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INSIDE

ERT and Ovarian Cancer: The Controversy Continues

By William T. Elliott, MD, FACP

Two recent studies are creating more controversy regarding **estrogen replacement therapy** (ERT). The first from the American Cancer Society looked at the rate of ovarian cancer in more than 200,000 postmenopausal women. Over the 14-year study period, women who used ERT had a significantly higher mortality rate from ovarian cancer (risk ratio, 1.51) than women who never used ERT. The duration of therapy increased the risk, with women on ERT for more than 10 years at the highest risk (risk ratio, 2.20). However, the overall incidence of fatal ovarian cancer was low, with 944 deaths out of 200,000 women over the 14 years, and Rodriguez and colleagues point out that this has to be weighed against any possible benefit from reduced rates of heart disease or osteoporosis associated with ERT (*JAMA*. 2001;285:1460-1465). A second small study refutes earlier data suggesting that ERT may protect against **Alzheimer's disease** (AD). In a review of 59 women with AD and 221 matched women without the disease, no difference was found in the rate of ERT use among cases or controls. Women who used ERT for more than 5 years were no different than women who used it for less than 5 years. The findings suggest that ERT does not confer protection against AD (*Arch Neurol*. 2001;58:435-440).

Industry

The last 12 months have marked a year in which there have been an unprecedented number of drug shortages. Amid drug company mergers, shortages of raw materials, and production problems, there have also been charges of foul play and price gouging. Two of the most critical shortages have involved the **flu vaccine** and the **tetanus vaccine**, both due to production problems. The short-acting narcotic **fentanyl** has also been in short supply as has **succinylcholine**, a **neuromuscular blocker**, and **naloxone**, a narcotic antagonist. These drugs are commonly used in the operating rooms and emergency departments, and their shortages have created near crisis situations in some US hospitals. Some manufacturers are simply discontinuing the production of certain drugs because they are no longer profitable. This is the case with **hyaluronidase**, an eye drop commonly used to disperse anesthetics in eye surgery. Some common antibiotics are also running into supply problems. There are no easy answers for most of these issues, and shortages of many commonly used drugs are expected to continue.

Women's Health

Tamoxifen may be safely discontinued after 5 years in women with operable breast cancer according to data from the Scottish Adjuvant Tamoxifen Trial (SATT). At 15 years after surgery, benefit was still seen from tamoxifen treatment, but the benefit was the same whether women were randomized to continue tamoxifen or take placebo after an initial 5 years of therapy. The SATT study, which started in April 1978, has followed more than 1300 women with breast cancer who were initially treated with surgery or surgery and radiation therapy. This study is in accord with other research that indicates that 5 years of tamoxifen therapy is optimum (*J Natl Cancer Inst.* 2001;93:456-462).

Viral Infections

ViroPharma is announcing success with its antiviral drug **pleconaril** in treating **cold viruses**. Although the data are yet to be published, the company is reporting that the drug is effective against picornaviruses, the family of viruses responsible for about half of the common colds. The drug is reported to reduce the duration of the illness and to reduce viral shedding. The company is hoping that the oral medication, which is taken 3 times a day, will be on the market within a year.

Updated Recommendations

The National Cholesterol Education Program (NCEP) is expected to release updated recommendations by the Adult Treatment Panel this spring. In the 8 years since the last guidelines were published, there has been considerable research into issues such as primary prevention of coronary artery disease (CAD), treatment of **triglycerides**, differing risk factors between men and women, and cumulative risk factors such as **smoking**, **diabetes**, and **hypertension**. The guidelines will include wider screening recommendations and will generally recommend more aggressive therapy, up to and including drug therapy, especially for those with multiple risk factors. The guidelines are also expected to clarify treatment goals, including specific LDL goals. The NCEP guidelines are expected in May.

Coronary Artery Disease

There is much speculation about low HDL as an independent risk factor for **CAD**. A new study indicates that treating low HDL in men who have a history of CAD with gemfibrozil reduces the risk of future coronary events. The data come from the VA High-Density Lipoprotein Intervention Trial of more than 2500 men with a history of **coronary heart disease** and low levels of HDL as well as low LDL. The subjects were randomized to 1200 mg of gemfibrozil a day or placebo. Only increases in HDL were shown to reduce the risk of future events, with an 11% reduction in events for every 5 mg/dL increase in HDL. However, there is also evidence that gemfibrozil reduces inflammatory markers, including C-reactive protein, which may account for some of the benefit (*JAMA.* 2001;1585-1591). ■

QVAR — A Non-CFC Steroid Inhaler

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

A new steroid inhaler for the treatment of asthma has been released in a nonchlorofluorocarbon (CFC) metered dose form. Beclomethasone dipropionate has been reformulated in a nonozone-depleting propellant, hydrofluoroalkane-134a. The new formulation is a solution rather than a suspension, resulting in smaller particle sizes and better airway deposition. The product is manufactured by 3M Riker and comarketed by Johnson and Johnson as QVAR. The product represents the first hydrofluoroalkane (HFA) inhaled corticosteroid and the second HFA product following albuterol-HFA approved in the United States.

