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Mono Therapy with Inhaled Steroids: The New Standard for Asthma?

By William T. Elliott, MD, FACP

The standard of care for the treatment of mild asthma is moving to mono therapy with **inhaled steroids**. A study from the University of Helsinki compared inhaled steroid treatments to **inhaled terbutaline**, a **beta agonist**, in patients with mild asthma. At the end of six weeks of treatment, patients who used inhaled steroids had significant improvements in symptom scores, peak expiratory flow rates, and eosinophil counts compared to those who used terbutaline (*Allergy* 2000;55:505-509). In a separate study from New Zealand, researchers compared the use of **budesonide**, an **inhaled corticosteroid**, to the use of budesonide with an inhaled beta agonist. At the end of six weeks, the researchers found that the use of budesonide alone was at least as effective as the combination of the two drugs in preventing symptoms. They concluded that short-acting bronchodilators should only be used as needed for symptoms (*Am J Respir Crit Care Med* 2000;161:1459-1464).

The Centers for Disease Control have issued guidelines for the treatment of community-acquired pneumonia. Suitable regimens include a **macrolide (erythromycin, clarithromycin**, or **azithromycin**), **doxycycline**, or a **beta-lactam** with good activity against pneumococci. Hospitalized patients should receive an intravenous beta-lactam (**cefuroxime, ceftriaxone, cefotaxime**, or **ampicillin/sulbactam**) plus a **macrolide**. The newer **fluoroquinolones** are effective against drug resistant *Streptococcus pneumoniae*, but should be considered second line for initial therapy to limit the development of pneumococcal resistance to these drugs. Fluoroquinolones should be given if the patient fails other regimens, or if the strain of *S. pneumoniae* is highly drug resistant. **Vancomycin** is not routinely indicated for drug resistant *S. pneumoniae* (*Arch Intern Med* 2000;160:1399-1408).

Cardiovascular

Could lowering **cholesterol** with drugs or diet affect cognition? English researchers looked at the effects of **low-fat diet**, a **Mediterranean diet**, or **control diet** on psychological well-being and cognitive function of volunteers at six and 12 weeks. Both active dietary interventions reduced serum

cholesterol levels significantly. And while all three groups showed improvement in psychological well-being over the treatment period, the two groups that lowered their cholesterol levels did significantly worse on at least one measure of cognitive function (*Am J Med* 2000;108:547-553). The second study looked at cholesterol lowering with **lovastatin** (**Mevacor**). More than 200 healthy volunteers were randomized to six months therapy with 20 mg/d of lovastatin or placebo. At the end of six months, assessments of cognitive function and psychological well-being were performed. The placebo-treated patients showed improvement in all five neuropsychological tests, which is to be expected when tests are repeated over time. The lovastatin-treated group showed improvement only in the memory recall test. Although psychological well-being did not seem to be affected by lovastatin, the treated individuals showed small decrements in psychomotor speed and attention (*Am J Med* 2000;108:538-546).

It is a given that early administration of **thrombolytic therapy** for **acute myocardial infarction** results in better outcomes. Now researchers from Canada are suggesting that the best time to administer these drugs may be before the patient gets to the hospital. The pooled data from six randomized trials were the subject of a meta-analysis on the timing of thrombolytic therapy and outcomes. The results showed that pre-hospital administration of thrombolytic therapy was associated with a significant reduction in all-cause hospital mortality. The meta-analysis was of insufficient power to demonstrate a difference at one or two years (*JAMA* 2000;283:2686-2692).

Oncology

The FDA reports that the recently approved **breast cancer** drug **trastuzumab** (**Herceptin**) is associated with severe adverse reactions in women with advanced metastatic breast cancer, including 15 deaths. Most of the fatal reactions have occurred in women with underlying lung disease, usually within 12 hours of the initial dose, and often during the initial infusion. The FDA still regards the drug safe for use in breast cancer patients but only with appropriate monitoring.

