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INSIDE

The Changing Face of Bacterial Meningitis

ABSTRACT & COMMENTARY

Synopsis: *The mortality associated with bacterial meningitis remains high, and the strongest risk factors for an unfavorable outcome are those that are indicative of systemic compromise, a low level of consciousness, and infection with* S. pneumoniae.

Source: van de Beek D, et al. Clinical Features and Prognostic Factors in Adults With Bacterial Meningitis. *N Engl J Med*. 2004;351:1849-1859.

THE PRESENT STUDY WAS A NATIONWIDE EXAMINATION OF ALL patients in the Netherlands from October of 1998 until April 2002 with community-acquired acute bacterial meningitis. This was confirmed by cerebrospinal fluid cultures. All patients were evaluated neurologically on admission and at discharge. van de Beek and colleagues determined predictors of an unfavorable outcome. They evaluated 696 cases of community-acquired bacterial meningitis. The most common pathogens were *Streptococcus pneumoniae* with 51% of the episodes, and *Neisseria meningitis* with 37%. Interestingly, the classic triad of fever, neck stiffness, and a change in mental status was only found in 44% of the patients. Ninety-five percent, however, had at least 2 of the 4 symptoms of headache, fever, neck stiffness, and altered mental status. At the time of admission, 14% of the patients were comatose and 33% had focal neurologic abnormalities. The overall mortality rate was 21%. The mortality rate was higher in patients with pneumococcal meningitis than in those with meningococcal meningitis. This was a mortality of 30% in the former and 7% in the latter. An unfavorable outcome, defined as a Glasgow Outcome Scale of 1-4. occurred at 34% of the cases at discharge. Risk factors for an unfavorable outcome were: advantaged stage, the presence of otitis or sinusitis, absence of rash, and a low score on Glasgow Coma Scale on admission. Other risk factors were tachycardia, positive blood culture, elevated erythrocyte sedimentation rate, thrombocytopenia, and a low cerebrospinal fluid white-cell count.

COMMENTARY

These findings show that the classic findings of meningitis seem to be less frequent than previously assumed. The prevalence of the classic triad of fever, neck stiffness, and altered mental status was found in only 44% of adults with community-acquired bacterial meningitis. Nevertheless, a high percentage had 2 out of the 4 signs of fever, headache, neck stiffness,

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and altered mental status. In addition, a high percentage of patients were admitted with focal neurologic deficits (33%). Overall, these findings suggest that one has to maintain a very high index of suspicion for bacterial meningitis. A lumbar puncture is mandatory in any suspected case of what is potentially a curable condition. — **M. FLINT BEAL**

Carotid Artery Plaque: Symptoms and Percent Stenosis Are Only Part of the Story

ABSTRACT & COMMENTARY

Synopsis: *These results demonstrate a major role of carotid thrombosis and inflammation in ischemic stroke in patients affected by carotid atherosclerotic disease.*

Source: Spagnoli LG, et al. Extracranial Thrombotically Active Carotid Plaque as a Risk Factor For Ischemic Stroke. *JAMA.* 2004;292:1845.

PATIENT SUITABILITY FOR CAROTID ARTERY REVASCULARIZATION, either endarterectomy (CEA) or stenting, is determined by 2 factors: the percent stenosis and the presence or absence of symptoms. In severe (> 70%) disease, there may be significant flow limitation on a mechanical basis. This, however, is thought to be a minor contributor to stroke, since most patients can compensate with an intact Circle of Willis. Rather, it is believed that thrombi forming at the site of carotid stenosis, propagate distally to the brain, producing TIA or stroke, or to the ophthalmic circulation, producing amaurosis fugax. Some carotid lesions are prone to produce stroke as a result of thrombosis, while others will remain asymptomatic, potentially for long periods of time. The pathological analyses of carotid plaque morphology presented here, provide elegant clinicopathological correlation for this hypothesis.

