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INSIDE

Ibuprofen May Block Aspirin's Beneficial Effects

By William T. Elliott, MD, FACP

In patients with vascular disease and arthritis, taking ibuprofen may block the beneficial anti-platelet aggregation effects of low-dose aspirin. Researchers from the University of Pennsylvania found that taking ibuprofen 400 mg 2 hours before taking aspirin significantly reduced aspirin's benefits. Conversely, taking aspirin 2 hours before ibuprofen had no effect on aspirin's anti-platelet action. It is speculated that ibuprofen occupies the hydrophobic channel of platelet Cox-1, effectively blocking aspirin's access to platelet cyclooxygenase. In the same study, pretreatment with acetaminophen or the selective Cox-II inhibitor rofecoxib had no effect on aspirin's action. The study also showed that therapeutic levels of the anti-inflammatory diclofenac did not affect aspirin's anti-platelet action, whereas regular doses of ibuprofen (400 mg 3 times a day) did block aspirin's beneficial action. This study concludes that ibuprofen, and perhaps some other nonselective NSAIDs, may block the beneficial platelet inhibition of aspirin (*N Engl J Med*. 2001;345:1809-1817; 1844-1876).

Droperidol Receives 'Black Box' Warning

Intravenous **droperidol** (Inapsine-Akorn pharmaceuticals) has received a "Black Box" warning from the FDA because of the risk of fatal heart arrythmias associated with the drug. The Black Box, the highest-level warning assigned to drugs, was accompanied by a "Dear Doctor" letter to US physicians. Droperidol is commonly used in the in-patient setting to treat nausea and anxiety. Low doses of the drug have been shown to result in prolongation of the QT interval, while higher doses (more than 25 mg) have been associated with fatal ventricular arrhythmias including torsade de pointes. The FDA is urging physicians to consider use of alternative medications for patients at high risk for cardiac arrhythmias.

Cardiovascular Events

The angiotensin-receptor blocker **valsartan** improves clinical signs and symptoms of congestive heart failure and may reduce the incidence of hospitalization in patients with advanced heart failure. More than 5000 patients with NYHA class II, III, or IV heart failure were randomly assigned to receive 160 mg valsartan or placebo. Patients had been on a fixed-dose regimen of **ACE inhibitors**, **diuretics**, **digoxin**, and/or **beta-blockers**. The primary outcomes were mortality and the combined end point of mortality and morbidity including cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous heart fail-

ure of medications. The overall mortality of the 2 groups was not different, however the incidence of the combined end point was 13.2% lower in the valsartan group. This was primarily due to a decrease in the number of patients requiring hospitalization. Valsartan also improved ejection fraction, signs and symptoms of heart failure, and quality of life compared to placebo. Interestingly, when valsartan was combined with an ACE inhibitor and a beta blocker, there was an increase in mortality and morbidity (*N Engl J Med.* 2001;345:1667-1675).

Antidepressants

The 3 most commonly used antidepressants are all comparable in reducing depressive symptoms according to a recent large-scale trial. Paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft) were found to be equivalent in treating depression in the primary care setting. More than 570 patients with depression were randomized to receive paroxetine 20 mg/d, fluoxetine 20 mg/d, or sertraline 50 mg/d. Follow-up interviews were done at 1 month, 3 months, 6 months, and 9 months. All 3 drugs were equally effective and comparable on all measures at all time points. About 20% of patients switched drugs during the course of the study, although the rate of side effects was similar among all 3 drugs. The study concludes that the 3 drugs are similar in effectiveness for treatment of depressive symptoms up to 9 months of treatment (*JAMA.* 2001;286:2947-2955). The findings of the study are particularly interesting given that fluoxetine has recently lost its patent protection, and low-cost generics are available.

Common Cold

Zinc nasal spray is ineffective for preventing or treating the common cold according to a new study. Investigators from the University of Virginia tested intranasal zinc gluconate against a placebo nasal spray in nearly 100 patients who were inoculated with a rhinovirus. Patients were pretreated for 3 days prior to inoculation and for 6 days thereafter. The infection rate with placebo (74%) was the same as that with zinc gluconate (78%). There was also no difference in symptomatology including rhinorrhea, nasal obstruction, or other upper respiratory symptoms associated with use of zinc (*Clin Infect Dis.* 2001;33:1865-1870).

