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Ruptured Aneurysm: Clip or Coil? Superiority of Endovascular Treatment Continues to Mount

A B S T R A C T & C O M M E N T A R Y

Source: ISAT Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. *Lancet*. 2002;360:1267-1274.

NEUROSURGICAL CLIPPING HAS LONG BEEN THE MAINSTAY OF intracranial aneurysm treatment. Such therapy involves a large craniotomy, complex microsurgical dissection, and considerable up-front morbidity for the patient. In contrast, endovascular treatment with Guglielmi detachable coils (GDC) can be accomplished via transfemoral angiography and spares the patient a major neurosurgical procedure. Coiling further offers the prospect of treating aneurysms difficult or impossible for surgeons to access, such as at the basilar artery tip. Despite these advantages, neurosurgical clipping remains the more widely available established therapy, often relegating coiling to patients in poor neurological or medical condition, such as the elderly with Hunt and Hess grade III or IV subarachnoid hemorrhage (SAH). Such a practice is currently justifiable, as long-term durability data for GDC treatment (available since 1995) are only now starting to accrue. Young patients able to more easily tolerate craniotomy might be better clipped to avoid possible eventual aneurysm recurrence, which requires repeat treatment. Worse yet, they may suffer clinical rebleeding from an inadequately treated lesion. Aneurysm anatomy, such as a high dome to neck ratio or involvement of a parent vessel wall, may push treatment in one direction or another, but in many cases it is referral patterns rather than science that dictates how patients are treated. It is in the setting of this very controversial climate that the ISAT trial has been conducted.

The ISAT trial enrolled 2143 patients, primarily in Britain, with ruptured intracranial aneurysms and randomly assigned them to neurosurgical clipping (n = 1070) or GDC coils (n = 1073). Because interim analysis demonstrated a striking difference between these groups in favor of coiling, the trial was stopped short of its planned goal of 2500 patients. At 1-year follow-up, the risk of death or significant disability

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INSIDE

(Rankin score 3-6) was 30.6% in the neurosurgical group compared to 23.7% in the endovascular group. This was a 6.9% absolute and 22.6% relative risk reduction in favor of coiling. Many patients were screened but excluded from the study. Of 9559 patients initially assessed, only 20% were actually enrolled. In the remainder, a decision was made that clipping or coiling was clearly more favorable and thus the patient could not be subjected to a random treatment choice. Considerable bias could have been introduced into the study during this screening process.

The ISAT patients are not completely representative of the SAH population at large. Eighty-eight percent were of good clinical status (Hunt and Hess grade I or II), 93% of aneurysms were 10 mm or smaller in diameter, and 97% were in the anterior circulation. The generalizability of ISAT data is therefore limited. There was a significant occurrence of post-treatment rebleeding. This was found in 2.4% (26/1048) of endovascular cases compared with 1.0% (10/994) of clipped patients. While these results clearly favor neurosurgery, such an incidence of incompletely treated aneurysms is unusual for either therapy in experienced hands. There were additionally 11 cases (6 coiled, 5 clipped) that re-bled despite indications that complete aneurysm obliteration had been achieved. Such results have led some to question the skill of some of the investigators in the study, raising doubts about the validity of the study in general.

COMMENTARY

These data are unlikely to put this raging debate to rest, but certainly add another nail into the coffin of neurosurgical clipping. Although nonrandomized and retrospective, data from UCSF[1] indicate that similar morbidity, mortality, and cost-effectiveness differences in favor of coiling may be demonstrated in US centers. Despite these data, some will continue to argue that outcomes depend not only upon differences in these techniques but also upon the relative skill of the neurosurgical or endovascular operator. Coils, say the neurosurgeons, lack a lengthy track record of durability, whereas a clip is a guarantee against recurrence. We are currently engaged in a good old-fashioned turf war. With a new breed of "endovascular neurosurgeons," however, the cranial drill and the femoral catheter will not be in competition but rather options within a particular individual's armamentarium.