COX-2 inhibition may do more than reduce inflammation—it may also inhibit the growth of solid tumors. Investigators from Vanderbilt University have shown that the growth of **lung tumors** is inhibited when the gene for COX-2 is removed from mice, or in mice that are treated with a COX-2 inhibitor. The investigators have shown that the production of **endothelial growth factor** is dependent on COX-2. Mice without the gene showed a 94% reduction in the growth factor while mice treated with a COX-2 inhibitor showed 92% reduction. Endothelial growth factor is thought to be responsible for the development of blood vessels in solid tumors (*J Clin Invest* 2000;105:1589-1594).

Men's Health

Many physicians are reluctant to prescribe **sildenafil** (**Viagra**) to men with known **coronary artery disease (CAD)**. A study from the University of Pennsylvania looked at the hemodynamic effect of the drug on 14 men with severe coronary disease. Sildenafil caused a small decrease in system blood pressure but had minimal effect on other hemodynamics. The authors conclude that the drug was not associated with adverse cardiovascular effects in men with CAD. They still caution against the concomitant use of sidenafil and **nitrate-containing medications** (*N Engl J Med* 2000;342:1622-1626).

Saw palmetto is a reasonable first-line therapy for men with uncomplicated benign prostatic hypertrophy (BPH) according to researchers from UCLA. In a placebo-controlled study of 44 men, the herbal preparation was shown to cause a involution of the prostatic epithelium as shown on prostate biopsy. Clinical measures of the drug's effect were only slightly better than placebo and did not reach statistical significance over the six-month study period. Still, the researchers suggest that there is some evidence of a mechanism of action of saw palmetto, and that there were no side effects seen. They also suggest that clinical effects may occur over a longer period of time (*J Urol* 2000;163:1451-1456).

Rheumatology

COX-2 inhibitors are associated with lower rates of gastrointestinal irritation than non selective **NSAIDs**. Now there is evidence that **celecoxib** (**Celebrex**) may also have less adverse effect on the kidney as well. NSAIDs generally cause reduced renal perfusion and glomerular filtration rate (GFR), especially the high-dose, long acting NSAIDs. Researchers from Maryland looked at 29 healthy elderly individuals, comparing renal function on maximal doses of celecoxib (400 mg b.i.d.) and maximal doses of naproxen (500 mg b.i.d.). **Naproxen** resulted in a significantly greater decrease in GFR by day 6 of treatment compared to celecoxib. The authors suggest that **COX-1** may play a bigger role in renal hemo dynamics than previously thought, COX-1 seems to be responsible for preserving GFR, while COX-2 is important in regulating a sodium and water balance (*Arch Intern Med* 2000;160:1465-1470). ■

Pneumococcal Conjugate Vaccine (Prevnar)

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

The fda has approved a new pneumococcal vaccine for use in children. The 7-valent pneumococcal conjugate vaccine (diphtheria CRM_{197} protein) was given approval in February for the prevention of invasive pneumococcal disease in infants and young children. *Streptococcus pneumoniae* is a leading cause of serious illness in young children including bacteremia, meningitis, pneumonia, and upper respiratory tract infections such as otitis media. The 7-valent vaccine covers serotypes that account for approximately 80% of invasive pneumococcal disease in children younger than 6 years of age.[1] The vaccine is marketed by Wyeth-Ayerst Laboratories under the name of Prevnar.

Indications

The vaccine is indicated for active immunization of infants and toddlers against invasive disease caused by *S. pneumoniae* due to capsular serotypes (4, 6B, 9V, 14, 18C, 19F, and 23 F).

Dosage

The routine immunization schedule is 2, 4, 6, and 12 - 15 months of age. For previously unvaccinated infants 7-11 months of age, two doses should be administered at least four weeks apart and the third dose after the 1-year birthday, separated from the second dose by at least two months. For children 12-23 months of age, two doses should be administered at least two months apart. For children 24 months or older through 9 years of age, one dose should be administered. However, two doses, two months apart, should be administered to children 24-59 months in high-risk groups (e.g., sickle cell disease or anatomic or functional asplensia, HIV infected or immunocompromised, chronic illness such as nephrotic syndrome, diabetes, chronic pulmonary conditions, and symptomatic heart conditions). The dose is 0.5 mL administered intramuscularly.[2]