DVT

The FDA has approved a new Factor Xa inhibitor for the prevention of postoperative deep venous thrombosis (DVT). Fondaparinux sodium (Arixtra) is approved for use after orthopedic procedures including hip fracture, hip replacement, and knee replacement. The drug is the first of the new class of agents designed to inhibit Factor X. The approval was based on randomized double-blind trials involving more than 4000 patients who had undergone orthopedic surgery. The drug is contraindicated in patients weighing less than 50 kilograms and those with severe renal impairment. It is also contraindicated in patients who have received spinal anesthesia or had a recent spinal puncture.

Steroids and Antibiotics

An intranasal steroid along with antibiotics improves success rates and speeds recovery in the treatment of rhinosinusitis. Researchers from North Carolina looked at 95 patients with a history of chronic rhinitis or recurrent sinusitis and evidence of an acute infection. All patients were treated with cefuroxime 250 mg twice daily for 10 days, along with the nasal decongestant for 3 days. Half the patients were randomized to fluticasone propionate nasal spray or placebo nasal spray in each nostril once per day for 3 weeks. Patients were followed-up for 2 months. Patients receiving fluticasone improved more rapidly and achieved a significantly higher rate of clinical success than patients receiving placebo. The study recommends consideration of intranasal steroids as part of the therapeutic regimen for treatment of acute sinusitis in the patient with a history recurrent or chronic sinus infections (*JAMA.* 2001;285:3097-3105).

HRT

A new study gives guidance as to which menopausal women will benefit more from hormone replacement therapy (HRT) or the selective estrogen receptor modulator raloxifene. Researchers at Penn used a time-dependant Markov model to estimate the life expectancy using either modality. These findings suggest women who are at average risk for breast cancer and coronary heart disease may benefit more from HRT, while women with one or more major breast cancer risks will benefit more from raloxifene. This study assumes a 20% or higher reduction in the risk of CAD with HRT (*Obstet Gynecol.* 2001;98:996-1003). ■

Xigris—A New Treatment for Severe Sepsis

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

The fda recently approved the first biologic treatment for severe sepsis. Drotrecogin alfa (activated), a glycoprotein serine protease produced by

genetic engineering, has the same amino acid sequence as human plasma-derived Activated Protein C. It appears to have antithrombotic, anti-inflammatory, and profibrinolytic action in patients with sepsis. Drotrecogin alfa will be marketed by Lilly as Xigris.

Indications

Drotrecogin is indicated for the reduction of mortality in adult patients with sepsis associated with acute organ failure (ie, severe sepsis) who have a high risk of mortality.[1] In the clinical study, risk of mortality was determined by acute physiology and chronic health evaluation score (APACHE II).

Dosage

Drotrecogin should be infused intravenously at a rate of 24 μg/kg/h of a total of 96 hours.

It is supplied as 5 mg and 20 mg single-use vials. The lyophilized powder should be stored under refrigeration and protected from light.[1]

Potential Advantages

In patients with systemic inflammation and organ failure due to acute infection, drotrecogin was associated with a absolute reduction in the risk of death of 6.1% (24.7% vs 30.8%) 28 days after the start of infusion.[2]

Potential Disadvantages

Bleeding is the most common adverse effect of drotrecogin. The incidence of serious bleeding (eg, intracranial hemorrhage, life-threatening bleeding) compared to placebo was 3.5% vs. 2.0%.[2] Patients at risk for bleeding should be evaluated on a risk to benefit basis. Drotrecogin is contraindicated in patients with active internal bleeding, recent hemorrhagic stroke or intracranial or intraspinal surgery, severe head trauma, other trauma associated with an increased risk of life-threatening bleeding, presence of an epidural catheter, or intracranial neoplasm, mass lesion, or evidence of cerebral herniation.[1]

