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Montelukast vs. Beclomethasone for Asthma

ABSTRACT & COMMENTARY

Synopsis: *Both agents provided clinical benefit to patients with chronic asthma that suggests their use as controller medications for this condition.*

Source: Malmstrom K, et al, for the Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999;130:487-495.

Montelukast, a once-daily oral leukotriene, was compared with inhaled beclomethasone, 200 mcg, twice daily over a 12-week treatment period in 895 chronic asthmatic patients using a double-blind, double-dummy, placebo-controlled design. Both agents improved peak expiratory flow rates and quality of life. Both agents also increased the number of asthma-controlled days and decreased nocturnal awakenings and asthma exacerbations compared to placebo. Over the 12-week study, the side effect profile was similar and no different from placebo.

Beclomethasone had a greater mean clinical benefit, as measured by FEV_1, which was 13.1% compared to an FEV_1 of 7.4% with montelukast, and a daytime symptoms score of -0.62 for beclomethasone, compared to -0.41 for montelukast. However, montelukast has a faster onset of action and greater initial effect. Thus, both agents provided clinical benefit to patients with chronic asthma that suggests their use as controller medications for this condition.

COMMENT BY SHELDON L. SPECTOR, MD

Inhaled corticosteroids are the most frequently prescribed controller medications in the treatment of asthma. They are recommended in virtually every asthmatic patient, except the most mild, due to their anti-inflammatory properties and long-term benefit.[1,2]

Although antileukotrienes are also anti-inflammatory, they were recommended in the 1997 NHLBI guidelines only for mild, persistent asthma.[3] Current usage includes more severe patients,[4] so a head-to-head comparison as described in the study by Malmstrom

INSIDE

and associates is welcomed. In fact, a recent study by Nathan and colleagues demonstrated a better effect with more moderate patients using another antileukotriene.[5] Currently, there are no comparison studies between antileukotrienes or of other antileukotrienes with different inhaled cortocosteroids. In the present study, beclomethasone had some clinical advantages; however, montelukast has a faster onset of action and greater initial effect.

Although compliance was good for both groups, the literature supports better compliance with an oral medication and once-daily therapy.[6] Moreover, it is not clear if a subgroup of patients would respond better to antileukotrienes than inhaled corticosteroids. A combination of inhaled corticosteroids with the antileukotriene would also be attractive in view of their different modes of action and the potential ability to reduce high-dose corticosteroid aerosols and thereby decrease the chance for steroid side effects. ❖

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HRT and Risk of Breast Cancer with a Favorable Histology

TRIAL COVERAGE

Synopsis: *Gapstur and colleagues found a positive association between HRT use and incidence of breast cancer only for those with breast cancers deemed favorable. Conversely, the incidence of DCIS and invasive ductal or lobular carcinoma was not related to past or current use, regardless of duration.*

Source: Gapstur SM, et al. *JAMA* 1999;281:2091-2097.

The iowa women's health study is a population-based random sample of postmenopausal women who were aged 55-69 in 1986. A total of 1520 incident breast cancers have occurred in the at-risk cohort of 37,105 women. Gapstur and colleagues used this population sample to determine if past or current hormone replacement theory (HRT) use was a risk factor for the development of breast cancer. The survey instrument was a questionnaire, but the type of HRT used was not elicited. To make this analysis more informative, Gapstur et al asked whether the relationship between postmenopausal hormone use and breast cancer varied by tumor type. Based on standard histologic criteria, the breast cancers were put into one of four categories. Ductal carcinoma in situ (DCIS) accounted for 11.5%, 5.4% were deemed invasive breast cancer with a favorable histology, 76.6% were called infiltrating ductal or lobular carcinoma, and 7% were other. The last group was not

included in the analysis. Age at menarche, age at menopause, and type of menopause were not related to the age-adjusted incidence of any tumor type. A positive association between age at first birth and breast cancer risk was seen for all histological tumor types. Family history of breast cancer increased the risk of DCIS and invasive ductal or lobular carcinoma with an unfavorable prognosis. Overall, Gapstur et al found a positive association between HRT use and incidence of breast cancer only for those with breast cancers deemed favorable. This subgroup accounted for only 5% of the tumors, and the risk was largely confined to current use. Interestingly, in this subset, the risk of breast cancer was less in those who used hormones more than five years than in those who used hormones postmenopausally for less than five years. Conversely, the incidence of DCIS and invasive ductal or lobular carcinoma was not related to past or current use, regardless of duration.