Additional questions remain, such as how to treat unruptured incidentally diagnosed aneurysms. Extrapolation from the ISAT data is helpful, but it is not completely accurate to consider ruptured and unruptured aneurysms as one and the same. The best answer might come from neurologists involved in stroke and critical care. When asked, "How would you wish to be treated should you be diagnosed with an aneurysm?" no one that I know of has ever opted for the knife.

The gulf between craniotomy and endovascular therapy is furthermore likely to continue to widen in favor of coils. The continual development of new types of catheters, coils, balloons, and stents has already pushed the endovascular envelope far beyond the ISAT trial and will continue to do so in the coming years.

— ALAN Z. SEGAL

Reference

1. Johnston, et al. *Stroke*. 2002;33:2536-2544.

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Mitochondrial Defects Play Role in Parkinson's Disease

ABSTRACT & COMMENTARY

Source: Shults CW, et al. Effects of coenzyme Q10 in early Parkinson disease. *Arch Neurol*. 2002;59:1541-1550.

THERE IS SUBSTANTIAL EVIDENCE THAT MITOCHONDRIAL defects and oxidative damage play a role in the

pathogenesis of Parkinson's disease (PD). For instance, decreased complex-I activity has been found in the substantia nigra, platelets, and muscle of PD patients. There is substantial evidence showing that there is increased oxidative damage in PD substantia nigra. The present report, on which I am author, is the first clinical trial to examine whether administration of coenzyme Q10 can slow the functional decline of PD. Coenzyme Q10 is an essential component of the electron transport chain. It is the electron acceptor for complexes I and II and is also a potent anti-oxidant.

The present clinical trial was carried out by the Parkinson Study Group. Clifford Shults at the University of California in San Diego was the principal investigator. The trial enrolled 80 patients who were randomly assigned to placebo or coenzyme Q10 at doses of 300, 600, or 1200 mg/d. The primary outcome measure was the Unified Parkinson's Disease Rating Scale (UPDRS), which was administered at screening, baseline, and 1, 4, 8, 12, and 16 months. The subjects were patients with early PD who did not require treatment (levodopa) for their disability. They were followed up for 16 months or until disability requiring treatment with levodopa had developed. Only 1 patient was lost to follow-up. The primary response variable was the change in the total score on the UPDRS from baseline to the last visit. The subjects were very well matched with regard to their ages, gender, and clinical disability at baseline. No significant side effects were encountered.

The findings were an increase in the adjusted mean total UPDRS score of 11.99 for the placebo group, 8.81 for the 300 mg/d, 10.82 for the 600 mg/d group, and 6.69 for the 1200 mg/d group. The primary analysis was a test of the linear trend between the dosage and the mean change in the UPDRS, which had a *P* value of 0.09 and was the prespecified criteria for a positive effect. Secondary analysis was a comparison of each treatment group with placebo group. The difference between the 1200 mg/d and placebo groups was significant with a $P = .04$. The overall slowing of disability in the 1200 mg/d group was 44% at 16 months.

A number of other biochemical end points were examined. Plasma coenzyme Q10 levels showed dose-dependent increases. Interestingly, the 300-mg and 600-mg doses produced increases in plasma concentrations, which were roughly comparable, at approximately 2 mg/mL. The 1200-mg dose, however, produced a 2-fold increase above the 300-mg and 600-mg doses to approximately 4 mg/mL. An assay of mitochondrial complex I activity, which depends on the endogenous levels of coenzyme Q10 in the mitochondria, showed increases in all of the treated groups.

Interestingly, all 3 subscores of the UPDRS showed improvement. This included the mental score, the activities of daily living score, as well as the motor score. Another interesting aspect was that the initial changes in the total UPDRS score were roughly comparable to the varying groups over the first month, and only at the 4-month and later time points was there increasing separation of the groups, consistent with a possible neuroprotective effect. The number of patients who completed 16 months without needing levodopa were 5 in the placebo group, 7 in the 300 mg/d, 0 in the 600 mg/d group, and 11 in the 1200 mg/d group.

