bioavailable testosterone. Estrogen levels and SHBG did not change. Most adverse events were mild or moderate and did not result in discontinuation of the study drug. Women grew slightly more facial hair, suffered site reactions, and were slightly more prone to acne, but did not experience deepening of the voice or alopecia. There were no significant changes in clinical laboratory values, including lipid profiles, carbohydrate metabolism, hematology, and liver and renal function, in either group.

COMMENTARY

Think you have heard this somewhere before? Well, you have. In fact, these data were released in national conferences and widely promoted by the pharmaceutical company nearly two years ago when the testosterone patch being studied was up for FDA approval. Finally, we all hoped—a quick fix for low sex drive! Despite the study showing that sort-term use is safe and effective, the US Food and Drug Administration rejected approval of transdermal testosterone use for HSDD, citing the lack of long-term safety data. Thus far, in all of the transdermal testosterone trials, clinical improvement is seen only with higher than normal blood levels of testosterone. The risks of these higher testosterone levels are unknown. These medicines can decrease HDL (good cholesterol) levels significantly. Thus, testosterone use in women remains experimental. As most are well aware, there has been much controversy about treatment with other exogenous hormones, particularly since the publication of the Women's Health Initiative. Dr. Shifren responded to the criticism that modest gains may not outweigh unknown risks, "To focus on the one or two satisfying sexual events in 4 weeks is to miss the picture. We measured other aspects of sexual function, all of which were statistically significantly improved compared to placebo, such as sexual self-image, arousal, and orgasmic response." She feels that women and their physicians are capable of evaluating the risks and benefits of such therapies. The hormone controversy continues. ■

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Pharmacology Update

Ranibizumab Intravitreal Injection (Lucentis™)

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

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 relationships to this field of study.

A NEW AGENT HAS BEEN APPROVED FOR THE TREATment of the neovascular (wet) form of age-related macular degeneration (AMD). Ranibizumab is a fragment of bevacizumab (Avastin), a monoclonal antibody that binds to vascular growth factor and has been used for the treatment of various cancers. Ranibizumab, produced by recombinant technology, is marketed by Genentech as Lucentis™.

Indications

Ranibizumab is indicated for the treatment of neovascular (wet) AMD.[1]

Dosage

The recommended dose is 0.5 mg (0.05 mL) given by intravitreal injection monthly. The dose may be reduced to injections every 3 months after the first four doses, although this is less effective than monthly dosing.[1] Ranibizumab is supplied as a single-dose vial (0.05 mL of 10 mg/mL).

Potential Advantages

Ranibizumab is more effective than photodynamic therapy with verteporfin in classic neovascular AMD.[2] It also appears to be effective for the occult (minimally classic) form of AMD.[3]

Potential Disadvantages

Uveitis, endophthalmitis, and retinal detachment have been associated with ranibizumab. These appear to be rare (1% or less). The frequency of adverse events categorized as intraocular inflammation was 15%. Post injection, transient increase in intraocular pressure has been observed in about 9% of patients.[2]

Comments

In contrast to pegaptanib that binds to one isoform, ranibizumab, a fragment of bevacizumab, binds to the two key isoforms of vascular endothelial growth factor.[4,5] Two pivotal phase III studies (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD [MARINA] and Anti-VEGF Antibody for the treatment of Predominately Classic Choroidal Neovascularization in AMD [ANCHOR]) were the keys for FDA approval. In studies with minimally classic or occult AMD (n = 716), 94.6% of patients given monthly ranibizumab (0.5 mg) lost fewer than 15 letters at 1 year compared to 62.2% receiving sham injections.[3] Visual acuity improved by 15 letters in 33.8% of patients compared to 5% for sham injections. The benefit appears to be maintained for 24 months. In patients with classic AMD, ranibizumab was more effective than photodynamic therapy (PDT) with verteporfin (n = 423). In patients receiving monthly ranibizumab (0.5 mg), 96.4% lost fewer than 15 letters in one year compared to 64.3% for PDT. Visual acuity improved by 15 letters in 40.3% compared to 5.6% for PDT. Trials are currently in progress to determine the effectiveness of less frequent injections.[4] The combination of PDT and ranibizumab does not appear to improve effectiveness in predominately classic AMD. Ranibizumab is generally well tolerated. Rare serious adverse events include uveitis and endophthalmitis. Other more common less serious adverse events include conjunctival hemorrhage, eye pain, blurred vision, floaters, iris and uveal tract inflammation and transient increase in intraocular pressure.[1,5] Non-ocular adverse events include nasopharyngitis and a small increase in blood pressure. The cost of ranibizumab is $1,950 per monthly injection.