Indications

Beclomethasone-HFA (BDP-HFA) is indicated for the maintenance treatment of asthma as prophylatic therapy in patients 12 years of age and older. It is also indicated for asthma patients who require systemic corticosteroid administration where the addition of BDP-HFA may reduce or eliminate the need for systemic corticosteroids.[1]

Dosage

The recommended starting dose for BDP-HFA is 40-80 mcg twice daily in patients on bronchodilators alone. For patients previously on inhaled corticosteroids, the recommended starting dose is 40-160 mcg twice daily. If adequate response has not been achieved after 3-4 weeks, a dose increase should be considered. The maximum dose is 320 mcg twice daily.[1] For stable patients maintained on systemic steroids, a reduction in steroid dose may be considered after 1-2 weeks of therapy with BDP-HFA. Systemic steroid withdrawal should be done slowly and each decriment should not exceed 2.5 mg of pred-

nisone or equivalent.[1]

The manufacturer indicates that QVAR does not need to be used with a spacer.

BDP-HFA is supplied as 40 mcg or 80 mcg in 7.3 g canisters providing 100 actuations.

Potential Advantages

The HFA formulation provides much smaller droplets compared to the CFC formulation. About 55-60% of the actuated dose of BDP in the HFA formulation is deposited in the lungs compared to 4-7% with the BDP in the CFC formulation.[2] In general, CFC and dry powder formulations deposit about 5-30% of the drug in the lungs with the remainder deposited in the oropharynx. About one-half the dose of BDP-HFA is needed for asthma control compared to BDP-CFC.[3,4] BDP-HFA may have a more favorable therapeutic ratio than BDP-HFA as the greatest systemic availability did not appear to be associated with greater adrenal effects at the same dose of BDP-CFC.[5,8] This was based on the affect on 24-hour urinary free cortisol comparing doses of 800 mcg/d of BDP-HFA and BDP-CFC for 14 days.[8] HFA does not contain chlorine, does not deplete ozone, and has a shorter life in the atmosphere than CFCs.[5] BDF-HFA is a solution and, as such, does not have to be shaken before use and provides a consistent delivery of drug throughout the life of the inhaler.

Potential Disadvantages

The most common side effects are headache (25%) and pharyngitis (27%).[1] All inhaled corticosteroids have shown dose-related systemic side effects. These include adrenal suppression, growth suppression in children, increased risk of osteoporosis, development of posterior subcapsular cataracts, and thinning and bruising of the skin.[6] The doses per actuation between QVAR and current beclomethasone products (Vanceril, Beclovent) are similar, 40 or 80 mcg for QVAR and 42-84 mcg for Vanceril and Beclovent. Care must be taken to avoid confusion over dosing which may result in a higher than optimal dose of QVAR.

Comments

QVAR is the reformulation of a commonly used inhaled corticosteroid, beclomethasone. The HFA (1,1,1,2 tetrafluoroethane) formulation is more environmentally friendly and provides a much smaller particle size (1.1 microns vs 3.5 microns) and better lung penetration. BDP-HFA is about twice as potent as BDP-CFC. Patients switched from BDP-CFC to BDP-HFA should begin with one-half the previous dose.[7] Studies comparing QVAR to other inhaled steroids are limited. The average cost per day ranges from about $1 to $2.

For an equivalent dose, the 80 mcg strength is about 60% less costly than the 40 mcg strength ($1.60-3.30). QVAR prices are generally competitive with the other inhaled corticosteroids.