In a collaborative effort between the Mayo Clinic and the University of Rome, pathology from carotid plaques obtained at the time of CEA was studied. A total of 269 plaques were analyzed; 96 from patients with major ipsilateral stroke, 91 from patients with TIA, and 82 from asymptomatic patients. Stroke and TIA cases were carefully chosen to reflect true symptomatic carotid disease, with exclusion of patients having probable cardiac embolic sources, or patients with distal atherosclerotic disease of > 50% severity.

A thrombotically active plaque (TAP) was observed in 71/96 stroke patients (74%), compared with 32/91 TIA patients (35%, P <0.001), and 12/82 asymptomatic patients (15%, P <0.001). All 32 patients with stroke within the past 2 months had TAP, while TAP was still present in the majority of patients (54%) who had strokes as remotely as 13 to 24 months prior to CEA. Plaque morphology, in association with thrombosis, was defined as either plaque rupture or erosion. In cases of rupture, there was complete disruption of the fibrous cap over an underlying lipid pool. Erosion was defined as plaque de-endothelialization, but not direct contact with the lipid pool. The vast majority of stroke patients (90%) had plaque rupture, while erosion was a more common finding in TIA (present in 11/32 plaques with TAP).

Among stroke patients, ruptured plaques were more frequently and densely affected by inflammation, compared with both TIA and asymptomatic patients. These plaques contained monocytes, macrophages, and T-lymphocytes, and showed a high expression of IL-6, an inflammatory marker.

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COMMENTARY

These data support the fact that not all carotid stenoses are created equal, and that severity of lumen stenosis is not the sole determinant of stroke risk. The challenge is to discover methods short of direct pathology from CEA to non-invasively detect these changes. While carotid duplex ultrasonography may identify soft vs hard plaque and occasionally identify thrombus, other methods such as high resolution CT scanning may be more useful and less user dependent in defining this anatomy. Screening for inflammatory markers, such as cytokines or C-reactive protein, may also provide clues to why patients have a more aggressive type of atherosclerotic biology.

The clinical implications of these data are myriad. For patients with a recent stroke, understanding of plaque morphology would be helpful to determine the optimal timing for CEA. While revascularization is typically delayed by weeks to months to allow the stroke to heal and minimize risk of reperfusion bleeding, if a large burden of active clot were identified, more urgent intervention could be pursued. Plaque morphology might also have important implications in choosing between CEA and carotid artery stenting. Perhaps most importantly, plaque morphology could be crucial in choosing optimal asymptomatic patients for intervention. Given its marginal benefit, CEA would be much more appropriate for patients having an aggressive, as opposed to a benign, natural history. — **ALAN Z. SEGAL**

Atherothrombosis and Atrial Fibrillation: Mixing Treatments to Match Pathophysiology

ABSTRACTS & COMMENTARY

Synopsis: *Current clinical trial evidence favors the use of aspirin or clopidogrel as first-line agents for the majority of patients with vascular disease.*

Sources: Tran H, et al. Oral Antiplatelet Therapy in Cerebrovascular Disease, Coronary Artery Disease, and Peripheral Arterial Disease. JAMA. 2004;292:1867-1874; Shireman TI, et al. Combined Anticoagulant-Antiplatelet Use and Major Bleeding Events in Elderly Atrial Fibrillation Patients. *Stroke*. 2004;35:2362-2367.

Atherothrombosis, namely the superimposition of thrombus on preexisting atherosclerosis, is a pathophysiologic process that affects the cerebral, coronary, and peripheral arterial circulations. Oral antiplatelet drugs, because they prevent initiation and propagation of thrombus formation, are the drugs of choice to prevent ischemic events in patients with vascular disease. There is controversy, however, regarding the choice of oral antiplatelet therapy in patients with cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral arterial disease (PAD). Clinicians believe that each vascular condition is different: Neurologists tend to use aspirin (ASA) combined with extended-release dipyridamole (ER-DP) for patients with CVD. Cardiologists prefer ASA, clopidogrel, or their combination for patients with CAD, and the optimal antiplatelet treatment for PAD is uncertain.

