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ACE Inhibitors and ARBs—Should They be Used Together?

ABSTRACT & COMMENTARY

Synopsis: *The resulting data demonstrated that losartan improved the peak aerobic capacity and relieved symptoms in patients with congestive heart failure who remained severely symptomatic despite treatment with optimal doses of ACE inhibitors, digoxin, and loop diuretics.*

Source: Hamroff G, et al. *Circulation* 1999;99:990-992; Domanski M, et al. *J Am Coll Cardiol* 1999;33:588-604.

The study of left ventricular dysfunction (solvd) treatment trials[1] and numerous other studies[2,3] have clearly demonstrated that angiotensin-converting enzyme (ACE) inhibitors reduce mortality in patients with symptomatic heart failure. A second SOLVD prevention trial[4] also concluded that ACE inhibitors reduce the combined incidence of death or hospitalization for heart failure in patients with symptomatic left ventricular dysfunction. Angiotensin II receptor blockers (ARBs) have been introduced only relatively recently and, therefore, outcome and efficacy studies have been limited; however, as indicated above, a large volume of data has been produced in studies using standard ACE inhibition therapy in congestive heart failure patients. As a result, most physicians currently use standard ACE inhibitor therapy for the treatment of patients with congestive heart failure whereas ACE II inhibitors have generally been used only in those individuals who have been unable to tolerate standard ACE inhibition therapy.

Marked elevations of angiotensin II, norepinephrine, and aldosterone plasma levels have been demonstrated to be associated with the progression of left ventricular dilatation in some patients with congestive heart failure even if they have been treated with recommended doses of ACE inhibitors, suggesting that long-term ACE inhibition may only partially suppress the activated renin-angiotensin system.[4,5] Hamroff and associates[6] from the Albert Einstein College of Medicine in New York performed a study in which they used an ARB (i.e., losartan) in

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patients with severe congestive heart failure who had been maximally treated with ACE inhibitors in addition to standard therapy. The study was undertaken to determine the effect of losartan vs. placebo on exercise capacity and functional class in patients with congestive heart failure who were severely symptomatic despite treatment with optimal doses of ACE inhibitors, digoxin, and diuretics. Peak oxygen uptake, clinical assessments, and laboratory evaluations were obtained weekly for one month and monthly thereafter. The resulting data demonstrated that losartan improved the peak aerobic capacity and relieved symptoms in patients with congestive heart failure who remained severely symptomatic despite treatment with optimal doses of ACE inhibitors, digoxin, and loop diuretics.

COMMENT BY HAROLD L. KARPMAN, MD

Even though there were only 33 patients in Hamroff et al's study, the results seemed to suggest that angiotensin II blockers significantly improved the clinical status of congestive heart failure patients who were already being treated with recommended doses of ACE inhibitors. This beneficial effect appears to be secondary to the fact that long-term ACE inhibition may suppress the activated renin-angiotensin system only incompletely; therefore, when an angiotensin II inhibitor is added to the therapeutic regimen, ACE suppression becomes complete or nearly complete, thereby improving the patient from a symptomatic point of view.

It is also interesting to note that a recently reported trial[7] from the National Heart, Lung, and Blood Institute demonstrated that ACE inhibitors decrease the risk of death following a recent myocardial infarction (MI) by reducing cardiovascular mortality and that the reduction in sudden cardiac death with the addition of ACE inhibitors was an important component of this survival benefit. It will be interesting to see whether this positive result is even further improved in subsequent clinical trials by the addition of angiotensin II blockers since, if the addition of these agents to ACE blocking agents improves exercise capacity in patients with severe congestive heart failure, it is entirely possible that the other manifestations of symptomatic coronary artery disease (i.e., sudden cardiac death, recurrent MIs, etc.) may be affected similarly in a positive way.