Potential Advantages

The conjugate vaccine is more immunogenic than the existing polysaccharide vaccine that is not effective in children younger than 2 years of age since it is T-cell independent and does not induce immunologic memory. Vaccination of infants at 2, 4, 6, and 12-15 months with Prevnar has been shown to be efficacious in preventing invasive pneumococcal disease caused by serotypes included in the vaccine.[2,10] Efficacy based on an intent-to-treat analysis (including all children who received at least 1 dose) was 93.9% (95% CI: 79.6-98.5%) for serotypes included in the vaccine. Per protocol analysis (events occurring ≥ 14 days after the third dose) showed efficacy of 97.4% (95% CI: 82.7-99.9%). The efficacy against all serotypes was 89% (95% CI: 73.7-95.4%).[1,10] Data also suggest that the vaccine reduced acute otitis media (AOM) caused by *S. pneumoniae* and AOM-related outcomes such as visits, episodes, frequent and severe otitis, and ventilatory tube placement.[9,10]

Potential Disadvantages

Prevnar will not protect against *S. pneumoniae* disease caused by serotypes other than those included in the vaccine. It is contraindicated in patients with known hypersensitivity to diphtheria toxoid. Side effects include fever, irritability, restless sleep, vomiting, diarrhea, and injection site reactions.[2] It is not certain how or if immunization against the seven serotypes would result in emergence of less common serotypes.

Comments

Prevnar is a pneumococcal vaccine prepared by the conjugation of seven serotypes of pneumococcal polysaccharide to protein carrier reactive molecule 197 (CRM 197). CRM 197 is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (ß197). The conjugated vaccine induces T cell-dependent immune response and is therefore immunogenic in children younger than 2 years of age.[6,7] The efficacy trial involving 37,816 infants (18,906 Prevnar and 18,910 control) was conducted at Kaiser Permanente of Northern California. The control vaccine was an investigational meningococccal group C conjugate vaccine (CRM_{197}).[2,10] Efficacy was more than 93% for serotypes included in the vaccine and 89% for all pneumococcal serotypes. Black and associates also reported efficacy against visits, episodes, frequent and severe otitis, and ventilatory tube placement of 8.9%, 7.0%, 9.3%, and 20.1%, respectively, with $P < 0.04$ for all.[1] In a study conducted in Finland, Eskola and associates reported a per protocol reduction of 57% (95% CI: 44-67%) in culture-confirmed serotype specific AOM, a 34% (95% CI:21-45%) reduction in cultured-confirm pneumococcal (any serotype) AOM, and a 6% (95% CI: -4-16%) reduction in AOM irrespective of etiology.[9]

Clinical Implications

The previously available polysaccharide pneumococcal vaccine is not effective in children younger than 2 years of age. The development of the pneumococcal 7-valent conjugate vaccine has the potential to prevent significant *S. pneumonia*-related morbidity and mortality in children. The seven serotypes, out of about 90 known serotypes, are responsible for approximately 80% of invasive pneumococcal disease and 60% of AOM in children. The seven serotypes account for 74% of penicillin-nonsusceptible (intermediate or high-level resistance) *S. pneumoniae* (PNSP) and 100% of pneumococci with a high level of penicillin resistance.[1,4] *S. pneumoniae* is the most common cause of bacterial meningitis in children and is associated with 8% mortality as well as neurological sequelae and hearing loss.[5] The vaccine has been reported effective in preventing invasive disease, reducing AOM due to vaccine serotypes, reduction in AOM of any serotype, and reduction in AOM visits, episodes, frequent otitis, and ventilatory tube placement.[2,9,10] The preliminary recommendation of The Advisory Committee on Immunization Practices (ACIP) for Prevnar includes immunization of the birth cohort, catch-up immunization of infants up to 23 months of age, and children ages 24-59 months who are at risk for pneumococcal disease. These include children with sickle cell disease or anatomic or functional asplensia, HIV-infected or immunocompromised, chronic illness such as nephrotic syndrome, diabetes, chronic pulmonary conditions (excluding asthma), and symptomatic heart conditions. The vaccine may also be considered for children in certain ethnic groups such as American Indians, Alaskans, and African Americans.