Clinical Implications

CFCs are being phased out as common propellants for aerosols. Alternative propellants include powder inhalers (budesonide) and hydrofluoroalkanes (albuterol HFA). Inhaled steroids continue to be the mainstay anti-inflammatory drugs for the management of mild-to-severe persistent asthma. QVAR provides an environmentally safe, twice-a-day alternative to the other inhaled steroids on the market. ■

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Nexium — A New Proton Pump Inhibitor

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

Astrazeneca is launching its new proton pump inhibitor (PPI) esomeprazole (Nexium). The new drug is coming to market just as AstraZeneca is losing patent protection on its multibillion dollar PPI omeprazole (Prilosec). Esomeprazole, the S-isomer of omeprazole, is touted as being the most potent PPI available.

Indications

Esomeprazole is indicated for the healing of erosive

esophagitis, treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD) and the maintenance of healing of erosive esophagitis. It is also indicated for the eradication of *Helicobacter pylori* in combination with amoxicillin and clarithromycin.[1]

Dosage

The recommended dose for the treatment of erosive esophagitis is 20 or 40 mg once daily for 4-8 weeks. For the treatment of heartburn and other symptoms associated with GERD, the recommended dose is 20 mg once daily for 4-8 weeks. The dose for maintenance of healing of erosive esophagitis is 20 mg once daily. For the eradication of *H pylori* the dose is esomeprazole 40 mg once daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 10 days. Esomeprazole should be taken at least 1 hour before a meal. If the patient has difficulty in swallowing the capsule, the contents may be mixed with a tablespoon of apple sauce. The pellets should not be chewed or crushed.[1]

Potential Advantages

At the recommended doses, esomeprazole appears to be the most potent PPI on the market. It has greater acid suppression than omeprazole, lansoprazole, or pantoprazole.[4] Esomeprazole has greater systemic bioavailability than omeprazole due to a lower first-pass metabolism and nonlinear pharmacokinetics.[3,4] The systemic bioavailability is about 80% higher for esomeprazole 20 mg compared to omeprazole 20 mg and about 5 times greater with esomeprazole 40 mg. This results in greater acid suppression throughout the day. The mean duration for maintaining gastric pH more than 4 for esomeprazole 40 mg, esomeprazole 20 mg, and omeprazole 20 mg is 16.8 hours (95% CI, 15.0-18.4), 12.7 hours (95% CI, 11.0-14.4), and 10.5 hours (95% CI, 8.8-12.2), respectively.

More than 55% of patients maintain intragastric pH more than 4 with esomeprazole 40 mg compared to 24% for esomeprazole 20 mg and 14% for omeprazole 20 mg.[3]

Potential Disadvantages

Food decreases the extent of absorption of esomeprazole by 33-53%. The drug should be taken at least 1 hour before a meal. Esomeprazole may inhibit the metabolism of drugs which are metabolized via cytochrome P450 2C19. A 45% decrease in the clearance of diazepam has been reported.[1] The side effects of esomeprazole appear to be similar to those reported for omeprazole with headache, diarrhea, and abdominal pain being the most common with a frequency of 4-6%.

Comments

Esomeprazole is the S-isomer of omeprazole which is a racemic mixture (S- and R-isomers). They both have the same mechanism of action but differ in their pharmacokinetic and pharmacodynamic properties. Greater acid suppression throughout the day has been reported with esomeprazole compared to other PPIs.[3] The improved potency has resulted in modest improvements in the healing of erosive esophagitis. Four large studies (from 572-1216 subjects/arm) were reported by the manufacturer, 2 reported statistical differences between esomprazole and omeprazole and 2 did not.[1,2] Generally, the efficacy of esomeprazole and omeprazole did not differ dramatically. Healing rates were 64.7-69.5% for omeprazole 20 mg, 68.7-70.5% for esomprazole 20 mg, and 71.5-81.7% for esomeprazole 40 mg at 4 weeks. Healing rates at 8 weeks were 84.2-89.8%, 89.9-90.6%, and 92.2-94.1% for esomeprazole. One published study reported faster time to sustained resolution of symptoms.[2] Median time to sustained resolution for esomeprazole 40 mg, 20 mg, and omeprazole 20 mg were 5, 8, and 9 days, respectively. No real differences were seen in the median time to first symptom resolution, 2 days for each regimen. Esomeprazole is effective for maintaining healed erosive esophagitis.

Healing after 6 months was maintained in about 93% of patients treated with esomeprazole 40 mg or 20 mg compared to 29% with placebo and 57% with esomeprazole 10 mg.[6] Esomeprazole is approved for once daily dosing as part of a triple *H pylori* eradication regimen with amoxicillin and clarithromycin.[1,7] Eradication rates, 84-85%, are similar to the twice daily PPI-based regimens. AstraZeneca is pricing esomeprazole 40 mg and 20 mg similar to that of omeprazole 20 mg.