The ACC/AHA guidelines for the management of patients with acute MI concluded that "all trials in which only oral ACE inhibitors were used demonstrated a benefit in mortality." It may be that we will soon be adding ARB to standard ACE inhibitor therapy in all or most patients who have suffered an acute MI or are afflicted with coronary artery disease whether symptomatic or not and/or those who suffer from congestive heart failure of any cause. ❖

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Prediction of the Risk of Bleeding During Anticoagulation Treatment for Venous Thromboembolism

ABSTRACT & COMMENTARY

Synopsis: *Overall, this study emphasizes the importance of concurrent malignancy as a major risk factor for bleeding while on dicumarol.*

Source: Kuijer PM, et al. *Arch Intern Med* 1999;159:457-460.

The use of anticoagulation is increasingly common in clinical practice including atrial fibrillation, prosthetic heart valves, venous thromboembolism (VTE) and cardioembolic cerebrovascular events. The major adverse side effect of concern with anticoagulation is bleeding, which can range from mild to life threatening and varies from 10 to 17 per 100 patient-years for all bleeding complications and from 2 to 5 per 100 patient-years for major bleeding complications. Kuijer and associates attempted to construct a prediction rule based on easily identifiable variables that would be useful in clinical practice.

The study was conducted in two phases. In the first phase, Kuijer et al constructed a bleeding risk prediction score based on a careful literature review. Three variables were chosen: age, sex, and presence of malignancy. These variables were repeatedly associated in previous studies with an increased bleeding risk and are readily obtainable in clinical practice.

The score developed ranged from 0 to 5.1; 1.6 points for age older than 60; 1.3 points for female gender; and 2.2 for the presence of malignancy. The optimal cutoff points for the prediction of all bleeding complications as well as for major bleeding complications was determined using receiver operator curve (ROC) analysis. A cohort of 241 patients receiving anticoagulation for a clinical trial was used to construct the ROC. High-risk patients were defined as those with a score of 3 or more points, intermediate risk as a score of 1-3, and low risk as a score of 0. In the test group, a high-risk score was associated with a 26% incidence of all bleeding complications and a 14% incidence of major bleeding complications. In the test group, the high-risk category accounted for 60% of all bleeding complications and 78% of all major bleeding complications.

The score developed in the test phase was validated in a cohort of 780 patients. Using their bleeding risk score, those patients categorized as "high risk" (score > 3) had an incidence of 17% for all bleeding complications and 7% for major bleeding complications. Patients categorized as low risk (score = 0) had an incidence of 4% for all bleeding complications and 1% for major bleeding complications. Approximately 20% of all patients were categorized as low risk. The high-risk category accounted for 37% of all bleeding complications and 53% of all major bleeding complications.

COMMENT BY DAVID OST, MD

Because of broadening indications for anticoagulation, physicians face the dilemma of whether to initiate dicumarol in patients who have risks for bleeding complications. In such circumstances, the decision involves a careful assessment of risk vs. benefit. While major bleeding complications range from 0% to 15%,[1] reliable data are often lacking. In addition, many studies were done before the current international normalized ratio system replaced the prothrombin time. Independent predictors of bleeding include age older than 65 years, history of stroke, history of gastrointestinal bleeding, atrial fibrillation, and other serious comorbid conditions. Comorbid illnesses found to increase the risk of bleeding include heart disease, renal insufficiency, liver disease, malignancy, and use of NSAIDS and diuretics.[2] Three or more comorbid conditions were found to be an independent risk factor for bleeding in a multicenter study.[3]

The simple score reported in this survey is able to identify patients with approximately a 10% incidence of major bleeding episodes. However, the scoring system devised has several limitations. Malignancy is required for inclusion in the high-risk group. This is evidenced by the fact that high risk is defined as a score greater than 3 while the sum of the other two risk factors is 2.9. Also, this score was developed in patients with VTE and may not necessarily be expandable to other indications.