Wyeth-Ayerst is required to submit monthly adverse event reports to the FDA for the first year. It is also committed to conduct Phase IV postmarketing studies in previously unvaccinated children receiving "catch-up" therapy for all age groups.[8] The vaccine costs $58 per dose. ■

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Meloxicam (Mobic) A New NSAID

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

Given the popularity of the new cox-2 inhibitors, the introduction of a new nonsteroidal anti-inflammatory drug (NSAID) seems positively old fashioned, but that is exactly what Boehringer Ingelheim has done. Meloxicam is a new NSAID that was recently approved by the FDA for marketing. It is an oxicam nonsteroidal anti-inflammatory agent chemically similar to piroxicam (Feldene). In contrast to the recently introduced selective cyclooxygenase (COX)-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx) which are primarily inhibitors of COX-2, meloxicam has as preferential cyclooxygenase-2 selectivity.[1] Meloxicam will be marketed in this country by Boehringer Ingelheim and Abbott Laboratories.

Indications

Meloxicam is indicated for the relief of signs and symptoms of osteoarthritis (OA).

Dosage

The recommended starting and maintenance dose of meloxicam is 7.5 mg with a maximum dose of 15 mg/d.[2] It may be taken without regard to meals or antacids. The drug is supplied as 7.5-mg tablets.

Potential Advantages

Meloxicam has a long elimination half-life (about 20 h) and is dosed once daily. No dosage adjustment is required in patients with mild to moderate renal or hepatic impairment. Meloxicam does not appear to affect the pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, monitoring is recommended, particularly in the first few days after initiating or changing meloxicam therapy in patients taking warfarin.[2]

Potential Disadvantages

Similar to other NSAIDs, gastrointestinal (GI) adverse events were the most frequently reported events in the clinical trials.[2] GI side effects may be more frequent than originally expected as, after the product was launched in the United Kingdom, the product labeling had to be updated to include stronger warnings for GI side effects and skin reac-

tions. Forty-one percent of suspected adverse reactions reported (1330 in the first 21 months) were GI-related, including 18% perforations, ulcerations, and bleeding. Fourteen percent were dermatological side effects.[5,8] Meloxicam is only approved for use in OA.

Comments

Meloxicam is an oxicam NSAID with greater activity against the inducible isoform of COX-2 than the constitutive COX-1. Its efficacy is reported to be similar to other NSAIDs, such as piroxicam, diclofenac, or naproxen,[1,2,6] but early clinical trials suggest that meloxicam had improved gastrointestinal tolerability compared to piroxicam, diclofenac, or naproxen.[1,3,4,7] Meloxicam in doses of 7.5 mg-15 mg/d was compared to piroxicam 20 mg/d, diclofenac 100 mg/d, or naproxen 750 mg/d. A meta-analysis of meloxicam studies (10 randomized trials, n > 20,000, duration up to 24 weeks) suggests that it causes fewer GI adverse events than non-COX-2 selective NSAIDs, including less dypepsia, fewer PUBs, and less frequent withdrawal of NSAIDs because of adverse events.[3] However, the postmarketing experience in the United Kingdom suggests that GI events may be higher than suggested by these trials. A possible explanation of this difference may be the dose. The two largest trials—the Meloxicam Large-scale International Study Safety Assessment (MELISSA, n = 9323) and Safety and Efficacy Large-scale Evaluation of COX-Inhibiting Therapies (SELECT, n = 8656), were conducted with the lower, 7.5-mg dose. Thus, the preponderance of the safety evidence is based on this dose. Some patients may need a higher dose as there was some evidence that meloxicam may be less efficacious than other NSAIDs. In the MELISSA trial, there were more patients who discontinued meloxicam (7.5 mg/d) because of lack of efficacy compared than to diclofenac (100 mg/d) (odds ratio 1.66; 95% CI: 1.16-2.38).[4] Meloxicam in low doses may have less effect on platelet aggregation than non-COX-2 selective NSAIDs such as diclofenac or indomethacin.[9,10]

The product labeling for meloxicam, unlike the selective COX-2 inhibitors, did not mention reduced GI events with meloxicam and other NSAIDs.[2] Meloxicam (7.5 mg) costs about $2 per day, which is lower than celecoxib and rofecoxib, which are about $2.50 per day.