Tran and Anand have summarized the current state of evidence regarding oral antiplatelet treatment in various subgroups of patients with vascular disease. They searched the Medline database and the Cochrane Groups' trial register to identify studies published between 1960 and August 2004. They concluded that the weight of current evidence supports the use of ASA or clopidogrel as first line therapy to prevent recurrent TIA or stroke. ER-DP combined with ASA is only a possible alternative because the evidence supporting its use comes from a single trial, The European Stroke Prevention Study 2 (ESPS 2)[1], and because dipyridamole has the potential to cause coronary artery dilatation that can divert blood flow away from stenosed coronary arteries and produce myocardial ischemia during exercise. Therefore, current ACC/AHA guidelines recommend that dipyridamole not be used in patients with stable angina.[2] This recommendation, however, was based on the short-acting form not ER-DP.[3] No increase in cardiac events from the use of ER-DP was observed in ESPS 2.[4]

Appropriate oral antiplatelet therapy is ASA for patients with ST-segment elevation myocardial infarction ASA, clopidogrel for those with chronic stable angina or peripheral arterial disease, and ASA plus clopidogrel for those with non-ST-segment elevation acute coronary syndrome.

Anticoagulation with warfarin is the most effective agent for stroke prophylaxis in elderly patients with atrial fibrillation (AF). Patients on warfarin commonly have concomitant conditions such as CAD, CVD, or PAD, for which antiplatelet drugs are indicated. Therefore, combined warfarin-antiplatelet therapy is common clinical practice.

Shireman and colleagues retrospectively studied

elderly AF patients to determine the influence of patient-specific factors on concomitant warfarin-antiplatelet therapy, and the impact of combined therapy on major bleeding risk. They identified more than 10,000 patients, who were older than 65 years, in the National Stroke Project database, that had been discharged from hospital on warfarin. The cohort was divided evenly between men and women, and the mean age was 77 years. Approximately 20% of AF patients discharged on warfarin were simultaneously on an antiplatelet agent, principally ASA alone (90%), ASA plus clopridogrel or ticlopidine (6%), or clopidogrel or ticlopidine alone (4%). Antiplatelet use was less common among women, older persons, patients with terminal illness, cancer, dementia, and a history of bleeding. Patients with CAD were more likely to receive an antiplatelet agent. At 90 days after discharge, antiplatelet drugs increased major bleeding rates from 1.3% in the warfarin-only group to 1.9% in the combined therapy group (OR = 1.5, P = 0.052). Intracerebral hemorrhage was 3 times more frequent in the combined group, but the rates were 0.9% in the combined group vs 0.3% in the warfarin-only group.

After accounting for other risk factors, Shireman et al concluded that combined warfarin-antiplatelet therapy increased the risk of a major bleeding event by 50% during the 90-day follow-up period.

COMMENTARY

Tran and Anand summarized and critically reviewed the current evidence from clinical trials of antiplatelet drugs alone or in combination in patients with atherosclerosis of brain, heart, and limb arteries. On the basis of their analysis, they recommend ASA or clopidogrel for the majority of patients with vascular disease regardless of site. For patients who develop recurrent TIA or stroke while taking ASA or clopidogrel, an option for second-line therapy can be ASA combined with ER-DP, but only in the absence of symptomatic CAD.

Antiplatelet therapy remains central to the treatment of CAD because the pathophysiology of acute coronary artery occlusion often involves plaque rupture or fissure with platelet aggregation.[5] Therefore, it is not surprising that Shireman et al found that one-fifth of AF patients were discharged on combined warfarin-antiplatelet therapy, usually because of concomitant CAD. The bad news is that combined therapy resulted in an increase in major bleeding risks, especially for ICH. The good news is that the absolute rates remained low. Therefore, the clinician must carefully consider both the potential cardiac benefit and the bleeding risk in a particular elderly patient with AF before recommending combined warfarin-antiplatelet therapy. — **JOHN J. CARONNA**

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Porphyria, Neurology, and Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *The severity of the neuropathy and the availability of potential treatments, including avoidance of provocative factors, make identification important.*

Source: Albers JW, et al. Porphyric Neuropathy. *Muscle Nerve.* 2004;30;410-422.