Overall, this study emphasizes the importance of concurrent malignancy as a major risk factor for bleeding while on dicumarol. (*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.*) ❖

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LMWHs Appear to be as Safe and Effective as Unfractionated Heparin

ABSTRACT & COMMENTARY

Synopsis: *Low molecular weight heparins reduced the mortality rates over 3-6 months of patient follow-up (odds ratio 0.71; P = 0.02).*

Source: Gould MK, et al. *Ann Intern Med* 1999;130:800-809.

Low molecular weight heparins (lmwhs) simplify the treatment of acute deep venous thrombosis because they may be administered subcutaneously once or twice daily, without the need for laboratory monitoring or dose adjustment in most cases. A critical clinical issue is whether this more convenient therapy is as safe and effective as treatment with conventional unfractionated heparin.

Gould and colleagues completed a carefully orchestrated meta-analysis to incorporate the most recent data from clinical trials to resolve discrepancies among previous reviews. Only 11 of 37 studies met inclusion criteria for the three major outcomes considered (mortality rates over 3-6 months, major bleeding complications, and prevention of recurrences).

LMWH reduced the mortality rates over 3-6 months of patient follow-up (odds ratio, 0.71; P = 0.02). Odds ratio favored LMWH over unfractionated heparin for major bleeding complications and for preventing thromboemboli recurrences but the absolute risk reductions were small and not statistically significant.

COMMENT BY RALPH R. HALL, MD, FACP

This is an interesting and reassuring analysis. In the same issue of the *Annals of Internal Medicine*,[1] Gould et al report a cost analysis that demonstrated that although the initial cost of LMWH was higher, this was partially offset by reduced costs for early complications. Additionally, if as few as 8% of the patients could be treated as outpatients, the costs were further reduced and cost savings were significant. The number of patients receiving outpatient treatment with LMWH will easily exceed 8% in most institutions.

In the same issue of the *Annals of Internal Medicine*,[2] Milton C. Weinstein, PhD, the director of the Program on Economic Evaluation of Medical Technology at the Harvard School of Public Health, wrote an editorial on the cost of medical technology that should be read by all physicians interested in this area.

Weinstein states (in referring to the article on LMWH and an additional article,)[3] "The explicit and scientific nature of these studies places an appropriate burden on persons who claim that these technologies are not good value for money and should not be paid for."

Weinstein points out that the reduction in death from 6.7% to 5.1% in the LMWH study is similar to the absolute reduction in death attributed to tissue plasminogen activators compared to streptokinase in the GUSTO trial (from 7.4% to 6.3%).[4] ❖

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Antioxidants for Dementia: The Case for Vitamin E

SPECIAL REPORT

By Barak Gaster, MD

Alzheimer's dementia (ad) is one of the most tragic diseases of advancing age. In the course of my busy, geriatrics-filled practice, I make new diagnoses of AD several times a month. Treatment is never an easy subject, but in the past year it has become more difficult as families arrive carrying magazine advertisements and Internet reports of breakthroughs in the treatment of AD. The increasing popularity of these direct-to-consumer information campaigns puts even more pressure on primary care physicians to be familiar with the latest literature on purported "breakthroughs."

Background

During the past 20 years, vitamin E has been evaluated as a treatment for a wide range of conditions. The studies have shown vitamin E to be everything from probably helpful (secondary prevention of coronary artery disease) to possibly helpful (treating tardive dyskinesia, lower extremity claudication, premenstrual syndrome), to probably not helpful (treating Parkinson's disease and preventing cataracts).[1-6] Only recently has it been tested in AD.

Despite hopes that vitamin E may be the long-awaited breakthrough in the treatment of AD, current evidence suggests that it is likely to have only minimal benefit in delaying disease progression. Its low cost and

excellent safety profile, however, make it a reasonable option for those who wish to take it.

Mechanism of Action

Vitamin E is one of the most powerful antioxidants. It is essential for protecting cell lipid membranes from attack by free radicals, acting as a scavenger of these highly reactive molecules. Although much about the pathophysiology of AD remains unknown, there is mounting evidence that oxidative stress plays an important role in the neuronal death characteristic of AD.[7] Thus, it is postulated that vitamin E may have a neuroprotective effect.