Clinical Implications

GERD is a common chronic condition affecting about one-third of the population.[5] PPIs are generally regarded as the treatment of choice for severe cases although antireflux surgery is also an option. Esomeprazole appears to be marginally more potent than the available PPIs and may offer some benefit to those who have not adequately responded to existing PPIs. ■

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Treatment of Severe Sepsis—An Advance At Last!

Source: *Bernard GR, et al. N Engl J Med. 2001;344:699-709.*

Bernard and colleagues, in a double-blind, placebo-controlled trial, randomized 1690 patients with severe sepsis at 164 centers in 11 countries to receive adjunctive therapy with either placebo or drotrecogin alfa activated (DRA—Zovant™), a recombinant human activated protein C (aPC). Patients were eligible for randomization if they had known or suspected infection with 3 or more signs of systemic inflammation and sepsis-induced organ dysfunction of no more than 24 hours duration; treatment was initiated within 24 hours of having met inclusion criteria. DRA was given intravenously as a continuous infusion at a dose of 24 mg/kg/h for 96 hours. The infusion was temporarily interrupted 1 hour before percutaneous procedures or major surgery and was resumed, respectively, 1 and 12 hours later. Other therapies, including fluids, antibiotics, vasopressors, etc, were not specified by protocol. The primary efficacy end point was death from any cause by 28 days after the start of the infusion.

Protein C deficiency was detected in 87.6%, plasma d-dimer was present in 99.7%, and IL-6 in 98.5%. At 28 days, the all-cause mortality was 30.8% in the placebo group and 24.7% in the DRA recipients (P = .005). The reduction in relative risk of death was 19.4% (95% CI, 6.6-30.5%). Plasma d-dimer and IL-6 levels were significantly lower through day 7 in DRA recipients.

The overall incidence of serious adverse events was similar in the 2 groups, although serious bleeding occurred in 3.5% of DRA and only 2.0% of placebo recipients (P = .06). Fatal intracranial hemorrhage occurred in 2 DRA recipients during infusion and in 1 placebo recipient 6 days after the end of infusion. Neutralizing antibody against aPC was not detected.

Comment by Stan Deresinski, MD, FACP

This trial, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis study (PROWESS) was terminated on June 28, 2000, prior to completion of the total planned enrollment at the time of a scheduled interim analysis when it became apparent that statistical significance had been reached. Given the repeated failure of similar trials in the treatment of severe sepsis, even some of the investigators were probably surprised to find something that worked.

Severe sepsis is associated with a procoagulant, as well as a generalized inflammatory response.[1,2] The procoagulant state in sepsis may result in the depletion of 1 or more of the 3 primary endogenous inhibitors of coagulation: aPC, antithrombin III, and tissue factor pathway inhibitor. The activation of protein C, which normally occurs in the microcirculation following the binding of thrombin to the endothelial receptor thrombomodulin, is a critical defense mechanism against excess fibrin formation.[3]

Sepsis may cause impairment of the conversion of protein C to the activated state as a result of decreased production of thrombomodulin in response to proinflammatory cytokines. As a consequence, the majority of septic patients have reduced protein C levels and there is an association between increased mortality and the extent of protein C depletion.[4] In patients with meningococcemia, failure of this system is associated with the development of purpura fulminans. In fact, the administration of a protein C concentrate was associated with improved survival, relative to matched historical controls, in patients with severe meningococcemia.[5]

Restoration of balance in the coagulation system is, however, probably not the only reason for the efficacy of DRA: aPC also inhibits monocyte production of IL-1b and TNF-a in response to exposure to lipopolysaccharide.[6] It also inhibits LPS-induced nuclear translocation of NFkB, inhibits neutrophil activation, downregulates the expression of several endothelial cell adhesion molecules, including ICAM-1, E-selectin, and VCAM-1.[7]

Bernard et al have demonstrated the efficacy of aPC infusion in patients with severe sepsis. Now the challenge will be to learn how to optimally use this advance in therapy. ■

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Statins and the Risk of Dementia

Source: *Jick H, et al. Lancet. 2000;356:1627-1631.*

Cognitive impairment in elderly people, also known as senile dementia, is a heterogeneous condition that in most cases has pathological and clinical features consistent with Alzheimer's disease (AD).[1] There is evidence to suggest a relationship between lipids and vascular changes involving the brain in patients with dementia, although the precise mechanism is poorly understood at the present time.[2-5]

Jick and associates from the Framingham Heart Study, Boston University, and the Department of Epidemiology of the Harvard School of Public Health evaluated information obtained from 368 practices which contributed data to the UK-based General Practice Research Database. Patients 50 years of age and older were separated into three groups: group 1 consisted of all individuals with a clinical diagnosis of untreated hyperlipidemia, group 2 included those individuals who received lipid-lowering agents, and group 3 consisted of all cases with a computer-recorded clinical diagnosis of dementia. The study demonstrated that individuals 50 years of age and older who were prescribed statins had a substantially lower risk of developing dementia independent of the presence or absence of untreated hyperlipidemia or the exposure to nonstatin lipid-lowering agents.