Heme biosynthesis, the primary objective of porphyrin metabolism, begins in the mitochondria, where glycine binds succinyl coenzyme A to form delta-amino-levulinic acid (ALA) catalyzed by the rate-limiting enzyme, ALA synthase. ALA then enters the cell cytoplasm, and sequentially, is transformed into porphobilinogen (catalyzed by ALA dehydratase), uroporphyrinogen (catalyzed by porphobilinogen deaminase and composed of 4 porphobilinogen molecules), and finally, coproporphyrinogen (catalyzed by uroporphyrinogen decarboxylase). Coproporphyrinogen returns to the mitochondria, where oxidase enzymes convert it, sequentially, into protoporphyrinogen and protoporphyrin IX. Iron is then added by ferrochelatase to form heme.

Acute intermittent porphyria, the most common hepatic porphyria, hereditary coproporphyria, variegate porphyria, and least commonly, ALA dehydratase deficiency constitute the acute hepatic porphyrias associated with neuropsychiatric complica-

tions, including neuropathy. Diagnosis may be confusing, but is usually achieved, during an attack, by measuring heme precursors in a 24-hour collection of urine and feces and determining, by the pattern of their elevation, which enzyme is deficient (*see Table*).

Genetic mutation analysis is available for definitive diagnosis. Unlike most hereditary enzyme deficiencies, hepatic porphyrias are autosomal dominant, with the exception of autosomal recessive ALA dehydratase deficiency.

Extrahepatic manifestations of the hepatic porphyrias, involving both the central and peripheral nervous system, are similar except that skin lesions do not occur in acute intermittent porphyria, whereas they are seen in hereditary coproporphyria and variegate porphyria. Abdominal pain, psychosis, and neuropathy compose the classic triad of the porphyrias, and most attacks follow a predictable course. Medications usually precipitate an attack, as may starvation and altered hormonal levels. Abdominal pain, typically dramatically severe, poorly localized, and associated with nausea and vomiting, is usually followed by nonspecific psychiatric and mental status changes. Restlessness, insomnia, and agitation may be followed by hysteria, delirium, or hallucinations, even coma. Posterior leukoencephalopathy can be seen, with cortical blindness due to occipital infarcts.

Up to 40% develop combined autonomic (hence the abdominal pain) and peripheral neuropathy, the latter typically within 1 month of the abdominal pain, which may render the patient quadriplegic and ventilatory dependant. Typically, areflexic motor neuropathy resembling Guillain-Barre syndrome (GBS), including cytoalbuminogenic dissociation, is seen, with labile hypertension and tachycardia, implicating autonomic neuropathy. Curiously, 50% have an upper extremity onset, and 80% are worse proximally. One-third have leg weakness initially, and the remainder are diffusely weak at onset. Lack of symmetry is common. Differential diagnosis usually includes, in addition to GBS, vasculitis, heavy metal poisoning, and polio. Unlike GBS, electrodiagnostic studies demonstrate acute axonal neuropathy with loss of motor amplitudes, but retained distal latency and velocity measurements. Conduction block and temporal dispersion are not seen, and sensory responses are relatively spared. A needle electromyographic study shows abundant positive sharp waves with decreased recruitment.

Prognosis is good, with neuropathy recovering last, as it requires axonal regeneration. With repeated attacks, recovery may be incomplete, and a fixed deficit may result. Treatment is primarily preventive and abortive, and supportive in the acute phase. Medications, which activate the cytochrome P450 enzyme system, are to be avoided, and lists of safe medications should be consulted as needed. The American Porphyria Association is a good source of up-to-date safe-drug information.