Pharmacokinetics

Vitamin E is a fat-soluble essential vitamin. As a result, the bioavailability of vitamin E is dependent on the absorption of fat. Vitamin E is metabolized primarily in the liver and excreted in the bile. Its half-life is long, varying from 50 to 250 hours depending on its route of administration. Plasma levels remain elevated for days following a large dose. It does not appear to cross the blood-brain barrier easily.[8]

Efficacy Data

Vitamin E intake and serum levels have consistently been associated with a lower incidence and a slower rate of progression of AD in epidemiological studies. In one well-designed study from Austria, low serum levels of vitamin E (alpha-tocopherol) were significantly associated with a decline in cognitive function (P = 0.019), while those of nine other common antioxidants were not.[9]

In the only randomized controlled trial to date, Sano and colleagues randomized 169 patients with AD of moderate severity to either two years of dl-alpha-tocopherol (synthetic vitamin E) 1000 IU bid or to placebo.[10] The four primary end points of the study were death, institutionalization, loss of the ability to perform basic activities of daily living (ADLs), or the development of severe dementia by a standardized clinical dementia rating.

At the end of two years, the only outcome to be statistically different between the two groups was rate of institutionalization (26% in the vitamin E group vs 39% in the placebo group; P = 0.003). There were no significant differences in the rate of death, onset of severe dementia, or loss of ADLs.

The vitamin E group took 71 days longer, on average, to reach one of these primary end points compared to the placebo group (597 days vs 526 days), although this difference did not reach statistical significance (P = 0.077). The deck may have been stacked against vitamin E, however, as the vitamin E group started out with a significantly lower baseline score on the Mini-Mental State Examination despite careful randomization.

When Sano et al adjusted their data for this difference in baseline cognitive function, the difference in time to reach one of the end points was statistically significant (670 days vs 440 days; P = 0.001). Although this type of adjustment adds uncertainty to the study's conclusion, the fact that the unadjusted result missed statistical significance by only a small margin adds some credence to a cautiously positive interpretation of the finding.

Cognitive function as measured by the Alzheimer's Dementia Assessment Scale was a secondary outcome in this study. Oddly enough, patients given vitamin E did not fare better on cognitive testing than those given placebo, in contrast to studies of the other three publicized treatments for dementia. In fact, there was a nonsignificant worsening in cognitive function in the vitamin E group as compared to the placebo group, possibly attributable to that group's poorer function at baseline.

The lack of a significant effect on cognitive function, global dementia severity, and ability to perform ADLs in this study makes the finding of the slower rate of institutionalization somewhat difficult to explain. Some have speculated that this finding may be attributable to a cardioprotective effect of vitamin E, although no significant difference was found in the incidence of major cardiovascular events between the two groups.

This trial also examined the effect of combining vitamin E with selegiline, which is a selective MAO inhibitor. Combination therapy in this case had no advantage over vitamin E monotherapy. Vitamin E has never been tested as therapy for dementia other than the Alzheimer's type or directly compared to a cholinesterase inhibitor such as donepezil.

Adverse Effects

Vitamin E appears to be very safe. In contrast to other fat-soluble vitamins such as vitamin A, which can cause serious hepatotoxicity in high doses, no serious adverse effects have been reliably linked to vitamin E. Rarely, patients may experience mild nausea, diarrhea, or fatigue.[11]

In the randomized trial by Sano et al,[10] the only adverse events that occurred more often in patients taking vitamin E were falls (14% vs 5%) and syncope (7% vs 3%). The mechanism for such events is unclear and may have been related to the difference in rates of institutionalization between the two groups.