There is currently no evidence to suggest that patients with severe sepsis but with a lower risk of death would benefit from drotrecogin.[1]

Comments

Sepsis is the systemic inflammatory response to infection. Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion, or hypotension.[3,4] The sequelae of sepsis are the result of interplay between the inflammatory cascade and the coagulation cascade. Protein C is one of the body's defenses against thrombosis. It possesses antithrombotic, anti-inflammatory, and profibrinolytic effects. Data indicate that protein C deficiency might be predictive of death associated with sepsis.[5-7] The safety and efficacy of drotrecogin, which is a genetically engineered version of naturally occurring Activated Protein C, was demonstrated in Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial and was the basis for the approval of the agent.[2] Patients were eligible for the trial if they had a known or suspected infection and the following criteria within a 24-hour period: 3 or more signs of systemic inflammation and sepsis-induced dysfunction of at least 1 organ or system that lasted no longer than 24 hours. Signs of systemic inflammation are temperature ≥ 38°C or ≤ 36°C, heart rate ≥ 90 bpm, respiratory rate ≥ 20 breaths/min or $PaCO_2$ ≤ 32 mm Hg, or WBC count ≥ 12,000/mm^3 or ≤ 4000/mm^3 or > 10% immature neutrophils. Patients in the trial had an average APACHE II score of 25, more than 73% were on mechanical ventilation and more than 70% were in shock. Time to initiation of antibiotics was within 48 hours. Patients at risk for bleeding disorders, those not expected to survive 28 days, those treated with drugs such as heparin, anticoagulants, or antiplatelet agents, and others with suppressed immune systems were excluded. Eight hundred and forty (840) were assigned to placebo and 850 to drotrecogin (24 μg/kg/h × 96 h). Baseline characteristics were generally comparable except there were more patients in the placebo groups on mechanical ventilation (77.6% vs 73.3%). Drotrecogin, administered no later than 24 hours after meeting study inclusion criteria resulted in an absolute reduction in risk of all-cause 28-day mortality of 6.1% (24.7% vs 30.8%, P = 0.005). Treatment with drotrecogin resulted in lower plasma D-dimer levels, and greater decreases in serum interleukin-6 levels, indicators of antithrombotic and anti-inflammatory activity, respectively. Those who received drotrecogin also appeared to have greater numbers of vasopressor and ventilator-free days.[8,9] The results also suggest that patients with a greater number of organ failures had a greater absolute risk reduction in mortality, although the study was not sufficiently powered to distinguish these potential differences.[9] Protein C levels may not be a predictor of drotrecogin success in this population. Serious bleeding was higher in the drotrecogin group compared to placebo (3.5% vs 2.0%, P = 0.06). Neutralizing antibodies against drotrecogin were not detected.

Drotrecogin is expensive with a wholesale cost of $6800 per patient.

Clinical Implications

It is estimated that about 750,000 cases of severe sepsis occur each year in the United States with about a 30%

mortality.[10] The hospital cost is estimated at $17 billion and more than $22,000 per case. Drotrecogin alfa (activated) is the first agent approved to treat severe sepsis. Balancing the cost and benefit of this agent will be a challenge for decision makers. Based on the study results, 1 life would be saved for about every 16 patients treated with drotrecogin. This translates to about $108,800 per life saved. If the PROWESS entry criteria are generally accepted, the number of treated patients could be substantial. Padkin et al indicated that 28% of all intensive care admissions met the criteria.[11]

The role will ultimately be determined as clinicians gain broader experience. ■

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Ortho Evra—A New Transdermal Birth Control Patch

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

The fda has approved the first hormonal contraceptive skin patch. Ortho-McNeil's Ortho Evra patch is a small (one-and-three-quarter-inch square) patch that delivers ethinyl estradiol and norelgestromin transdermally. The patch is worn for 1 week, then replaced. Similar to oral contraceptives, the patch is used for 3 weeks, then left off for the fourth week each month. Although the patch was developed by Ortho-McNeil, it will be marketed by RW Johnson.

Indications

The norelgestromin/ethinyl estradiol (NGMN/EE) transdermal system is indicated for the prevention of pregnancy.