COMMENTARY

What are the magnetic resonance imaging and cerebrospinal fluid findings between attacks of acute intermittent porphyria (AIP)? Among 16 AIP gene carriers who were not experiencing an acute event, ages 30 to 62 years, half with and half without any previous episode, 2 patients in each group had several high-signal, white matter lesions on T2 weighted images, but fewer (< 5) were seen in those

Table 1

ALADD ALA dehydratase deficiency, AIP acute intermittent porphyria, HCP hereditary coproporphyria, VP variegate porphyria, PBG porphobilinogen, Copro coproporphyrinogen, Proto protoporphyrinogen, Uro uroporphyrinogen

	Deficiency	Urine	Feces
ALADD	ALA dehydratase	ALA, Copro	Normal
AIP	PBG deaminase	ALA, PBG, Uro	Normal
HCP	Copro oxidase	ALA, PBG, Uro, Copro	Copro > Proto
VP	Proto oxidase	ALA, PBG, Uro, Copro	Proto > Copro

with no previous attack (Bylesjo I, et al. *Eur Neurol.* 2004;51:1-5). No patient demonstrated oligoclonal bands, and cerebrospinal fluid protein was elevated in only one. Interestingly, 10 patients had elevated (n = 7), or borderline (n = 3), levels of hemoglobin A1c.

Cure is not yet available, but liver transplantation may be an option in severe cases of porphyria (Soonawalla ZF, et al. *Lancet.* 2004,363;705-706). Urine concentrations of heme precursors returned to normal, and quality of life was improved in a 19-year-old woman with acute intermittent porphyria who underwent such surgery in an attempt to replace her enzyme deficiency, holding out hope for future patients. — **MICHAEL RUBIN**

Sudden-Onset Sleep in Parkinson's Disease: Who is at Risk?

ABSTRACTS & COMMENTARY

Synopsis: *SOS, in part, can be attributed to PD-specific pathology because disease duration and subjective disease severity have been shown to be predictors of SOS.*

Sources: Korner,Y et al. Predictors of Sudden Onset of Sleep in Parkinson's Disease. *Movement Disorders.* 2004;19:1298-1305; Rissling I, et al. Dopamine Receptor Gene Polymorphisms in Parkinson's Disease Patients Reporting "Sleep Attacks". *Movement Disorders.* 2004;19:1279-1284.

SUDDEN ONSET OF SLEEP (SOS) CAN OCCUR IN PEOPLE with Parkinson's disease (PD), and has potentially disastrous consequences, especially while driving. Sleep attacks were initially reported in patients taking non-ergoline dopamine agonists.[1] However, other medications, as well as characteristics of the disease itself, have since been implicated, and how to identify those at risk remains controversial. Two studies recently attempted to address this question and investigate a relationship to dopamine dysfunction, in very different ways. Korner and colleagues targeted 12,000 members of a nationwide German PD patient support group, with a questionnaire designed specifically for this study. The questionnaire contained items regarding disease duration and medications, the Epworth Sleepiness Scale, as well as sleep behavior at night and during the daytime. SOS was assessed based upon subjective responses to a set of questions, without the need for eyewitness account. Of 6620 respondents with PD, 42.9% reported SOS. Of these, fully 10% did not think they experienced prior warning symptoms of drowsiness. The strongest predictors of SOS were increasing age, male sex, longer disease duration, and presence of various sleep disturbances. Taking non-ergoline dopamine agonists was more strongly associated with SOS in patients below 70 years old and in those with disease duration less than 7 years. To further address a potential role for dopaminergic agents, 137 patients with SOS and 137 patients without SOS were identified from respondents by Rissling and colleagues. Blood was drawn for genetic analysis by each patient's general practitioner, and was subjected to testing for known polymorphisms in the dopamine D2 receptor family. A Taq IA polymorphism in DRD2 was significantly associated with SOS. No significant differences were observed for polymorphisms in the DRD3 and DRD4 genes.