Clinical Implications

Due to the aging population, the prevalence of AMD is expected to increase in the upcoming years. It is the leading cause of vision loss or blindness in those 65 years of age and older. Wet AMD, the less common (10%) but more serious form, involves abnormal growth of blood vessels beneath the retina and leaks into the retina causing scarring and loss of central vision. AMD is categorized into different types based on the nature and location of the lesions and their location in the fovea. These categories include classic or occult and extrafoveal or subfoveal. In classic AMD (the more severe form), new blood vessel growth, and scarring have very clear, delineated outlines beneath the retina (ie, classic choroidal neovascularization). In occult AMD, new blood vessel growth is less pronounced and leakage is less evident. Currently there are 3 treatment modalities; laser photocoagulation, PDT with verteporfin, and pegaptanib intravitreal injection. Ranibizumab appears to be an improvement over current therapy. There are currently no published comparative trials between ranibizumab and pegaptanib. Intravitreal injection of bevacizumab has also been shown to be effective in AMD at a fraction of the cost ($20-$50) posing a dilemma for clinicians.[4,6] ■

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CME Questions

25. Choose the true statement regarding the acetaminophen study.

a. Elevated ALT levels were noted as early as Day 2 of the study.
b. Subjects with elevated ALT levels had higher acetaminophen levels than those with not.
c. Hispanic subjects had almost twice the relative risk of developing ALT levels > 3× ULN.
d. Combining acetaminophen with an opioid increased the risk of developing elevated ALT levels.
e. Subjects with elevated ALT levels also had elevations in bilirubin or alkaline phosphatase.

26. What is *not* a perceived benefit of testosterone use in naturally menopausal women?

a. Improve sexual desire
b. Increase orgasm
c. Lowers personal distress
d. Prevents hair loss

Answers: 25 (c); 26 (d)

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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.

Diabetes Prevention: 7 Ways to Leave Your Sugar

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) appear to be the steps directly preceding the development of overt diabetes. Randomized clinical trials have demonstrated that several different interventions can reduce the development of diabetes for persons with IFG or IGT: acarbose, diet and exercise, or metformin. The thiazolidinedione troglitazone has also demonstrated efficacy, but was withdrawn from the market due to liver toxicity. Functional similarities between troglitazone and rosiglitazone (ROS) suggest that the latter should also be effective to prevent progression from IFG/IGT to frank diabetes, without the attendant risk of hepatic dysfunction.

The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)Trial randomized 5808 persons with either IGT or IFG (as determined by 75 g oral GTT) to ROS or placebo. Dosing of ROS was 4 mg/d × 2 months then 8 mg/d × 3 years.

ROS treatment reduced the composite primary end point (incident diabetes or death) by 60%, and the specific secondary end point of new onset diabetes by 62% ($P < 0.0001$ for each). Risk reduction was similar whether the subject entered the trial with IFG or IGT. Clinicians now have numerous evidence-based pathways from which to choose if they wish to intervene in persons with IFG or IGT to prevent diabetes. ■

The DREAM Trial Investigators. Lancet. 2006;368:1096-1105.

Mortality Amongst Persons with Hepatitis B or Hepatitis C

Both hepatitis B (HEPb) and hepatitis C (HEPc) may progress to advanced liver disease, but little data have addressed the long-term mortality associated with these infections. The Notifiable Diseases Database of Australia provides an opportunity to retrospectively examine outcomes in persons with hepatitis.

During the 1990-2002 period, 117,547 persons were identified with HEPb or HEPc. Standardized mortality ratios were greatly magnified for death from liver disease in persons with either HEPb or HEPc, and risk was compounded when co-infected with both. For instance, persons with HEPb incurred a risk of liver-related death 12-fold greater than age-matched persons without HEPb; for HEPb/HEPc coinfection, risk was magnified 33-fold.

One (perhaps) surprising data point emerged from this study: in persons with HEPc, risk of dying from illicit drug-related causes was actually greater than liver-related causes. Because 80% of HEPc in Australia is acquired through intravenous drug use, continued substance abuse remains a problem whose mortality outweighs that of the HEPc disease process itself. ■

Amin J, et al. Lancet. 2006;368: 938-945.

Medical Management of Kidney Stones

Kidney stones (KST) are epidemiologically important in the United States, being responsible for almost 2 million annual office or emergency department visits in recent years. Small distal ureteral stones (< 5 mm) will spontaneously pass most of the time, but surgical treatment is sometimes required.

Calcium channel blockers (CCB) and alpha-blockers (ALB) have physiologically appealing activity that could enhance likelihood of stone expulsion: they decrease ureteral smooth muscle spasm, while allowing continued physiologic ureteral peristalsis.

Hollingsworth et al report upon a literature search of all randomized controlled trials (n = 417) of CCB or ALB to treat kidney stones (total patient n = 693). The pooled data indicate a 65% greater likelihood of stone passage in persons receiving CCBs or ALB than in persons treated with simple analgesia (eg, NSAIDs or other analgesics).