Dosage

The patch is applied each week for 3 weeks. The fourth week is patch free. Every new patch should be applied on the same day each week. The start day may be during the first 24 hours of the menstrual cycle or on the first Sunday after menstruation begins. If therapy begins after the first day of the menstrual period, a back-up contraception should be used concurrently during the first 7 days of the first treatment cycle. The patch should be applied to clean, dry, intact, healthy skin on the buttock, abdomen, upper outer arm, or upper torso. It should not be applied to the breast. If the patch is partially or completely detached for more than 1 day or for an unknown period, a new cycle should be started immediately. Back-up contraception should be used for the first week of the new cycle. If the patient forgets to change her patch, she should consult the detailed patient labeling for instructions. Patients switching from oral contraceptives should wait until menstruation occurs.[1]

The patch delivers 150 µg of norelgestromin (progestin) and 20 µg of ethinyl estradiol (estrogen) (NGMN/EE) every 24 hours. It is supplied as cartons of 1 cycle (3 patches).

Potential Advantages

The NGMN/EE patch has been reported to have a higher rate of compliance than an oral contraceptive (levonorgestrel 125 µg/ethinyl estradiol 30 µg—Triphasil).[2] The mean percent of patients with perfect compliance, patch vs. oral contraceptive, was 88.2% and 77.7%, respectively. Overall percentage of cycles with perfect compliance was 88.7% and 79.2%, respectively.[2] About 60% of oral contraceptive users in this trial were recent users.

Potential Disadvantages

The NGMN/EE patch may be less effective in women with a body weight greater than 198 lbs. The most common side effect is skin reactions. About 3% of patients withdrew from the clinical trials due to this reaction. Greater increases in total cholesterol (15.8 mg/dL vs 8.1 mg/dL; $P < 0.001$) and triglyceride (9.7 mg/dL vs 0.9 mg/dL; $P = 0.008$) were

observed with the patch compared to an oral contraceptive (levonorgestrel/ethinyl estradiol). An overall higher occurrence of breast discomfort was also observed with the patch, primarily with the first and second cycles.[2] The incidence of the breakthrough bleeding and spotting (but not breakthrough bleeding alone) was higher with the patch in the first 2 cycles only. The incidence of patch becoming detached varied from 2-6%.[1-3] In a clinical trial, about 5% of all patches were replaced for either complete or partial detachment.[2]

Comments

NGMN/EE is the first contraceptive patch to be marketed. The progestin component, norelgestromin, is the primary active (17-deacetylated) metabolite of norgestimate and is responsible for the progestogenic properties of norgestimate.[4] The latter is in Ortho-Cyclen and Ortho-Tri-Cyclen. NGMN/EE patches have been tested in more than 3000 women world wide.[1-3] A recent North American study compared NGMN/EE with levonorgestrel/ethinyl estradiol (Triphasil) on the basis of efficacy (Pearl Index and probability of pregnancy), cycle control, and safety. Subjects were randomized to the patch or oral contraceptive for 6 or 13 cycles. There was no statistical difference in efficacy in terms of overall Pearl Index between NGMN/EE patch and the oral contraceptive (1.24 vs 2.18), method-failure Pearl Index (0.99 vs 1.25), or the cumulative probability of pregnancy. The Pearl Index was defined as the number of pregnancies per 100 person-years of use. Method-failure pregnancy includes those where there was apparent dosing error (ie, compliance). Probability of pregnancy was estimated using the Kaplan-Meier method. In terms of cycle control, breakthrough bleeding and/or spotting were higher for the patch in cycle 1 and 2 only.

The cost of Ortho Evra is currently not available.