COMMENT BY SARAH L. BERGA, MD

In seeking to determine if postmenopausal hormone use increases the risk of breast cancer, Gapstur et al sought to improve upon the usual and customary design by stratifying breast cancer into histologic types and then considering the effect of HRT use upon these subtypes. Otherwise, the study is a standard epidemiological trial in which a large cohort of women were observed prospectively. I have long felt that it makes little sense to lump all breast cancers together. Certainly, not all breast cancers are the same. One must consider stage, host, histology, or causal molecular and cellular derangements. The logic of subtyping is compelling, but it is not clear which criteria should be used to subtype. For instance, it has been shown that mutations in tumor suppressor genes [p53, BRCA, BRCA 2, ATM (ataxia-telangiectasia, mutated)] or overexpression of oncogenes (such as Her-2-Neu) are causally related to the development of breast cancer. Ideally, one would subtype according to relevant molecular features. Since molecular fingerprinting of breast cancers was not possible, Gapstur et al resorted to the best criteria that could be devised in this setting. It is debatable if the subtypes represent relevant biological groups. If they do not, one can argue that the data must remain aggregated rather than segregated. If the data remain aggregated, then this is a large study showing that current and past HRT use does not increase the risk of breast cancer. If one allows that the subtyping is biologically valid, then the study suggests, as have others like it, that HRT use may promote the development of breast cancers with a favorable prognosis in a small minority of women. Put another way, cancers that develop in women due to HRT have a good prognosis. However, given the tentative nature of the subgroups, the most conservative conclusion to draw from this data set is that HRT use does not promote the development of breast cancer. Most breast cancers occur independently of past or current HRT use. I tell patients that we do know a little about what causes breast cancer, and it does not appear to be estrogen exposure. (*Dr. Berga is Associate Professor, Departments of Obstetrics, Gynecology, Reproductive Sciences, and Psychiatry, University of Pittsburgh.*) ❖

A Cure for the Common Cold?

ABSTRACT & COMMENTARY

Synopsis: *Studies of tremacamra, which competes with the cellular receptor for the virus, used prophylactically in humans with experimental rhinovirus infections showed efficacy in diminishing the incidence and severity of the common cold. While promising, the clinical usefulness of this strategy requires further study.*

Source: Turner RB, et al. *JAMA* 1999;281:1797-1804.

In randomized, double-blind, placebo-controlled trials conducted in humans, experimental rhinovirus type 39 inoculation was tested with preinoculation or postinoculation administration of tremacamra or placebo. Tremcacamra was associated with decreased incidence of clinical colds (44% ± 11% vs 67% ± 9%), improved total symptom scores (9.6 ± 2.9 vs 17.6 ± 2.7), and decreased nasal mucus weight (14.5 ± 9.4 vs 32.9 ± 8.8 g) ($P < 0.001$ for all comparisons). Tremacamra was not associated with any adverse effects or evidence of absorption through the nasal mucosa and did not interfere with development of neutralizing antibody to rhinovirus.

COMMENT BY HAL B. JENSON, MD, FAAP

We continue to search for the cure for the most common human infection, the common cold. Strategies that have been attempted include antivirals, which show some promise when used prophylactically but not once symptoms develop, and symptomatic treatments such as antihistamines, decongestants, and anti-inflammatory

agents, all of which have limited efficacy and on only some but not all of the typical cold symptoms.

Of the 101 types of rhinoviruses, which account for 70% of upper respiratory tract infections, 90 types use intercellular adhesion molecule 1 (ICAM-1) as the cellular receptor for cell entry. This is the basis for this particular strategy to attempt to prevent or treat rhinovirus infections by intranasal administration of the soluble extracellular portion of the ICAM-1 molecule to compete with virion binding.