Drug Interactions

Vitamin E interacts with components of the clotting cascade and has been shown to potentiate bleeding in patients taking oral anticoagulants. As a result, vitamin E supplementation should be avoided in patients taking oral anticoagulants.[12] Vitamin E does not appear to have antiplatelet action in vitro, so no drug interactions would be expected on this basis.[13]

Formulation

Eight naturally occurring compounds have been shown to have vitamin E activity, including tocopherols

(alpha, beta, gamma, and delta) and tocotrienols. Because these substances are ubiquitous in many foods, dietary deficiency is almost unheard of except in rare inherited conditions. The highest concentrations of vitamin E are found in fruits, vegetables, whole grains (especially wheat germ), seed oils, and vegetable oils.

Of the eight naturally occurring compounds, d-alpha-tocopherol has the most potent antioxidant activity. Synthetic forms of vitamin E are primarily a racemic mixture of d-alpha-tocopherol, designated as dl-alpha-tocopherol. It is this formulation that was used in the clinical trial by Sano et al.[10] Some have questioned whether better results might be attainable using a natural form of vitamin E, containing a full mix of the eight compounds.[14] No data are available to support this hypothesis. Depending on the formulation of vitamin E, there are between 0.6 and 1.4 mg of vitamin E per IU.

Dosage

In the trial by Sano et al, the vitamin E group received 1000 IU bid.[10] This is significantly higher than the doses used in the trial of high-dose vitamin E for coronary disease in which patients received 800 IU or 400 IU daily.[1] Whether a higher dose is needed to treat CNS disease because vitamin E crosses the blood-brain barrier poorly is unknown.[8] Vitamin E is probably better absorbed if taken with food that contains some amount of fat. The RDI for vitamin E is 15 IU for men and 12 IU for women daily.

Conclusion

Given the mixed results of a single randomized trial, it is premature to recommend vitamin E for the treatment of AD. There is, however, consistent indirect evidence that it may be mildly effective, especially in slowing the rate of institutionalization, and there is no evidence that it is harmful. This is in contrast to the antioxidant provitamin beta-carotene, which has been shown to increase the rate of certain cancers in smokers.[15]

Recommendation

Given vitamin E's low cost and safety profile, it is a reasonable treatment option for those who wish to take it to attempt to delay progression of disease. (*Dr. Gaster is an Acting Assistant Professor of Medicine at the University of Washington in Seattle.*) ❖

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Pharmacology Update

Synthetic Conjugated Estrogens, A Tablets (Cenestin—Duramed)

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

In the business world, as in life, be careful what you wish for. Wyeth-Ayerst, the manufacturer of Premarin, learned this last month when the FDA approved a New Drug Application (NDA) for Duramed's conjugated estrogen, A (Cenestin). Wyeth had successfully blocked Duramed's application of an Abbreviated New Drug Application (ANDA)—a request for generic equivalency to Premarin in 1997, when it proved that Duramed's product did not contain all the estrogenic components present in Premarin. Duramed retooled and applied to the FDA as a unique drug, calling its product "conjugated estrogens, A" to distinguish it from conjugated estrogens. Approval was granted in March for short-term use in the treatment of vasomotor symptoms. Duramed's conjugated estrogens A is a mixture of nine synthetic estrogenic substances derived from plant sources, as opposed to Premarin, which is derived from the urine of pregnant mares and contains 10 identified and quantified estrogenic compounds.

Indications

Cenestin is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause.

Dosage

Cenestin is supplied as 0.625 mg and 0.9 mg tablets. The recommended initial dose is 0.625 mg per day and

may be titrated up to 1.25 mg. The lowest dose should be used that would adequately control vasomotor symptoms associated with menopause.

Potential Advantages

Synthetic conjugated estrogens are derived from plant sources—not from pregnant mare's urine. Animal rights groups such as PETA have objected to the treatment of these pregnant mares. There may also be a patient preference for product derived from plants than from animals.