COMMENTARY

The importance of coenzyme Q10 for central nervous system function is corroborated by children in whom a marked coenzyme Q10 deficiency has been documented. Patients have suffered from progressive muscle weakness, seizures, and cerebellar ataxia. The symptoms resolve with coenzyme Q10 supplementation. In some patients with mitochondrial encephalopathy, lactic acidosis and stroke (MELAS) coenzyme Q10 produces both biochemical and clinical improvement. On account of this we became interested in it as a possible neuroprotective agent for treatment of neurodegenerative diseases, in which there is substantial evidence for mitochondrial dysfunction. The MPTP model of PD involves metabolism into MPP+, which then inhibits complex I of the electron transport chain. Other mitochondrial toxins such as malonate and 3-nitropropionic acid are succinate dehydrogenase inhibitors, which have been used to model Huntington's disease. We showed that oral administration of coenzyme Q10 could significantly attenuate MPTP neurotoxicity and it significantly attenuated malonate, and 3-nitropropionic acid induced toxicity. It improved ATP levels and reduced increases in lactate concentrations and attenuated oxidative damage.

We subsequently demonstrated that coenzyme Q10 administration significantly extended survival and attenuated the pathologic changes in transgenic mouse models of both ALS and Huntington's disease. Coenzyme Q10 administration produces time-dependent increases in brain concentrations both in tissue homogenates, as well as in mitochondria.

The results of the present trial appear extremely promising. The studies showed dose-dependent slowing of disease progression. There were no sig-

nificant side effects. The finding that there was improved complex I activity suggests that the beneficial effects may be mediated by improvements in mitochondrial function. It, however, remains possible that the major benefits may be through a reduction in oxidative damage, or recently described effects of coenzyme Q10 on mitochondrial uncoupling proteins, which may exert protective effects against neuronal damage.

What do these findings mean in terms of patient care? As yet, coenzyme Q10 cannot be definitely recommended. Although the results of this study are extremely promising, they need to be replicated in a much larger patient sample. The results reached significance, but the number of patients in each subgroup were relatively small. A major issue is the cost of coenzyme Q10 at the doses used in the study, which at the 1200-mg dose is about $200 monthly. This at present is a deterrent to using coenzyme Q10. Nevertheless, this is still less than the cost of levodopa. We are planning a much larger phase III trial. If these preliminary results can be confirmed in a larger study, this will be a major breakthrough in our ability to achieve neuroprotection for PD. — **M. FLINT BEAL**