Comment by Harold L. Karpman, MD, FACC, FACP

Dementia effects an estimated 10% of the population older than 65 years of age. As many as 90% of the patients diagnosed with either dementia or AD by the database practitioners in the United Kingdom were found on detailed analysis to have progressive dementia.[6] The Jick et al study of this data clearly demonstrated that patients in the United Kingdom who were prescribed statin drugs had a risk of clinically diagnosed dementia that was 30-70% lower than those individuals who do not have hyperlipidemia and were not put on lipid-lowering drug therapy. The statin drugs themselves, therefore, appear to reduce the risk of dementia although one cannot exclude the possibility that some of the characteristics of the statin recipients not measured in this study may be associated with a lowered risk of dementia.

Statins are known to competitively inhibit the synthesis of cholesterol thereby preventing the conversion of 3hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) to mevalonate. They also reduce the formation and entry of LDL cholesterol into the circulation, upgrade LDL receptor activity, lower serum LDL cholesterol and triglycerides, and increase HDL cholesterol.[7] Statins also apparently have beneficial effects on the microvasculature which may be of major importance since some investigators have suggested that cerebral perfusion is decreased in affected areas of the brain in patients with AD. Statins may improve cerebral perfusion both because of specific beneficial effects of these drugs on the cerebral capillary endothelium as well as other properties of the agents. A second question addressed by the study was whether the positive effects of the statin drugs in the treatment of dementia might also be noted when using statin drugs in the treatment for other dementing disorders. Jick et al, therefore, determined the relative risk of dementia in the group diagnosed as "dementia" compared with those diagnosed as "Alzheimer's disease" and found no material difference in drug effect suggesting that there may be a common risk factor for dementia which is positively effected by statin drug therapy.

The base population in the study consisted of 24,480 individuals who were users of lipid-lowering agents, 11,421 patients with a diagnosis of hyperlipidemia who did not receive lipid-lowering agents, and 25,000 patients who did not receive lipid-lowering agents and did not have a recorded diagnosis of hyperlipidemia. Despite the significantly large number of patients in the three examined groups, it is important to recognize that Jick et al's study is a purely observational study, and that its results correlated well with findings of another recently published study on this subject.[8] The positive findings of these two studies suggest that the use of statins may significantly reduce the risk of dementia in the elderly either by delaying its onset or by stabilizing (or even reversing) specific or general age-related changes that result in cognitive impairment. It is therefore critically important that additional well designed, double-blind, placebo-controlled studies of an acceptable size be mounted as soon as possible since most clinicians would almost certainly recommend statin therapy to broad segments of their patient population if these studies demonstrated the unequivocal efficacy of the statins in preventing senile dementia. ■

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Enoxaparin Proves Equivalent to Unfractionated Heparin for Treatment of DVT

Source: *Merli G, et al. Ann Intern Med. 2001;134:191-202.*

Deep vein thrombosis (dvt) remains a major cause of morbidity and mortality. Typically, patients with diagnosed DVT are treated with 5-10 days of unfractionated heparin intravenously, as initial treatment and warfarin is added within the first few days. Recently, low molecular-weight heparins (LMWH) have been introduced and have been used successfully for both prevention and treatment of DVT.[1,2] Randomized trials and meta-analysis have shown subcutaneously administered LMWH to have antithrombotic efficacy equal to [3-6] or greater than[7-9] that of continuously administered unfractionated heparin in the initial treatment of DVT, and equal to that of unfractionated heparin in the treatment of pulmonary embolism (PE).[10,11] However, many of these trials were small, did not biochemically monitor LMWH activity, and used intermediate end points, such as venographic, plethysmographic, or scintigraphic end points rather than clinical end points such as recurrent DVT or PE.