COMMENTARY

Daytime somnolence is a serious problem for many with PD. Brainstem pathology in PD likely impacts on sleep-wake disturbances, through dysfunction of mesocorticolimbic (and possibly mesostriatal) circuitry that contributes to wakefulness, as well as involvement of other structures such as the pedunculopontine nucleus (PPN). A Canadian study, performed by direct evaluation and interview, found 51% of highly functional, non-demented PD patients to have excessive daytime sleepiness.[2] Almost 4% of those still driving had experienced at least 1 episode of falling asleep at the wheel, and some patients report sleep attacks, without warning signs of prior drowsiness. The issue is complicated by the possibility that any warning signs may be misjudged or later forgotten by patients. How then, should we counsel our patients about these occurrences? Identifying associations via observational studies is a first step. The study design utilized by Korner et al is, of course, subject to bias: we cannot be sure that respondents indeed have idiopathic PD, those with daytime drowsiness might be more likely to respond, and subjective reports in this realm are quite unreliable. However, associations of age, male sex, and disease duration, demonstrated in this study, are plausible, and are consistent with those

noted previously. The study also highlights a potential contribution of dopaminergic medications. Dopamine plays a complex role in normal and pathologic sleep-wake cycles, and anti-Parkinson's medications can negatively impact both nighttime sleep and daytime alertness. How this occurs is unclear, but non-ergoline dopamine agonists have negligible binding to the dopamine D1 receptor family. Rissling et al, therefore, sought to concentrate efforts on the D2 receptor family. It is intriguing that association of a DRD2 gene polymorphism with SOS was demonstrated in this population. This needs to be confirmed, but could be a first step to better understanding the molecular underpinnings of abnormalities of sleep and wakefulness in PD. For the present, questioning about sleep habits and daytime drowsiness should be part of our clinical evaluation of a PD patient, with careful counseling and monitoring when it comes to choice of medication. — **CLAIRE HENCHCLIFFE**

Dr. Henchcliffe is Assistant Professor of the Department of Neurology, Weill Medical College of Cornell University.

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Chronic Immune Sensory Polyradiculopathy: A Possibly Treatable Sensory Ataxia

ABSTRACT & COMMENTARY

Synopsis: *This condition preferentially affects large myelinated fibers of the posterior roots, may respond favorably to treatment, and may be a restricted form of chronic inflammatory demyelinating polyradiculoneuropathy.*

Source: Sinnreich M, et al. *Neurology*. 2004;63:1662-1669.

SINNREICH AND COLLEAGUES REPORT THAT PATIENTS presenting with ataxic sensory neuropathy and normal nerve conductions may be suffering from chronic immune sensory polyradiculopathy, a variant of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) that is responsive to immune therapy. The pathology in these patients is localized to the sensory roots, explaining the normal peripheral conduction studies.

Fifteen patients were described. Sensory polyradiculopathy was suspected because of abnormal somatosensory evoked responses, or enlargement of lumbar nerve roots, some with enhancement. CSF protein was elevated in 13/14 patients, as is often seen in CIDP. Three had lumbar sensory root biopsies that showed primary demyelination and endoneurial inflammation. Six of 6 patients, that were treated with immune modulating therapy, had marked improvement in their ambulation.

COMMENTARY

The diagnosis of CIDP is not unlike that of multiple sclerosis, in that both require demonstration of lesions with demyelination. CIDP is a more difficult diagnosis to make, however, as it relies on electrodiagnostic rather than imaging studies. Sensory conductions, in particular, are notoriously insensitive for detecting demyelination, so that when only the sensory nerves are affected, a sural nerve biopsy may be required to make the diagnosis. Even that, however, may not be sufficient, if the lesions are confined to the sensory roots, as reported in this paper.

Now that Sinnreich et al have established that the entity exists, how does one make a diagnosis of immune sensory polyradiculopathy? Given the insensitivity of current nerve imaging studies, should all patients that present with sensory ataxic neuropathy, abnormal somatosensory responses, and increased CSF protein, have a trial of immune modulating therapy. If so, what therapeutic modalities should one use, and how should improvement be measured? If not, how many potentially treatable patients would be denied therapy? These are important issues, as sensory ataxic neuropathy is relatively common in clinical practice, particularly in the aging population. Perhaps more emphasis should be given to the development of reliable nerve imaging studies, so that the diagnosis of CIDP could becomes as easy to make as that of multiple sclerosis. — **NORM LATOV**

Dr. Latov is a Professor of Neurology and Neuroscience and Director of the Peripheral Neuropathy Center, Weill Medical College of Cornell University.