West Nile Virus' Spread Tracked Across United States

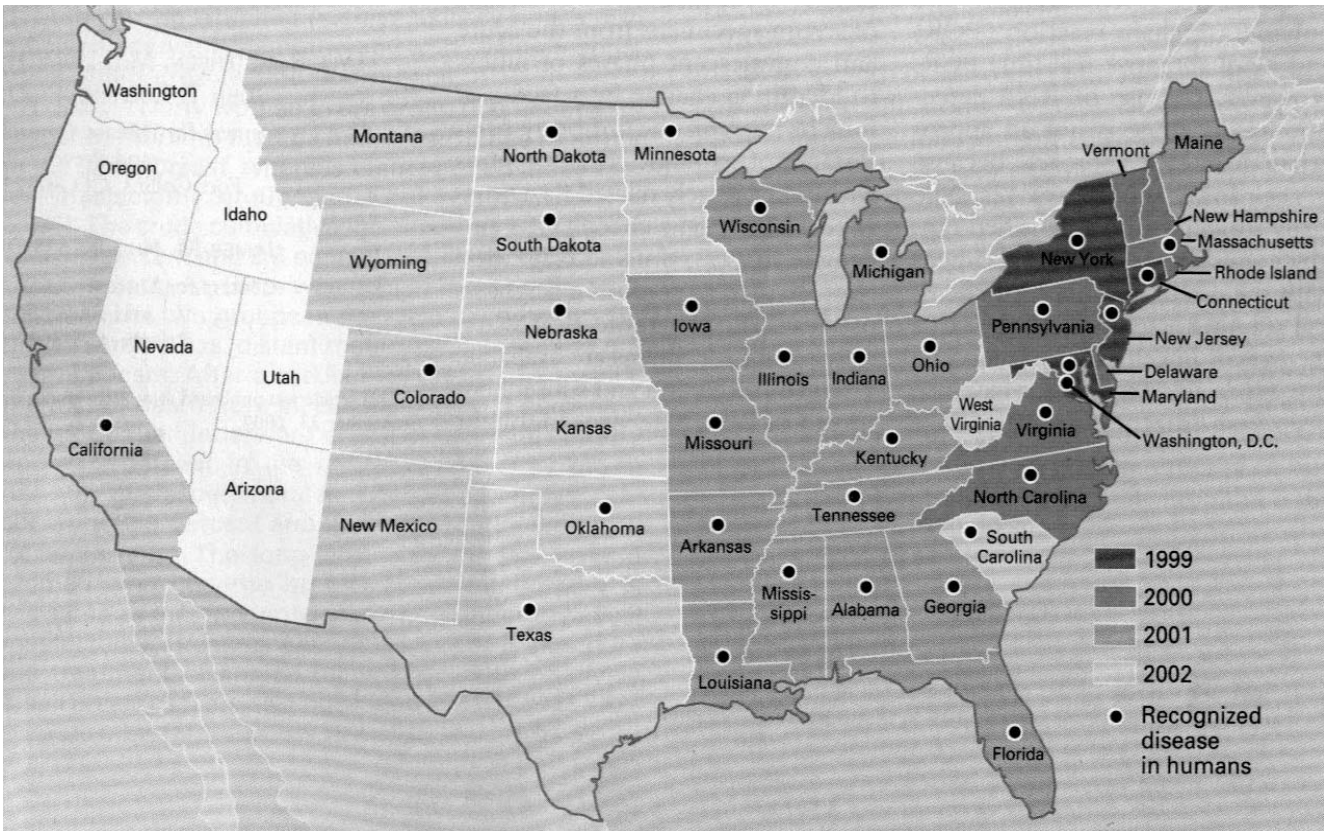
ABSTRACTS & COMMENTARY

Sources: Petersen LR, Roehrig JT, Hughes JM. West Nile virus encephalitis. *N Engl J Med*. 2002;347:1225-1226; Leis AA, et al. A poliomyelitis-like syndrome from West Nile virus infection. *N Engl J Med*. 2002;347:1279-1280; Glass JD, et al. Poliomyelitis due to West Nile virus. *N Engl J Med*. 2002;347:1280-1281; Gadoth N, et al. Acute anterior myelitis complicating West Nile fever. *Arch Neurol*. 1979;36:172-173.

WEST NILE VIRUS, OTHERWISE CALLED WEST NILE encephalitis, has slowly become a growing American and Canadian viral disease since its first apparent invasion into the Western Hemisphere in 1999. The virus was first identified in Uganda in 1937 and spread to humans by birds and mosquitoes causing infrequent human cases across Northwest Africa, South Europe, and East Asia. Recently, large epidemic outbreaks have occurred in Romania (1996), Russia (1999), and Israel

Figure

Spread of West Nile Virus, in Birds, Horses, Mosquitoes, Other Animals, and Humans in the United States, 1999-2002.



Reprinted with permission from: *Peterson LR, Roehrig JT, Hughes JM. West Nile virus encephalitis. N Engl J Med. 2002;347:1225-1226.*

(2000). Harbored by a mosquito-borne flavivirus, the agent primarily infects birds and calicine mosquitoes, which transfer the virus into humans and horses. In seasonal weather areas such as the United States, the bird-mosquito-bird cycle begins in early spring and steadily generates clinical cases up to their maximum number and geography in late summer. As it evolves in one area, infected birds spread the virus to adjoining areas each year. As the geographical map demonstrates, the first onset sources in the United States appeared in the summer of 1999 in New York, Connecticut, New Jersey, Maryland, and Washington DC. In the first winter following the appearance of the virus in America (1999), John Roehrig and associates of the US Arbo Virus Diseases Branch inspected New York's sewers and other spots where mosquitoes hibernated. "Was the virus there?" others asked. The answer was yes. The following year (2000), the virus had been carried into 8 more adjacent north and south Atlantic states as shown on the map (*see Figure*).