Clinical Implications

NGMN/EE provides an alternative to other methods of contraception but should not be used in patients with body weight greater than 198 lbs. Once-weekly administration may improve compliance in some patients. ■

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Inappropriate Drug Use in Older Persons

Source: *Giron MS, et al. J Am Geriatr Soc. 2001;49:277-283.*

As part of an ongoing population study in Sweden, all individuals born in 1912 or earlier living in a certain district were invited to participate in this study, and 1810 enrolled (76% of eligible residents). Women made up 78% of the sample, and 13% resided in institutions. Dementia was established with both the MMSE exam and clinical confirmation when the study began in 1987-1989, with reassessment on all participants every 3 years. Drug data were collected during the follow-up in 1994-1996 through interviews and collection of the actual drug containers.

The mean number of drugs used in the overall sample was 4.6, with a range of 0 to 21. This rose to 4.8 drugs for those aged 90 and older who were not demented, and to 5.8 for that age who were demented. Less than 8% of any of these age groups used no drugs at all, and for institutionalized persons 100% fully used a mean number of 7 drugs.

The most commonly reported drugs used by both demented and nondemented groups were diuretics (39% and 30%), followed by analgesics (27% and 30%). Laxatives were next for demented elderly (28%), but only 13% for nondemented. Hypnotics and sedatives followed in high use for both groups.

Anticholinergic properties were found in 13% of drugs used by demented elderly, most often antipsychotics of low potency, and this group also had the most duplication of more than 1 drug from the same therapeutic/pharmacological class. Duplicate laxative drugs were found in 9% of demented elderly, who also had duplicate anxiolytics to use as needed in 3% of their drugs.

The most common potential drug-drug interactions found were in the use of digoxin with furosemide, where no potassium supplements were used in 69% of demented and 52% of nondemented cases. Another potential problem for 3% of demented elderly was the use of antidepressants and antipsychotics together.

The most common drug-disease interactions involved congestive heart failure, where beta-blockers were used in 12% of nondemented elderly. For patients with peptic ulcer disease, 27% were using systemic glucocorticoids, 18% aspirin, and 9% NSAIDs. For both groups, anticholinergic drugs were commonly used with BPH (14% of nondemented and 29% of demented elderly).

Finally, the average daily drug doses used were com-

pared to maintenance recommendations, and found to be lower in 87% of demented and 75% of nondemented elderly. Only 13% and 18%, respectively, had daily doses exceeding recommendations.

Comment By Mary Elina Ferris, MD

In this population study of older persons with and without dementia, Giron and colleagues found several problems with physician prescribing. Giron et al claim that it is the first published study to evaluate appropriate drug use in this "very old" population, although similar studies have been published for elderly community-dwelling and nursing home residents. Consistent with those previous studies, potentially inappropriate medications were found in double-digit percentages, suggesting poor quality of health care for the elderly.[1,2]

However, a closer look at the potentially inappropriate categories reveals the weakness of the allegations. Who would be surprised that vital antipsychotic medications have anticholinergic effects? Or that demented male patients older than 80 with BPH would still be prescribed such medications to control behavioral problems? Particularly in these frail older ages, the risks and benefits of any therapy must be balanced for the best effect. Futhermore, the use of multiple medications in a single category may indicate a complex problem rather than a deficiency in care.

The information does provide an interesting perspective on what medications patients are actually taking, since they obtained the data from the patients themselves and not from medical records. The number of drugs used was not surprisingly high (perhaps reflecting more about Sweden than the US), and the fact that lower doses were being prescribed reflects well on the geriatric skill of the practitioners, using the adage "start low and go slow" in prescribing for the elderly. The prevalence of potential disease-drug interactions, particularly with ulcers and ASA/NSAIDS, reminds us once again what has been shown in previous studies, that we need to ask our patients about all the multiple drugs they may be taking at home.[3] ■

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Dr. Ferris is Clinical Associate Professor, University of Southern California, Los Angeles, Calif.