CME Questions

17. In a TIA or stroke patient without AF, first-line treatment is:

a. Warfarin and an antiplatelet agent
b. ASA and extended release dipyridamole
c. ASA and clopridogrel
d. ASA or clopridogrel
e. Ticlopidine.

18. The hepatic porphyrias which demonstrate neurologic accompaniments include:

a. Acute intermittent porphyria
b. Hereditary coproporphyria
c. Variegate porphyria
d. delta-amino-levulinic acid (ALA) dehydratase deficiency
e. All the above

Answers: 17. (d); 18. (e)

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Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			97	97

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17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda J. Mooney Publisher — Date: 9/27/04

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PS Form **3526**, September 1999 *(Reverse)*

In Future Issues:

Intermediate Filament Proteins and Their Diseases

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

ACE Inhibitors and Receptor Blockers: Which is Inferior?

The first head-to-head comparison study of an ACE inhibitor and an angiotensin receptor blocker, to assess renoprotective effects in type 2 diabetes, has shown that the drugs are comparable in their benefit. It has been known for more than a decade that ACE inhibitors prevent progression of microalbuminuria in type 2 diabetes, out of proportion to their blood pressure lowering effects. It has also been shown that angiotensin receptor blockers are renoprotective, but it has not been shown that the drug classes are equivalent in their benefit. The Diabetics Exposed to Telmisartan and Enalapril Study Group (DETAIL study) was designed in 1996 to compare the 2 drugs in 250 patients with type 2 diabetes and early nephropathy. Patients were randomized to 80 mg of telmisartan or 20 mg enalapril daily. The primary end point was the change in Glomerular Filtration Rate (GFR) during 5 years of the study. Secondary end points included annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; the rates of end stage renal disease and cardiovascular events; and all-cause mortality. After 5 years, the change in GFR was -17.9 mL/min with telmisartan and -14.9 mL/min with enalapril (the 95% CI, -7.6- 1.6 mL/min). The data suggest that telmisartan is not inferior to enalapril in providing long-term renotection in patients with type 2 diabetes (*N Engl J Med*. 2004;351:1952-1961). In the same issue of the *Journal*, researchers in Italy compared the ACE inhibitor trandolapril plus verapamil, trandolapril alone, verapamil alone, or placebo in patients with hypertension and type 2 diabetes, and normal urinary albumin excretion. The end point was the development of persistent microalbuminuria. Over 3 years of treatment, the percentage of those patients developing microalbuminuria were: trandolapril 6%, trandolapril plus verapamil 5.7%, verapamil alone 11.9%, and placebo 10%. The authors conclude that trandolapril plus verapamil and trandolapril alone decrease the incidence of microalbuminuria to similar extent, whereas the effectiveness of verapamil alone was similar to that of placebo (*N Engl J Med*. 2004; 351:1941-1951).

The Infection Risk of Acid-Suppressing Drugs

Ever since cimetadine was first marketed in 1977, physicians have been concerned about the risk of infection associated with acid-suppressing drugs. Now researchers from the Netherlands have shown that concern is warranted, by demonstrating a link between acid-suppressing drugs and community-acquired pneumonia (CAP). Utilizing the Integrated Primary Care Information database in the Netherlands between 1995 and 2002, incidence rates for pneumonia were calculated for those exposed to acid-suppressive drugs and those who were unexposed. A case control analysis was conducted, nested in a cohort of incident users of acid-suppressive drugs, with up to 10 controls matched to each case for practice, year of birth, sex, and index date.

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The main outcome was CAP. The incidence rates for pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 in 2.45 per hundred person-years, respectively. The adjusted relative risk for pneumonia among persons currently using a proton pump inhibitor (PPI), compared with those who stopped using a PPI, was 1.89 (95% CI, 1.36-2.62). The risk for current users of H2 antagonists was 1.63 (95% CI, 1.07-2.48). The authors conclude that acid-suppressive drugs, especially proton pump inhibitors (PPIs), are associated with an increased risk of pneumonia, and suggest that these drugs should be used with caution, and at the lowest possible doses in patients who are at risk for pneumonia (*JAMA.* 2004;292:1955-1960). An accompanying editorial points out the biological plausibility of the findings and suggest that, while acid-suppressive drugs are indicated for a wide variety GI conditions, long-term, chronic use of these drugs should always be balanced with patient safety (*JAMA.* 2004;292:2012-2013).