Potential Disadvantages

Cenestin is not identical to Premarin. While Cenestin contains 9 of the 10 known estrogenic substances contained in Premarin, it does not contain delta 8,9-dehydroestrone sulfate and possibly other unidentified estrogenic and progestational agents.[2] It is not certain if Cenestin is pharmacologically "identical" to Premarin. Cenestin is currently approved for short-term treatment of vasomotor symptoms associated with menopause but not for the treatment of osteoporosis. Cenestin is currently only available in two doses, 0.625 mg and 0.9 mg, while Premarin is also available in 0.3 mg- and 1.25 mg-strengths.

Comments

Cenestin is the first synthetic conjugated estrogen approved by the FDA. It has been designated as conjugated estrogens A, and subsequent products will be designated as B, C, D, etc.[3] Its approval was based on a randomized, placebo-controlled multicenter trial in patients with vasomotor symptoms.[1] One hundred twenty women were randomized to receive placebo or Cenestin 0.625 mg daily. The dose was titrated upward (2 × 0.625 mg) or reduced (0.3 mg) as necessary. Efficacy was assessed at four, eight, and 12 weeks. Results have not been published; however, the product labeling stated that a reduction in moderate-severe vasomotor symptoms occurred at all time points.[1] There are no comparative trials with Premarin; therefore, dose equivalence is not known. In the placebo-controlled trial, 77% of patients required two 0.625 mg-tablets to control symptoms. This compares to the recommended dose of Premarin to treat these symptoms.

The wholesale cost for Cenestin 0.625 mg is $0.42 per tab, which is comparable to Premarin $0.42. However, if patients need a 1.25 mg-dose (77% needed that dose), then Premarin is less expensive ($0.59) since there is no 1.25 mg-strength for Cenestin.

Clinical Implications

Cenestin provides an alternative to Premarin as well as other estrogens such as estradiol. Premarin has the lion's share of the market, estimated to be about $2 billion yearly. Wyeth Ayerst has aggressively opposed the approval of Cenestin as a generic equivalent to Premarin, contending that delta 8,9-dehydroestrone sulfate and unidentified components of Premarin contribute to its pharmacologic activity.[1] After much debate, the FDA did conclude that delta 8,9-dehydroestrone sulfate is active and may contribute to the overall effect of Premarin. The magnitude of the effect has not been determined. The contribution of other unidentified components has also not been determined. There are currently no comparative trials between Premarin and Cenestin and none is required by the FDA. Until the components of Premarin have been adequately characterized, the FDA would only consider approving a generic version if it came from the same natural source (i.e., pregnant mare's urine). However, synthetic versions may be approved as new drugs. Cenestin is effective for the short-term treatment of vasomotor symptom, but its long-term effectiveness for indications such as osteoporosis is still uncertain. ❖

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CME Questions

40. The most important risk factor in prediction of bleeding while on dicumarol is:

a. sex.
b. presence of malignancy.
c. hypertension.
d. age.

41. Which of the following statements regarding heparin use is correct?

a. LMWH significantly reduces recurrences of venous thrombosis when compared to unfractionated heparin.
b. LMWH produces more bleeding complications than unfractionated heparin.
c. LMWH is not cost effective when compared to unfractionated heparin.
d. LMWH was associated with less mortality than unfractionated heparin.

42. Which of the following drugs should *not* be taken in combination with vitamin E?

a. Warfarin
b. Phenytoin
c. Cimetidine
d. Erythromycin

43. Which of the following outcomes has been shown to be improved with vitamin E therapy in Alzheimer's patients?

a. Mortality
b. Cognitive function
c. Rate of falls
d. Rate of institutionalization

By Louis Kuritzky, MD

Transcutaneous Nitroglycerine in the Treatment of Erectile Dysfunction

The role of nitric oxide (no) as an important neurotransmitter responsible for dilation of penile arteries and relaxation of sinusoidal chambers of the corpora cavernosa and corpus spongiosum to allow erection is well defined. Nitroglycerin is known to enhance NO availability and leads directly to NO formation. Case reports of beneficial effects of topical nitroglycerin on erectile function have encouraged further evaluation of this modality.