This study included both preinoculation and postinoculation administration, but both were actually prophylactic since clinical symptoms had not yet appeared. Thus, this strategy is not curative, but rather preventive. Tremacamra has been studied with one rhinovirus type 39, which appears to be particularly susceptible to the effects of tremacamra. The effects on the other rhinoviruses remain to be proved. Soluble tremacamra is cleared rapidly from the nasal mucosa. In these studies, two formulations were used—one solution and the other a mannitol-based powder with carboxymethylcellulose to retard clearance of the drug from the nasal cavity. Unfortunately, the carboxymethylcellulose was associated with nasal irritation. It is enticing that a strategy such as this actually shows efficacy, but we remain a long way from being able to use this clinically. (*Dr. Jenson is Chief, Pediatric Infectious Diseases, University of Texas Health Science Center, San Antonio, TX.*) ❖

Does Aspirin Attenuate the Beneficial Effects of ACE Inhibitors?

ABSTRACT & COMMENTARY

Synopsis: *In coronary artery disease subjects treated with both an ACE inhibitor and aspirin, survival is enhanced, and the beneficial association is even more prominent in subjects with heart failure.*

Source: Leor J, et al. *J Am Coll Cardiol* 1999;33:1920-1925.

For the past several years, there has been a contradiction regarding a possible adverse reaction between the use of aspirin and ACE inhibitors regarding major clinical end points. Several important clinical trials, including SOLVD, CONSENSUS II, GUSTO-I, and GISSI-3, all demonstrated in retrospective analyses a reduction of benefits when aspirin was used with ACE inhibitors. Furthermore, several hemodynamic studies in patients with congestive heart failure demonstrate attenuation of the beneficial effects of ACE inhibitors on a variety of renal and cardiac parameters; on the other hand, other small studies have not shown a negative interaction. Investigators from the Benzafibrate Infarction Prevention (BIP) study performed a retrospective analysis on a large BIP registry cohort. A total of 1196 subjects were identified who were treated with ACE inhibitors and were followed for at least five years. These patients represented 11% of the entire cohort registry. ACE inhibitors and aspirin were given to 618 subjects, whereas 579 received only an ACE inhibitor. A subgroup analysis was also done on 464 patients with clinical congestive heart failure, NYHA Class II or greater. Total and cardiovascular mortality as well as adjusted survival for age, gender, and a variety of other clinical conditions were calculated. The results indicated a substantial difference in total and cardiovascular mortality for the entire cohort, as well as for approximately 50% of individuals with heart failure. Thus, the five-year mortality for those on combination therapy was 19% vs. 27% for the patients on ACE inhibitors alone ($P = 0.002$). Cardiovascular mortality was 12% vs. 18%, respectively. These differences remained robust after adjustment for a variety of parameters. In the heart failure cohort, similar findings were noted, with 35% total mortality in the nonaspirin users compared to 24% in the combination therapy cohort. Cardiovascular mortality was 17% in aspirin users vs. 26% in nonaspirin users. Again, there was a significant risk reduction after adjustment for age, gender, diabetes, and various medications. Leor and colleagues conclude that in coronary artery disease subjects treated with both an ACE inhibitor and aspirin, survival is enhanced and the beneficial association is even more prominent in subjects with heart failure.

Leor et al emphasize the classic pharmacophysiologic rationale for a potential negative interaction, which is impairment of bradykinin generation due to use of aspirin (or nonsteroidals), resulting in a decrease in production of vasodilator prostaglandins and nitric oxide. Several studies from Europe have demonstrated inhibition of the hemodynamic effects of ACE inhibitors when aspirin is co-administered. Furthermore, a report suggests that enalapril may reduce the formation of thromboxane A2, resulting in an independent antithrombotic effect of ACE inhibitors that might attenuate the beneficial effects of aspirin. On the other hand, a recent study suggests that aspirin may improve endothelial function.

Thus, there are a number of conflicting mechanisms that could explain both a positive and negative interaction of these two agents.