Clinical Implications

It is not clear if meloxicam offers any clear advantage over non-COX-2 selective NSAIDs. There have been no published comparative trials between meloxicam and COX-2 preferential inhibitors, such as nabumetone or etodolac, or COX-2 selective agents, such as celcoxib and rofecoxib. ■

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Glucosamine and Chondroitin Sulfate for Treatment of OA

Source: *McAlindon TE, et al. JAMA 2000;283:1469-1475.*

Osteoarthritis (oa) is a major public health problem and treatment with nonsteroidal anti-inflammatories is associated with frequent adverse effects. Since, as McAlindon and colleagues state, glucosamine and chondroitin sulfate are relatively safe preparations, they will have great use in the treatment of OA if they are effective.

McAlindon et al searched for clinical trials in Medline (June 1966-June 1999) and several other sources and contacted study authors and manufacturers of glucosamine and chondroitin. Studies were included if they were published or unpublished double-blind, randomized, placebo-controlled trials of four or more weeks duration that tested for knee or hip OA and reported extractable data on the effect of treatment on symptoms. Fifteen of 37 studies were included in the analysis.

The overall quality score was not significantly different from the mean quality scores of other peer-reviewed journals. Only two studies reviewed reported intent-to-treat analysis. Most were supported by a manufacturer. The aggregated effect sizes were significant at the 95% confidence levels: -0.44 for glucosamine and 0.78 for chondroitin. The effects were diminished when only high-quality or large trials were considered.

McAlindon et al conclude that the glucosamine and

chondroitin preparations for OA symptoms demonstrate moderate to large effects but quality issues and likely publication bias suggest these effects were exaggerated. Nevertheless, some degree of efficacy appears probable for these preparations.

Comment by Ralph R. Hall, MD, FACP

Physicians will welcome therapy for OA that is effective and safe. There are, however, several barriers to the use of glucosamine and chondroitin.

The editorial accompanying this meta-analysis of studies evaluating the use of glucosamine and chondroitin is a short and excellent text on the use of meta-analysis and the bias involved when the studies are supported by manufacturers.[1] Both the editorial and several letters to the editor in the same issue of *JAMA* note that the quality of the studies supporting the use of pharmaceuticals and supplements that are, in turn, supported by the manufacturer are peer reviewed and usually of good quality. Bias is introduced because the manufacturers fail to report negative studies.

More to the point, however, and not mentioned in any of the articles cited, is the possibility that the product may not contain sufficient amounts, or any, of the product listed on the label. Since there is no oversite by the FDA, the products are not taken to task by the FDA unless there is an event that clearly demonstrates that the product has taken a life or is dangerous for some other reason.

A relatively new organization has undertaken the task of analyzing many of the supplements and publishes their results on the Internet. Its recent review of glucosamine and chondroitin is of special interest.[2] They tested 25 brands of glucosamine, chondroitin, and combined glucosamine/chondroitin products. The products were tested to determine if they possessed the labeled amounts claimed.

"Overall, nearly one-third of the products did not pass testing. Among glucosamine/chondroitin combination products; however, almost half (6 out of 13) did not pass—all due to low chondroitin levels. Similarly, the two chondroitin-only products tested did not pass. In contrast, all 10 of the glucosamine-only products passed testing."

One explanation given by the testers is that chondroitin is much more expensive than glucosamine; therefore, the manufacturers do not include adequate amounts in their preparations.

An additional concern has recently been brought to our attention. This is particularly important since there have to date not been long-term studies that establish the safety of these two products. Glucosamine given over a 12-week period was associated with increasing insulin resistance.[3] This study had a small number of patients but it does raise concerns.