Is Rosuvastatin As Safe As Other Statins?

Rosuvastatin (Crestor), AstraZeneca's entry into the high potency statin market, has not achieved marketshare comparable to Pfizer's atorvastatin (Lipitor) or Merck's simvastatin (Zocor). This, despite the facts that the drug is very potent and AstraZeneca has priced the drug 15-20% lower than Lipitor. Some physicians remember the cerivistatin (Baycol) withdrawal from the market, and may be concerned regarding the highest doses of rosuvastatin, especially since European regulators issued a warning earlier this year about the drug. New postmarketing data suggest, however, that rosuvastatin is as safe and well-tolerated as other statins. The records of 12,400 patients who received 5-40 mg/day were reviewed, representing 12,212 continuous patient years. In fixed dose trials with comparator statins, 5-40 mg of rosuvastatin showed an adverse event profile similar to those for 10-80 mg of atorvastatin, 10-80 mg of simvastatin, and 10-40 mg of pravastatin. Clinically significant increases in liver transaminases were uncommon (≤ 0.2%) in all groups. Myopathy with creatine kinase increases > 10 times the upper limit of normal, with muscle symptoms occurring in ≤ 0.03 % of patients who took rosuvastatin at doses of 40 mg or less. Proteinuria, at the same doses, was comparable to the rate seen with other statins as well. There were no deaths and no cases of rhabdomyolysis in patients on 40 mg or less of rosuvastatin. The authors conclude that rosuvastatin was well-tolerated, and out of safety profile similar to other commonly statins (*Am J Cardiol.* 2004;94:882-888).

Which Estrogen Preparation is the Safest?

Is esterified estrogen safer than conjugated equine estrogen? At least with regard to venous thrombosis, the answer may be yes, according to a recent study. Group Health Cooperative in Washington State, a large HMO, switched their patients from conjugated equine estrogen (CEE) to esterified estrogens (EE) in 1999. Records of perimenopausal and postmenopausal women were studied between January 1995 and the end of 2001. The primary outcome was the risk of first venous thrombosis, in relation to current use of either estrogen with or without a progestin. There were 586 cases of venous thrombosis identified. Compared with women not currently using hormones, current users of EE had no increase in venous thrombotic risk (odds ratio, 0.92; 95% CI, 0.69-1.22). Women taking CEE however, had an elevated risk (OR, 1.65; 95% CI, 1.24-2.19). Comparing users of the 2 estrogens, current users of CEE had an odds ratio of 1.78 for venous thrombosis, compared to users of EE (95% CI, 1.11-2.84), and higher doses of CEE were associated with a higher risk. Among all estrogen users, concomitant use of progestin was associated with an increased risk, compared to use with estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). The authors conclude that conjugated equine estrogen, but not esterified estrogen, is associated with an increased risk of venous thrombosis (*JAMA.* 2004; 292:1581-1587). While the authors acknowledge that these data need to be replicated, the study raises the interesting question of the differences between various estrogen preparations and the potential risks associated with them, especially when noting that conjugated equine estrogen was the only estrogen preparation used in the Women's Health Initiative.

FDA Actions

Serono has been given approval to market recombinant human luteinizing hormone (Luveris) for the treatment of infertility in women. The drug, which was granted orphan status, has been available in more than 60 countries for several years.

The FDA and Centocor have issued a warning to health care professionals about the increase risk of lymphoma associated with inflixamab (Remicade) in patients with rheumatoid arthritis and Crohn's disease. The warning applies to all tumor necrosis factor blocking agents. The drugs are associated with a 1 in 1400 risk of lymphoma, according to MedWatch, the FDA's safety information program.