During the summer of 2001, Peterson, Roehrig, and Hughes noted that the virus had straddled the shores of both sides of the Mississippi River, expanding all the way up from the Gulf of Mexico to Minnesota. Only 2 of the remaining Eastern states remained not infected. By August 12 of this year, 138 human cases of West Nile virus had been identified in 7 states. Most of these came from Louisiana, Mississippi, and Texas. Thus far, the virus has also been detected in mosquitoes, birds, and horses along with 36 cases in the District of Columbia. Only 6 far-western states have yet escaped evidence of the disease.

Transmission of West Nile virus from mosquitoes is not the only source of transmission into persons. Evidence indicates that person-to-person transmission has occurred after the transplantation of 4 infected body organs from a single donor. Blood products are presently being examined to determine the risk of transfusion of blood or body parts from anyone carrying an unknown active infection.

Peterson et al state that in persons younger than 50 and infected with West Nile virus, only a few may become very sick. Out of every 150 infected individuals 1 will develop meningitis or encephalitis. Out of a cohort of infected patients older than 50 years, however, the disease carries a high risk of neurological damage. Over age 50, fever, muscular weakness, and sometimes delirium become apparent and an accurate diagnosis should be promptly considered. Symptoms may become serious and threatening, and a few patients die.

Of note is the recent identification of poliomyelitis accompanying infection by West Nile virus. It is known that West Nile virus causes poliomyelitis in monkeys, horses, and birds. Gadoth and colleagues identify a young, healthy man of 22 who was tested for clinically apparent positive West Nile encephalitis. Neurologically, along with the acute attack, he developed motor deficits in the face and flaccid paralysis of the left lower extremity with loss of deep-tendon reflexes, but no sensory changes. Within days after onset, the facial paralysis recovered and at 18 months the leg strength had improved, but it remained still "diminished."

Leis et al described 3 male patients, 56, 57, and 50 years old. Two were feverish, 1 was not. All 3 suffered from acute motor paralysis and areflexia, and 2 had bladder dysfunction and acute respiratory distress. Abnormal electrodiagnostic responses identified involvement of either the anterior horn cells or motor axons. Glass and associates described a 50-year-old woman who suffered an acute severe illness characterized by headache, severe myalgia, and severe, sustained general weakness requiring intubation and ventilator support. All 4 patients tested positive for West Nile virus.

COMMENTARY

This excellent map constructed by Peterson, Roehrig, and Hughes identifies the steady, dynamic invasion and explosive pattern of the spread of West Nile virus in the United States, 1999-2002. Black dots identify the geography of the human disease and density, and the background indicates birds, horses, mosquitoes, and other animals but not humans. Only Arizona, Utah, Nevada, Idaho, Oregon, and Washington remain uninvaded from the disease.

The present reports expand the clinical spectrum of illness attributed to West Nile virus, showing that it can cause a poliomyelitis syndrome with involvement of anterior horn cells. None of the cases were confirmed neuropathologically, but the clinical and electrodiagnostic findings are convincing. Although there is no specific treatment for West Nile virus-induced poliomyelitis, it is important to distinguish these patients from those suffering from Gullian-Barré syndrome to avoid inappropriate treatment. — **FRED PLUM**

Very Mildly Demented Patients Can Draw Clocks

ABSTRACT & COMMENTARY

Source: Powlishta KK, et al. The clock drawing test is a poor screen for very mild dementia. *Neurology*. 2002;59:898-903.

THE CLOCK DRAWING TEST IS USED BY MANY PHYSICIANS and other health professionals to rapidly detect

signs of cognitive impairment. This test involves asking the patient to draw the face of an analog clock, fill in all the numbers, and set the hands to a fixed time. The Clock Drawing Test can be rapidly administered, scored in a quantifiable way, and is sensitive to deficits in a variety of cognitive domains. Although past studies have shown that the Clock Drawing Test is frequently abnormal in patients with mild dementia associated with Alzheimer's disease (AD), few studies have examined its usefulness in detecting the very earliest signs of dementia. In a longitudinal study of 75 patients that included 25 with the earliest detectable stage of dementia, Powlishta and colleagues found that clock drawing had unacceptably low sensitivity in detecting the very earliest stages of AD.