A review of the methods and purpose of www.consumerlabs.com is reassuring. The company appears to be reputable, have capable scientists and serve as an important source of information. It supplies information about the collection of products, where the products have been tested, and the testing methods. I urge you to check this Web site. It is a valuable source of information for both you and your patient.

A major thrust, however, should be for us all to encourage the organizations to which we belong, to get Congress to pass laws mandating that the FDA be given more oversight authority for the labeling and the safety of these products. Not only are there safety and efficacy concerns but, with the attention given to cost effectiveness, the millions of wasted dollars spent for ineffective supplements is an outrage. ■

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Dr. Hall is Emeritus Professor of Medicine, University of Missouri-Kansas City School of Medicine.

Antidepressants for Fibromyalgia

Source: *Arnold LM, et al. Psychosomatics 2000;41(2):104-113.*

Although antidepressants have been used as treatment for fibromyalgia, there is no consensus in the literature as to the efficacy of various agents. The current report is a meta-analysis that examines available clinical trials of antidepressants and cyclobenzaprine for the treatment of fibromyalgia. The idea of antidepressants in the treatment of fibromyalgia was initially based, in part, on the finding of abnormal sleep architecture, specifically insertion of alpha waves into deep sleep, which may be due to a central serotonergic mechanism. Arnold and colleagues reviewed randomized, controlled trials of antidepressants for treatment of fibromyalgia.

The methodology, results, and potential predictors of response of suitable controlled trials were studied by meta-analysis. Of 21 controlled trials, 16 involving tri-

cyclic agents were identified, and nine were suitable for meta-analysis. Suitability for inclusion in meta-analysis was based on the presence of sufficient statistical data for effect size computations (i.e., means and standard deviations for continuous outcomes, proportions for binary outcomes). Effect sizes were calculated for measurements of physician and patient overall assessment, pain, stiffness, tenderness, fatigue, and sleep quality.

The antidepressants that were included in the analysis were mostly tertiary amine tricyclics, including amitriptyline and dothiepin. Cyclobenzaprine (Flexeril) was also included in the analysis due to its similarity to the tricyclic antidepressants and its reported effects on serotonin and norepinephrine. Compared with placebo, tricyclic agents were associated with effect sizes that were substantially larger than zero for all measurements. The mean effect size for all studies was approximately normally distributed, with a mean treatment effect of 0.44 of a standard deviation. Based on universally accepted principles of inferential statistics, an effect of this magnitude would be classified as "medium" and would be recognized clinically.

Arnold et al reported that the largest improvements were associated with measures of sleep quality; the most modest improvement was found in measures of stiffness and tenderness. Amid these extremes, global measures, as well as measures of pain and fatigue, showed moderate improvement.

In the review of reports of antidepressant treatments that were not suitable for meta-analysis, Arnold et al found results that were fairly consistent with the findings in the meta-analysis. The selective serotonin reuptake inhibitors (SSRIs) citalopram and fluoxetine were studied. These were associated with high dropout rates and did not demonstrate efficacy. Additionally, past history of depressive episodes were found to be possible predictors of antidepressant treatment response.

Comment by Michael F. Barber, PharmD

Fibromyalgia is a debilitating disease with many symptoms that may either overlap or exhibit similarities with depressive symptoms. This meta-analysis is particularly useful because it helps sort out the actual effects of treating fibromyalgia with antidepressants. Clearly, if the symptoms of fibromyalgia approached complete resolution after 4-6 weeks of treatment, one might question whether the patient is actually being treated for depression. However, the results from the meta-analysis showed only medium treatment effects, most prominently on sleep disturbance. This suggests that there are target symptoms of fibromyalgia that may respond somewhat to antidepressant therapy, even in the absence of the commonly reported symptoms of depression (depressed mood, reduced energy, impaired concentration, helplessness, hopelessness, or suicidality).