Most of the clinical trials employing CCB or ALB have been published in subspecialty literature. The authors suggest that the available evidence supports inclusion of medical therapy (alpha blockers or calcium channel blockers) to enhance likelihood of KST passage. Tamsulosin and nifedipine were the most commonly reported agents representative of ALB and CCB respectively. Because both classes of drugs have a high degree of familiarity to clinicians, and the adverse effect profiles are excellent, CCB/ALB treatment may reduce the need for surgical intervention in persons suffering KST and deserve consideration by primary care clinicians as appropriate medical therapy. ■

Hollingsworth JM, et al. Lancet. 2006;368:1171-1179.

Arrows & Tachycardia

By Ken Grauer, MD, *Professor, Dept. of Community Health and Family Medicine, University of Florida.*

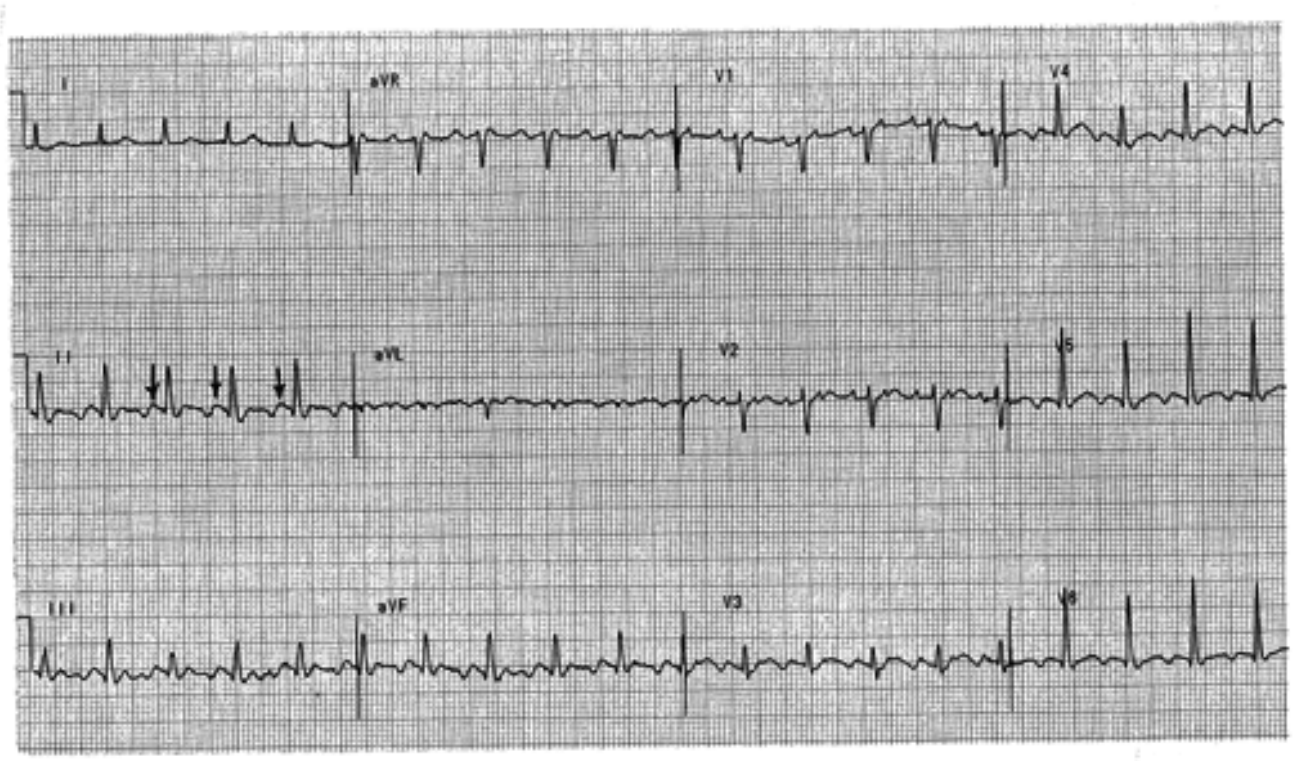

Figure. 12-lead ECG obtained from an elderly woman with shortness of breath.

Clinical Scenario: The ECG in the Figure was obtained from an elderly woman who was being seen in the office for shortness of breath. No chest pain. What do you make of her "arrows and tachycardia?"

Interpretation/Answer: The QRS complex is narrow and regular at a rate of about 120 beats/minute. The arrows in lead II initially suggest that the rhythm may be sinus tachycardia, however this is not the case. Instead, the small negative undulations in the baseline of the inferior leads should lead one to suspect additional atrial activity. Leads V_1 and V_2 show this phenomenon best. Two small, pointed upright deflections are seen within each R-R interval in these two leads. This represents regular atrial activity occurring at a rate of 240/minute. The *only* rhythm that manifests regular atrial activity at this rapid a rate is atrial flutter, shown here with 2:1 AV conduction.

Atrial flutter is by far the most commonly overlooked arrhythmia diagnosis. The key to not missing it is to always maintain a high index of suspicion for the diagnosis, especially when presented with a regular SVT (supraventricular tachycardia) in which the nature of atrial activity is uncertain. ■

In Future Issues: **Importance of HDL Cholesterol in ACS**