This study evaluated 18 men with erectile dysfunction of a variety of etiologies. This double-blind placebo-controlled trial evaluated the erectile response to trandsdermal application of nitroglycerin by means of a Rigiscan monitor in the laboratory; a home study portion of the trial assessed patient-reported success in achieving a good, moderate, or no effect in response to topical nitroglycerin.

In this study, transdermal nitroglycerin did not demonstrate activity greater than placebo in either the laboratory or the home setting. Additionally, headache, the most frequently reported side effect of nitrates seen in cardiovascular use, was the most commonly reported adverse event in this group, including a female sex partner who also suffered post-coital headache attributed to nitroglycerin.

Gramkow and associates conclude that nitroglycerin transdermally is not superior to placebo for treatment of erectile dysfunction. ❖

Gramkow J, et al. Int J Impotence Research 1999;11:35-39.

Hyponatremia: Evaluating the Correction Factor for Hyperglycemia

In 1949, seldin and tarail reported that elevated glucose resulted in a lower serum sodium concentration, which they attributed to a shift of water to the extracellular space due to the osmotic effect of glucose. At that time, the correction factor of 2.8 was suggested (i.e., it was stated that for every 100 mg/dL increase in blood glucose over the normal level of 100, a drop of 2.8 in sodium would be seen). This factor evolved based upon the assumption that 100 mg/dL of glucose (= 5.6 mmol) would have a similar osmotic behavior as 2.8 meq of sodium (= 5.6 mosm NaCl). Evolution of different theoretic concerns has prompted suggested revision of this correction factor so that reported conversion numbers range from 1.2-2.0.

To evaluate the effect of hyperglycemia on serum sodium concentration, Hillier and colleagues studied six healthy patients by suppressing insulin through somatostatin infusion, coupled with high-dose glucose infusion to achieve a plasma glucose of at least 600 mg/dL in less than one hour's time. Restoration of glucose to normal with insulin infusion followed. Serum sodium and plasma glucose were measured simultaneously every 10 minutes.

The response of serum sodium depression to acute hyperglycemia was essentially immediate; restoration of the serum sodium in response to serum glucose normalization was equally acute. Overall, a 2.4 meq/L sodium change was seen per 100 mg/dL glucose elevation. However, this change was not uniform (e.g., in blood sugars < 400 mg/dL, the conversion factor was 1.6, whereas for sugars > 440, the conversion factor was 4.0). Hillier et al note that the conversion factor of 2.4 is perhaps the more useful tool, since at severe levels of hyperglycemia, in which correction of sodium level is most important, this number is more accurate than the 1.6 conversion factor currently in use. ❖

Hillier TA, et al. Am J Med 1999;106: 399-403.

Occult Vitamin D Deficiency

European studies have shown that up to one-third of women with hip fractures have signs of osteomalacia, which is often caused by vitamin D deficiency. U.S. studies to date have demonstrated less substantial (up to 25%), but still impressive, frequency of osteomalacia with hip fracture. The current study compared the prevalence of low vitamin D levels and high PTH among subjects with acute osteoporotic fractures, compared with patients scheduled for joint replacement surgery without hip fractures (the latter group chosen to represent normal, or even below normal bone mineral density).

Among the 805 women studied, 543 were in the elective joint replacement group and 262 in the acute hip fracture group. Fifty percent of the study group with postmenopausal acute hip fractures had subnormal vitamin D levels, and 36.7% had elevated PTH. The median PTH level of women with osteoporotic fractures was 1.5 times higher than in the control group.

Leboff and associates demonstrate that postmenopausal women with acute hip fracture have a noteworthy incidence of otherwise subclinical vitamin D deficiency, with accompanying PTH elevation. Such deficits are generally remediable with supplementation. ❖

Leboff MS, et al. JAMA 1999; 281:1505-1511.

In Future Issues:

Is Pulse Oximetry Accurate in Sickle Cell Disease?