The BIP investigators recognize that major clinical trials do not support a favorable interaction or association between ACE inhibitors and aspirin. They point out the limitations of their study being a post hoc analysis, with the therapeutic designation based on a single report form. They believe that possible crossover between the groups regarding aspirin use might underestimate the benefits associated with combination therapy. They call for further research in this area and suggest that low-dose aspirin (most patients received less than 250 mg/d) are safe and can be given with an ACE inhibitor in patients with heart failure and coronary artery disease (CAD).

COMMENT BY JONATHAN ABRAMS, MD

This controversy is important. Because all currently support the use of aspirin in patients with CAD, it is inappropriate to preclude this compound. It is known that the majority of patients with heart failure have CAD as the primary etiology. Thus, the potential downside of a negative interaction between two commonly used agents is of widespread interest. Adequate data are clearly not available to resolve this question. The BIP registry experience data are reassuring; however, it is unclear how and when the diagnosis of heart failure was made, how long the patients were treated with an ACE inhibitor and aspirin or ACE inhibitor alone, or why an ACE inhibitor was chosen. The indications for ACE inhibitors are increasing beyond patients with abnormal ventricular systolic function. The unreported results of the HOPE Trial indicate that an ACE inhibitor may improve survival in high-risk subjects who do not have overt CAD. Other data are concordant with a beneficial effect of ACE inhibitors in postinfarction patients regarding recurrent myocardial infarction and unstable angina.

Given the absence of prospective data, the differences in patient populations, and drug use among the various studies, it seems prudent not to withhold aspirin from patients with CAD with or without congestive heart failure who are taking an ACE inhibitor. The data from BIP do not prove that there is no negative interaction, but they are inconsistent with an adverse association. Whether individuals treated with ACE inhibitors should be given a lower dose of aspirin, as suggested by the BIP investigators, is unresolved but seems like a harmless and prudent strategy. (*Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.*) ❖

Lowering LDL Cholesterol in Patients with Severe Coronary Disease

ABSTRACTS & COMMENTARY

Synopsis: *Statins should be given to all hyperlipidemic patients early during acute ischemic syndromes and physicians should not withhold statin therapy in women or the elderly.*

Sources: Dupuis J, et al. *Circulation* 1999;99:3227-3233; Waters D. *Circulation* 1999;99:3215-3217; Campeau L, et al. *Circulation* 1999;99:3241-3247.

Two recent studies support the use of a statin in patients with severe coronary artery disease. The Montreal Heart Institute reported the RECIFE Trial, which demonstrated in a small placebo-controlled cohort of acute myocardial infarction or unstable angina patients with elevated cholesterol, that six weeks of pravastatin therapy (30 mg/d) improved endothelial function, as assessed by serial brachial artery ultrasound flow-mediated dilatation (FMD). Total and LDL baseline cholesterol levels were similar in both groups; cholesterol decreased with pravastatin, but not placebo. FMD, initially comparable between the two groups, was unchanged at six weeks with placebo, but increased by approximately 40% in the pravastatin cohort. Clinical events were not reported. Thrombostatic measurements of endothelial and other platelet products were assessed. Platelet activation and an enhanced thrombogenic state was observed in both groups at baseline, improving almost to normal by six weeks, with no difference between pravastatin and placebo. Dupuis and colleagues conclude that a statin should be given to all patients early during acute ischemic syndromes, such as unstable angina or myocardial infarction, if baseline total or LDL cholesterol are elevated. Blood lipids were drawn on admission; baseline total cholesterol was 243 mg/dL and LDL 160 mg/dL. Dupuis et al suggest that the rapid improvement of endothelial function at six weeks should result in important clinical benefits, short and long term, and state that delays in initiating statin therapy in hyperlipidemic patients admitted to a coronary care unit are not justified. They acknowledge that it remains unclear as to whether improvement in FMD/endothelial function can be interpreted as a surrogate for subsequent clinical benefits, as have been

shown by large secondary prevention trials in chronic CAD patients.