In this study, 6 different scoring systems for the Clock Drawing Test were compared. Good inter-rater reliability (91-97%) was found among all 6 scoring systems. Powlishta et al examined the performance on clock drawing as a function of dementia severity as measured by the Clinical Dementia Rating (CDR) scale. While 80-97% of patients with mild dementia (CDR = 1) scored abnormally on the Clock Drawing Test, only 20-60% of those with very mild impairment (CDR = 0.5) scored below the cutoffs for normal. The Mendez scoring system had the best sensitivity for very mild impairment but had the lowest (60%) specificity.

Powlishta et al emphasize that clock drawing should not be used in isolation when screen for the earliest signs of AD. Instead, diagnosis requires a thorough clinical assessment that incorporates medical assessment, multiple measures of cognition, and a careful history from a collateral source.

COMMENTARY

Clock drawing is an appealing cognitive screening test in many respects. It is quick and easy to administer, easy to score, and results can generally be reproduced across examiners and multiple test sessions. Results correlate reasonably well with the Folstein Minimental State Examination in selected patient populations. The pattern of deficits found on clock drawing often provides valuable clues to the nature of the cognitive domains impaired by a variety of brain disorders. For example, the clocks drawn in the context of visuospatial impairments may be distinctly different from those produced by patients with executive dysfunction or memory loss as their primary deficits.

As with all brief cognitive tests, clock drawing has its limitations. This particular study examined a relatively small number of cases and used published cutoffs for distinguishing normal from demented cases. Unfortunately, it did not use a Receiver Operating Characteristic (ROC) analysis to evaluate which scoring system and cutoff values provide optimal sensitivity and specificity in detecting very mild dementia. Nevertheless, the results suggest that impaired performance on clock drawing is a useful correlate of frank dementia in conditions such as AD but may not be sensitive enough to detect the very mildest cases. A recent study suggests that Mild Cognitive Impairment (MCI) may be detectable by repeatedly performing a small set of computerized cognitive tests over a single day.[1] Until such approaches are validated, MCI is best identified through the use of sensitive tests of memory, particularly delayed recall, coupled with other cognitive measures and information culled from interviews with the patient and a knowledgeable informant. Clock drawing still has a place in screening for dementia but should not be used in isolation when screening for very mild cognitive deficits. — **NORMAN R. RELKIN**

Reference

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Valproate for Diabetic Painful Neuropathy

ABSTRACT & COMMENTARY

Source: Kochar DK, et al. Sodium valproate in the management of painful neuropathy in type 2 diabetes—A randomized placebo controlled trial. *Acta Neurol Scand*. 2002;106:248-252.

Diabetic painful sensory neuropathy (DPSN) remains difficult to treat, witness the persistence of ongoing and upcoming clinical trials searching for the magic bullet and the large number of medication options available (none work superbly in all cases). In this randomized, double-blind, placebo-controlled trial, sodium valproate, 400 mg p.o. t.i.d., was administered to 30 patients with efficacy and safety compared to 30 placebo-control patients. All 60 patients were demographically matched with documented DPSN, and they were excluded if they demonstrated hepatic disease, TB, or other cause of neuropathy including uremia, vitamin deficiency, paraneoplastic or hereditary neuropathy, or alcoholism. Detailed clinical and neurological examinations were performed and the short-form McGill pain

questionnaire was used to quantify pain severity at study entry, week 1, and after 4 weeks of therapy. Motor and sensory nerve conduction studies were performed at study onset and after 4 weeks. Student's t-test provided statistical analysis.

Among 28 patients who completed 4 weeks of the active drug arm, 20 reported pain relief compared to 5 of 24 in the placebo arm. Pain severity was significantly decreased ($P < 0.05$) after 4 weeks on active therapy, though no significant change was appreciated after 1 week. Electrodiagnostic studies did not improve during this short study. Only 1 patient was withdrawn due to abnormal liver function tests while on valproate. Among the other patients who did not complete the study, 3 were for noncompliance (1 active arm, 2 placebo arm) and 2 due to lack of effect (placebo arm). Sodium valproate appears safe and effective for the management of DPSN.