Since the studies that showed the most improvement involved tertiary amine tricyclics (e.g., amitriptyline), combined with the lack of efficacy of SSRIs, amitriptyline should be considered as one of the preferred agents for this purpose. However, studies involving secondary amines such as desipramine or nortriptyline have not been conducted and cannot be ruled out in terms of efficacy. Since they are relatively better tolerated than the tertiary amines, clinicians may opt to use these agents as well. Of course, these agents should typically be avoided in patients with active suicidal thoughts. Further, a great deal of caution should be used in patients with a history of cardiovascular disease due to the propensity of tricyclics to induce arrhythmias. In such cases, it may be advisable to use cyclobenzaprine. ■

Dr. Barber is Assistant Professor of Clinical Sciences and Administration, University of Houston College of Pharmacy, Houston, Texas.

The Effect of Testosterone on Sexual Arousal in Women

Source: *Tuiten A, et al. Arch Gen Psychiatry 2000;57: 149-157.*

Female sex steroids are necessary for the expression of sexual behavior in many mammals. Copulation is typically limited to the period of ovulation, except in higher primates (i.e., humans) who have sex outside the periovulatory period; testosterone is believed to be involved in this. A lack of testosterone (e.g., ovariectomy) is associated with a loss of libido, which is reversed upon replenishment.[1-2] Physiological responses to sexual stimuli are an important aspect of sexual functioning, marked by vaginal vasocongestion. In females with hypothalamic amenorrhea, testosterone substitution enhanced vaginal responsiveness, but not in a parallel group with panhypopituitarism.[3]

Tuiten and colleagues investigated the effect of a single, sublingual dose of testosterone in eight sexually functional

women on physiological and subjective sexual arousal, using a double-masked, randomized, placebo-controlled, crossover design. Participants were tested within 10 days of the end of their period of menstruation, with five days separating the two periods of treatment. Subjects were exposed to pornographic or neutral videotape at six time intervals: immediately before, 15 minutes after, and every one-and-a-half hours for six hours after testosterone administration. Blood levels of testosterone were measured at all six intervals. Within 15 minutes of testosterone intake, there was a 10-fold+ increase in total testosterone levels and a return to baseline within 90 minutes. Compared to placebo, testosterone significantly increased genital responsiveness four-and-one-half hours after peak levels and was associated with increased genital arousal, as well as subjective reports of genital sensations and sexual lust. Tuiten et al concluded there is a lag in the effect of sublingually administered testosterone, perhaps due to the time it takes for neurophysiologic alterations in the brain.

Comment by Donald M. Hilty, MD

Testosterone may have an important clinical role in terms of sexual functioning. In aging men, testosterone levels decline with age and are correlated with symptoms of depression. Testosterone replacement is being evaluated at the present time. In HIV-positive men who often have hypogonadal symptoms, testosterone is well-tolerated and appears to restore libido and energy.[4] A recent study estimated that 43% of women suffer from sexual dysfunction, mainly low sexual desire (22%), sexual arousal problems (14%), and sexual pain (7%).[5] Intermittent testosterone may be helpful, though the four-hour delay in response may be an impediment to use. The "correct" dose is yet unclear and its use has potential adverse events. At doses 4-8 times normal levels, 4% of patients may become hypomanic; at 8+ times normal levels, over 18% of patients demonstrated psychosis or euphoria.[6] ■

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Dr. Hilty is Assistant Professor of Clinical Psychiatry, University of California, Davis, Sacramento, CA.

CME questions

Testing form inserted in the July 2000 issue

14. Compared to placebo, the use of testosterone in women:

a. significantly increased genital responsiveness four-and-one-half hours after peak levels.
b. was associated with increased genital arousal.
c. caused subjective reports of genital sensations and sexual lust.
d. All of the above

15. Which one of the following statements is true?

a. The FDA does not have direct oversight on the contents of herbs and supplements sold in the United States.
b. At least 95% of the preparations tested by www.consumerlabs.com contained the ingredients listed on the supplements label.
c. Manufacturers are required to report negative studies completed on their products.

16. A common symptom of depression is:

a. hopelessness.
b. reduced energy.
c. impared concentration.
d. helplessness.
e. all of the above.

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