An updated report from the post-CABG trial confirms that aggressive LDL cholesterol lowering is equally beneficial in the elderly, women, and individuals with a variety of risk factors, including low HDL and high triglycerides, smoking, and diabetes. The improvements in angiographic status of the bypass grafts were comparable in all patients who received aggressive LDL lowering, regardless of baseline CAD risk profile (individuals received 80 mg of lovastatin for 4-5 years). Conversely, in the moderate LDL cholesterol lowering group (2½-5.5 mg of lovastatin per day), baseline CAD risk factors predicted a more adverse angiographic outcome. In the high-dose lovastatin cohort, the statin resulted in LDL levels of less than 93-97 mg/dL, which completely eliminated the adverse graft and outcomes associated with multiple CAD risk factors. Dupuis et al conclude that physicians should not withhold statin therapy in women or the elderly. They suggest that an isolated elevation of LDL cholesterol in the absence of other risk factors may not impart as much hazard as a less elevated cholesterol associated with multiple risk factors, and that major benefits will accrue to those individuals in the latter category with aggressive LDL lowering. A target LDL cholesterol of less than 100 should be sought for all post-CABG patients, regardless of age or sex.

COMMENT BY JONATHAN ABRAMS, MD

These two studies enhance the database supporting aggressive lowering of LDL cholesterol. While neither provides clinical end point data (because of small sample size), the endothelial function improvement and reduction in angiographic graft progression with statins should ultimately be beneficial in these patients with CAD by decreasing morbidity and mortality. In an accompanianing editorial, Waters also recommends that physicians should not delay initiating lipid-lowering therapy in patients who are admitted with an acute coronary syndrome. He emphasizes abnormal platelet-thrombogenic factors improvement related to the benefits of LDL cholesterol lowering; in spite of the absence of clinical trial data in unstable angina or recent infarction patients, 'starting cholesterol lowering therapy at the time of an acute coronary syndrome can now be justified, but only on the basis of the clear, long-term benefit documented in stable coronary patients.' Thus, a statin should be considered as part of early discharge therapy for virtually all patients admitted for acute ischemic syndromes unless the baseline lipid levels are documented to be low normal, with LDL cholesterol close to 100 mg/dL on the initial blood draw. ❖

Pharmacology Update

Lidocaine Patch 5% (Lidoderm—Endo Pharmaceuticals)

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

Recently, the fda approved endo pharmaceutical's Lidoderm, the first product ever approved for the relief of pain associated with postherpetic neuralgia (PHN). The product consists of lidocaine, formulated as an adhesive patch for local anesthetic activity. When applied to the skin, the topical lidocaine causes local analgesia, relieving the symptoms of PHN, a complication of herpes zoster or shingles, and one of the most difficult clinical entities to treat. Lidoderm is manufactured by Teikodu Seiyaku Co. in Japan and marketed by Endo Pharmaceuticals.

Indications

Lidocaine patch is indicated for the relief of pain associated with PHN.

Dosage

Lidocaine patch should be applied to intact skin covering the most painful area. Up to three patches may be applied, but only for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes. Application on broken or inflamed skin is not recommended.[1]

Potential Advantages

Lidocaine patch provides a nonsystemic, easy-to-use formulation to reduce the pain intensity of PHN. Lidocaine patch has been reported to show statistical evidence of efficacy over placebo patch in reducing pain intensity from four to 12 hours of application.[2] The patch may also provide some protection from mechanical stimulation, such as clothing or inadvertent touching. While there was some evidence that the patch reduced allodynia, this end point was not an efficacy variable in the study protocol and the results are considered exploratory by the FDA.

Potential Disadvantages

Application of more than three patches (420 cm^2) and duration greater than 12 hours should be avoided since the amount of lidocaine absorbed systemically, and the potential for systemic side effects, is dependent on the surface area covered and the duration of skin contact. Local cutaneous reactions have been reported with the patch, including erythema, edema, or locus of abnormal sensations. These reactions are generally mild and transient.