Interferon Alfa-2b Treatment of Acute Hepatitis C Leads to Sustained Virologic Response

Source: *Jaeckel E, et al. N Engl J Med. 2001;345:1452-1457.*

In a multi-center study conducted in germany, Jaeckel and colleagues identified 44 patients with acute hepatitis C infection. All patients had elevated alanine aminotransferase levels (885 ± 554 U/L) and hepatitis C virus (HCV) RNA was detectable in blood by PCR. Needlestick injury was the most common source of infection (32%), followed by sexual contact with an infected partner (23%), IV drug abuse (20%), and medical procedures (16%). Sixty-one percent of patients were infected with HCV genotype.[1]

Patients received 5 million units of interferon alfa-2b subcutaneously on a daily basis for 4 weeks, followed by 5 million units 3 times a week for 20 weeks. The primary end point was sustained virologic response, defined as undetectable serum levels of HCV RNA at 24 weeks after the completion of therapy. Forty-three patients completed 24 weeks of therapy. In all patients, serum HCV RNA became undetectable during therapy, at an average time of 3.2 weeks. At 24 weeks after the end of therapy, 43 (98%) still had undectable HCV RNA in serum. Eighty percent of patients had normal transaminase levels at the end of therapy, and all had normal levels at the end of treatment. One patient stopped therapy at 12 weeks due to alopecia and flu-like symptoms. She experienced a flare of hepatitis with recurrent viremia 8 weeks later, both completely resolved. Another patient had relapse of hepatitis and virema following therapy. She was treated with combination interferon alfa-2b and ribavirin therapy with complete biochemical and virologic response. With the exception of the single patient that withdrew, therapy was well tolerated. All patients experienced a modest decrease in leukocyte and platelet counts that was without apparent clinical significance.

Comment by Robert Muder, MD

Chronic hepatitis C infection is a major cause of liver disease, and the most frequent reason for liver

transplantation in the United States. Most acute infections are minimally symptomatic and unrecognized. Although estimates vary, 50-80% of patients will develop chronic infection, and 15-20% will develop clinically significant chronic liver disease.[1] Treatment of chronic infection is unsatisfactory. A 24-week course of interferon alfa leads to sustained virologic response in less than 10% of patients. The combination of interferon alfa and ribavirin given for 28 weeks is more effective, but the sustained virologic response rate is only 41%.[1] Patients infected with HCV genotype 1 have a poorer response than do patients infected with genotype 2 or 3.

Although the study was uncontrolled, the results of the trial conducted by Jaeckel et al are dramatic, with 98% of patients showing complete virologic and biochemical remission 24 weeks after cessation of interferon alfa therapy. The results were the same regardless of viral genotype. There can be little doubt that this outcome is considerably different than the natural history of acute HCV infection. The difficulty of conducting a randomized controlled trial is highlighted by the fact that the study was conducted at 24 centers in Germany with nationwide recruitment of patients. Acute hepatitis C infection is often unrecognized, and a large proportion occurs in users of illicit drugs, so finding appropriate patients to enroll in trials is difficult.

The study has a practical aspect for hospital epidemiologists and hospital employee health services. Hepatitis C is an occupational hazard for health care workers exposed to blood. Unlike hepatitis B, neither a vaccine nor postexposure prophylaxis is available. However, current CDC recommendations call for serologic monitoring of health care workers exposed to bloodborne pathogens as a result of a needlestick incident.[2] In the absence of effective postexposure prophylaxis, the major practical benefit of this follow-up has probably been the ability to document a workman's compensation claim. Based on the current study, I would recommend that employees who seroconvert to HCV after such exposure should have measurement of HCV RNA and transaminase levels. Those with viremia and evidence of hepatitis should be offered treatment with interferon alfa.* What to do with those who show viremia without evidence of hepatitis remains problematic. A period of observation may be a reasonable alternate strategy, with initiation of treatment in the event of biochemical hepatitis or persistent viremia. (***Editor's Note:** Some institutions are using a qualitative HCV RNA test at 2-6 weeks postexposure in order to detect acute infection as early as possible.*) ■

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Dr. Muder is Hospital Epidemiologist, Pittsburgh VA Medical Center, Pittsburgh, Penn.