The study conducted by the Enoxaparin Clinical Trial Group (and supported by Aventis) was designed to determine whether enoxaparin administered subcutaneously once or twice per day is as effective as continuously infused unfractionated heparin in the treatment of patients with acute, symptomatic venous thromboembolic disease. Patients with acute DVT (n = 900), including 287 (32%) with pulmonary embolus, from 74 hospitals in 16 countries were randomized to receive initial therapy with dose-adjusted intravenous unfractionated heparin compared with subcutaneous enoxaparin at fixed dosages of 1.0 mg/kg of body weight twice daily or 1.5 mg/kg once daily. Long-term oral anticoagulation (warfarin) was started in all patients within 72 hours of randomization.

Equivalent efficacy was seen in the heparin group and both enoxaparin groups. Recurrent DVTs occurred in 12 of 290 patients receiving unfractionated heparin (4.1%), 13 of 298 patients receiving once daily enoxaparin (4.4%), and nine of 312 patients receiving twice daily enoxaparin (2.9%). Compared with unfractionated heparin, the treatment difference was 0.2% (95% CI, 3.04-3.49%) for once-daily enoxaparin and -1.2% (95% CI, 14.2-1.7%) for twice-daily enoxaparin. Adverse events were comparable in the three groups. Major hemorrhage occurred in six of 290 patients (2.1%) in the unfractionated heparin group, five of 298 patients (1.7%) in the once-daily enoxaparin group, and four of 312 patients (1.3%) in the twice-daily enoxaparin group.

Subgroup analysis on the basis of age, sex, weight, medical history (prior PE, presence of cancer, etc.), and location of DVT did not reveal any significant differences in either efficacy or occurrence of adverse events in any particular subgroup.

Thus, Merli and colleagues concluded that subcutaneous enoxaparin once or twice daily is as effective and safe as dose-adjusted, continuously infused unfractionated heparin in the prevention of recurrent symptomatic venous thromboembolic disease.

Comment by William B. Ershler, MD

The introduction of LMWHs to hospital and community pharmacies has been a major advance in the past decade. Physicians have been quick to use these agents because they offer the advantage of ease of treatment and reduced length of hospital stay (and, thereby, costs). Furthermore, there has been a sense that adverse events were fewer, and the incidence of treatment-associated thrombocytopenia was reduced.[12] Yet, there is also a feeling of uncertainty because laboratory monitoring is not readily available.

Thus, the current study offers reassurance for those of us who have already adopted this approach for the management of acute DVT. Furthermore, it demonstrated that once-daily injection of a larger dose of enoxaparin was equivalent to the twice-daily dose. The rationale for trying the once-daily dose was based upon pharmacokinetic

studies that were specific for this particular LMWH, and should not be applied to other LMWHs, some of which already were shown to be effective at once-daily dosing. With regard to enoxaparin, however, a careful review of the data presented in this paper suggest that for the particularly high-risk patients (eg, those with cancer, prior PE, or obesity), there was a trend, albeit, not significant, that would suggest that twice-daily dosing was more efficacious than the single dosing. Perhaps, in a larger study, these trends would reach a level of significance.

This was a carefully performed, multi-center clinical investigation with outstanding design, cautious interpretation, and a clear presentation of results. Clinical trials designed to establish comparable efficacy with an agent already known to be efficacious in a great majority of patients are complicated, require large sample sizes, and clearly stated, statistical objectives. This report is an excellent example of the way it should be done, and is recommended in that light for those developing skills in clinical trial methodology. ■

Dr. Ershler is Director, Institute for Advanced Studies in Aging, Washington, DC.

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CME questions

Testing form inserted in the July 2001 issue

6. QVAR:
- a. is the first HFA inhaled corticosteroid approved in the United States.
- b. is environmentally safe, it does not deplete ozone.
- c. does not need to be used with a spacer.
- d. provides a consistent delivery of drug throughout the life of the inhaler.
- e. All of the above

7. Which one of the following is correct?
- a. Activated protein C has anti-inflammatory properties as a result, at least in part, of inhibition of the monocyte production of proinflammatory cytokines.
- b. Protein C levels are elevated in sepsis, accounting for the procoagulant state seen in this circumstance.
- c. DRA is a recombinant human antithrombin III molecule.
- d. The incidence of intracranial hemorrhage in patients receiving recombinant human protein C in the PROWESS trial was more than 20%.

8. Patients 50 years of age or older who were prescribed statins:
- a. had a higher risk of developing dementia.
- b. had a lower risk of developing dementia.
- c. always developed dementia.
- d. never developed dementia.

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