Comments

It appears that lidocaine patch was approved based on very limited data. The active patch was compared to a vehicle patch and no treatment in a single-dose trial involving 35 subjects. These subjects were elderly (mean age, 75 years) and had established PHN affecting the torso or extremities.[2] Patients were permitted to use oral medication commonly used in the treatment of PHN, including analgesic as needed ,[1] but they were not allowed to start new oral medications. Only constant pain was evaluated—not pain induced by sensory stimuli (dysesthesia). Pain relief was modest, as 40% of patients reported slight to moderate pain relief, 28.5% slight or no relief, 20% had moderate to lots of relief, 8.6% had complete relief, and 2.9% reported worst or no relief. This also corresponded to about a 12% decrease in the least-square mean pain intensity based on a visual analog scale. Even with a large placebo effect with the vehicle patch (vs no treatment), there was a statistically significant difference in favor of lidocaine patch from four to 12 hours after application. Subjects were able to peel off the patches with only minor and transient increase in pain. It is difficult to assess the efficacy of the patch alone as the study protocol permitted concurrent use of oral analgesics.

Lidocaine patch is expected to be available in mid-September. Price information was not available at the time of this writing.

Clinical Implications

The incidence of herpes zoster is estimated to be 600,000-1 million cases per year. It is caused by the same virus that causes childhood chickenpox, varicella-zoster. PHN is one of the major complications of herpes zoster (shingles), affecting up to 200,000 Americans. This condition is particularly problematic for the elderly. At the age of 60 years, there is about a 50% chance of significant pain persisting one month or longer after the onset of herpes zoster skin lesions.[4] This compares to 10% for the population as a whole. Pain is often severe in areas where the blisters occurred. The area is also highly sensitive to touch, heat, and cold. Prompt treatment of herpes zoster with antiviral drugs such as famciclovir may decrease the duration of PHN.[3] PHN has traditionally been treated with analgesics (narcotic and non-narcotic), antidepressants, anticonvulsants (e.g., gabapentin), capsaicin, and transcutaneous electrical stimulation. The efficacy of lidocaine patch, while modest, does provide another option for the management of a difficult clinical entity. ❖

References

1. Lidoderm Product Information. Endo Laboratories. March 1999.
2. Rowbotham MC, et al. *Pain* 1996;65(1):39-44.
3. CDC. http:/www.cdc.gov/ncidod/srp/varicella.htm
4. Watson CPN. *Neurology* 1995;45(suppl 8):S58-S60.

CME Questions

13. Which of the following is *not* a likely risk factor for the development of breast cancer?

a. Mutations in the tumor suppressor gene p53
b. Testing positive for the mutations BRCA1 and BRCA2
c. High expression of the oncogene Her-2-Neu
d. Estrogen use for more than five years
e. Mother who died of breast cancer

14. The combination of aspirin and ACE inhibitor:

a. results in inhibition of the ACE inhibitor.
b. is completely safe.
c. is particularly beneficial in CAD patients with heart failure.
d. is contraindicated.

15. LDL cholesterol lowering with a statin has been shown to:

a. increase flow-mediated vasodilation.
b. reduce the thrombogenic state.
c. improve the angiographic appearance of coronary bypass grafts.
d. a and c

16. Tremacamra, a soluble adhesion intercellular molecule:

a. has been shown to be effective in infections caused by a majority of the 101 rhinoviruses that produce upper respiratory disease in humans.
b. appears to be systemically absorbed through the cells of the respiratory epithelium.
c. appears to act prophylactically against cold symptoms when administered either experimentally pre- or postinoculation of RSV type 39.
d. appears to interfere with the immune response to RSV infection.

17. Which is *not* true about the lidocaine patch (Lidoderm)?

a. It can be applied on top of the zoster vesicles.
b. It should be used only for 12 out of 24 hours.
c. It may be cut to size.
d. There are no systemic effects of the patch.

By Louis Kuritzky, MD

Chronic Hyponatremic Encephalopathy

Most chronic hyponatremia occurs in postmenopausal women, either as a result of thiazide treatment or as a syndrome of inappropriate secretion of antidiuretic hormone. The best therapy for women with hyponatremia is controversial, with some sources suggesting intravenous sodium chloride treatment, and others suggesting fluid restriction. This study evaluated 53 consecutive postmenopausal women with symptomatic chronic hyponatremia, defined as a serum sodium less than 130 mmol/L accompanied by CNS manifestations.