Effects of Inhaled Glucocorticoids on Bone Density in Premenopausal Women

***Source:** Israel E, et al. N Engl J Med. 2001;345:941-947.*

One hundred nine premenopausal women with the diagnosis of asthma, between 18 and 45 years of age, were cohorted into 3 groups: those not taking inhaled glucocorticoids (n = 28); those taking 4-8 puffs per day of inhaled glucocorticoids (n = 39); and those taking more than 8 puffs per day (n = 42). No clinically relevant differences were seen among the 3 groups in weight, height, calcium intake, FEV1, physical activity, smoking history, oral contraceptive use, bone-density, or biochemical values except for age, history of oral glucocorticoid therapy, and past or current use of topical inhaled glucocorticoids. Among the exclusion criteria were women who had received more than 2 short courses (lasting 2 weeks or less) of oral or parenteral glucocorticoids in the preceding year or any oral or parenteral glucocorticoids in the preceding 3 months.

At baseline, spirometry and bone density of the total hip, trochanter, femoral neck, and lumbar spine were performed with measurement of biochemical markers. Physical activity was assessed by a validated questionnaire. At subsequent visits at 6 months, 1, 2, and 3 years, information on medication use, diet and activities, measured bone density, and biochemical markers were reviewed and updated.

Israel and colleagues demonstrated a negative linear association between the average number of puffs per day of inhaled glucocorticoids and the yearly change in bone density at both the total hip and the trochanter ($P = 0.01$ and $P = 0.005$, respectively).

Each additional daily puff of the inhaled glucocorticoid was associated with a decline in bone density of 0.00044 g per square centimeter per year at both sites, but there was no significant association with the degree of decline at the femoral neck and spine (-0.00005 and -0.00008 g per square centimeter per year per puff, respectively [P = 0.85 and P = 0.68, respectively]). This negative association was present even after adjustment for parental glucocorticoids, topical nasal glucocorticoids, and oral contraceptives. No correlation was found with urinary N-telopeptides, calcium, and cortisol values and serum osteocalcin, calcium, cortisol, and parathyroid hormones.

Comment by David Ost, MD, & Syed Rizvi, MD

Inhaled glucocorticoids have become a key element in the maintenance treatment of bronchial asthma.[1] It is well known that long-term systemic steroids cause osteoporosis,[2] whereas inhaled glucocorticoids have been believed to avoid such side effects. The results of previous prospective and cross-sectional studies of the effects of inhaled glucocorticoids on bone loss have been inconsistent.[3-6] These studies have been limited by small sample size, short duration, and presence of confounding factors such as intermittent use of systemic glucocorticoids, lack of appropriate controls, superimposed menopausal bone loss, and differences among participants in the severity of asthma that might have affected physical activity.

In the present study, Israel et al were able to demonstrate a dose-related negative effect of inhaled glucocorticoids on bone density even among patients who did not receive systemic steroids and who had adequate intake of calcium and vitamin D. Furthermore, urinary and serum biochemical markers did not predict the extent of bone loss. ■

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Dr. Ost is Assistant Professor of Medicine, NYU School of Medicine, Director of Interventional Pulmonology, Division of Pulmonary and Critical Care Medicine, Northshore University Hospital, Manhasset, NY.

CME questions

Testing form inserted in this issue

16. For an elderly person with known peptic ulcer disease, which of the following medications should be used with caution?

a. NSAIDs
b. Glucocorticoids
c. Aspirin
d. All of the above

17. All of the following have been used as "maintenance" treatment of bronchial asthma *except*:

a. inhaled corticosteroids.
b. leukotriene antagonist/inhibitors.
c. cromolyn sodium.
d. short-acting beta agonist.

18. Which of the following is correct with regard to the treatment of acute hepatitis C infection with interferon alpha in the study reported by Jaeckel and colleagues?

a. The sustained response rate was only 10-20%.
b. The sustained response rate was 20-40%.
c. The sustained response rate was 40-80%.
d. The sustained response rate was greater than 90%.

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In order to reveal any potential bias in this publication, and in accordance with the ACCME, we disclose that Dr. Ost is on the speaker's bureau of Merck, Roche, and Boehringer Ingelheim and does research for the American Lung Association. Dr. Muder does research for Ortho-McNeil, Aventis, and Pharmacia & Upjohn. Drs. Chan, Elliott, and Ferris report no financial relationships with companies having ties to this field of study.