Patients were divided into three groups. In group I, treatment consisted of IV saline prior to the onset of respiratory insufficiency; group two received IV saline after the onset of respiratory insufficient, and group 3 received only fluid restriction.

At 24 hours, the mean plasma sodium in the IV NACL groups (= 125) was substantially greater than that of fluid restriction recipients (= 112). Group 1 required a mean time to correction of 35 hours, and group 2 of 41 hours; but in group 3 (fluid restriction), 10 patients died within the first day. The mean cerebral performance category, a 5-point scale ranging from normal function or only slight disability to persistent vegetative state and death, showed clear benefits of early IV saline: the average cerebral performance category score was 1 for early IV saline, 3.0 for IV saline after onset of respiratory insufficiency, and 4.6 for fluid restriction. No patient who received early IV saline suffered brain damage after up to one year of follow-up, in contrast to patients who received delayed IV saline or fluid restriction. Ayuis and associates conclude that early administration of IV saline is preferred treatment for symptomatic chronic hyponatremia in postmenopausal women, and includes substantial preservation of life and cerebral function. ❖

Ayuis JC, Arieff AA. JAMA 1999;281: 2299-2304.

Incidental Findings on Brain MRI

In a variety of investigational protocols used at the NIH, MRI databases from normal, healthy individuals are required for comparison. This report analyzed brain MRI scans from 1000 healthy volunteers during the May 1996—June 1997 time period. Findings were categorized as: 1) no referral needed or commonly seen in asymptomatic persons (e.g., sinusitis); 2) nonurgent referral needed; 3) urgent referral needed (within weeks); and 4) immediate referral required (e.g., subdural hematoma).

Eighty-two percent of brain MRIs were normal. No finding among these studies required immediate referral. Indeed, more than 90% of the abnormalities found were category 1, with only about 10% requiring any referral and about 7% requiring urgent referral.

Findings included within the routine referral category included (partial listing) old lacunar infarct, pineal cyst, and empty sella; In the urgent category were seen arachnoid cyst, cavernous angioma, astrocytoma, and suspected aneurysm. More than 13% of the study participants manifest sinusitis. Katzman and colleagues note the discovery of several unsuspected CNS neoplasms in persons who, even after repeat thorough scrutiny manifest no related symptoms, may herald additional diagnostic yield and opportunity for early intervention as MRI studies are more widely used. ❖

Katzman GL, et al. JAMA 1999;282: 36-39.

Systemic Glucocorticoids on Exacerbations of COPD

Steroid therapy is commonly administered to patients with COPD at times of exacerbation, especially when exacerbation is sufficient to warrant hospitalization. Despite this practice being routinely applied, there is scant literature to support its efficacy either on immediate or long-term clinical end points. The current study (n = 271) evaluated the difference between treatment of COPD exacerbations requiring hospitalization with and without steroids. Outcomes assessed included first treatment failure, defined as death from any cause, need for intubation or mechanical ventilation, need for readmission due to COPD, or requirement for greater levels of pharmacologic therapy (e.g., adding theophylline, high-dose inhaled glucocorticoids, adding open-label systemic steroids). Also evaluated were changes in FEV-1, length of hospital stay, and death from any cause over a six-month follow-up period.

At admission, steroid was administered as IV methylprednisolone 125 mg q6h × 72 hours, followed by either a two-week or an eight-week progressively tapering course of once-daily prednisone, beginning with 60 mg/d.

Steroids significantly reduced the rate of first failure in the first 90 days of the study. Length of hospital stay was significantly longer in the placebo group, and FEV_1 improved more quickly in glucocorticoid recipients. Niewoehner and associates conclude that systemic steroids reduce treatment failure in the 90 days after an exacerbation, and that a two-week regimen is as effective as an eight-week regimen. ❖

Niewoehner DE, et al. N Engl J Med 1999;340:1941-1947.

In Future Issues:

Cost-Utility of Three Approaches to the Diagnosis of Sleep Apnea: Polysomnography, Home Testing, and Empirical Therapy