COMMENTARY

Why do some diabetics develop painful sensory neuropathy while in others the neuropathy is painless? Ten painful sensory neuropathy diabetics were matched with 10 diabetics with nonpainful sensory neuropathy for age, diabetes duration, insulin regimen, duration of neuropathy, and HbA1c. All were fitted with a continuous glucose-monitoring system (MiniMed Inc., Sylmar, Calif, US) for 3 days to determine if a relationship existed between glucose fluctuations and painful neuropathy. Patients with other causes for foot pain, including arterial disease, skin ulcers, or arthritis were excluded. Daily pain scores were recorded by the patients on a horizontal 10 cm scale. Analgesics were allowed as needed. Glucose excursions were measured as a mean amplitude over 24 hours and M-values, a quantitative measure of blood glucose deviations over a specified time period, were calculated.[1] Spearman's rank correlation coefficient and the Mann-Whitney U-test provided statistical analysis.

Frequency of glucose excursions, mean glucose value, and mean M-value were significantly greater in the painful neuropathy group compared to the painless group. However, the mean amplitude of glucose excursion did not differ between groups and no correlation was appreciated between episodes of pain and number or amplitude of glucose excursions. Greater glucose flux is associated with painful, rather than painless, neuropathy in diabetics. — **MICHAEL RUBIN**

Reference

1. Service FJ, et al. *Diabetes*. 1970;19:644-655.

A New Treatment for Left Spatial Neglect After Stroke

ABSTRACTS & COMMENTARY

Sources: Schindler F, et al. Neck muscle vibration induces lasting recovery in spatial neglect. *J Neurol Neurosurg Psychiatry*. 2002;73:412-419; Robertson IH. Editorial commentary: Brain rehabilitation. Cognitive neuroscience and brain rehabilitation: A promise kept. *J Neurol Neurosurg Psychiatry*. 2002;73:357.

An impaired response to contralateral space following right cerebral stroke causes patients to behave as if the left half of the world did not exist, which limits their potential to benefit from standard rehabilitation techniques. Therefore, to reduce neglect symptoms, various alternative techniques have been used including: attention training,[1] vestibular stimulation,[2] neck muscle vibration,[3] prism adaptation,[4] as well as others.

Schindler and colleagues in Munich evaluated whether visual exploration training alone or in combination with electromechanical vibration of the left neck muscles of patients while they engaged in visual search exercises were effective techniques for the rehabilitation of spatial neglect. They studied 2 matched groups each of 10 right-handed ischemic stroke patients with moderate-to-severe left hemiparesis and persistent neglect. After a baseline of 3 weeks to allow for spontaneous recovery, half of the patients received 15 sessions of visual exploration training. In the second phase, this treatment was combined with neck muscle vibration. The other half of the treatment group received the treatment in reverse order.

The effects of treatment were assessed with respect to different aspects of the neglect disorder, such as impaired perception of the body's normal coordinate frame of reference exploration deficits in visual and tactile modes and visual size distortion. The transfer of treatment effects of activities of daily living was tested by reading a questionnaire. Variables were measured at baseline, post-treatment, and after 2 months.

Combination treatment produced a marked and lasting reduction in visual neglect that transferred to the tactile mode and thus had practical benefits in real life. Schindler et al explained the positive results of neck muscle vibration on visual and tactile exploration in patients with neglect in terms of an effect on the "egocentric reference system for spatio-motor transformation by generating a corrective head-on-trunk signal."

COMMENTARY

Schindler et al compare the effect of their contralesional electromechanical neck muscle stimulation with standard contralesional caloric vestibular canal stimulation. Remember the mnemonic for the direction of caloric-induced nystagmus, COWS: Cold Opposite-Warm Same. Neck muscle stimulation seems easier to perform than warm water irrigation of the left external auditory canal and doesn't induce vertigo or vomiting.

As pointed out by Robertson in his editorial, Schindler et al have done something implausible: applied a vibrator temporarily combined with 15 treatment sessions over 3 weeks and obtained lasting results in a condition considered by many to be untreatable. If the results are validated by other groups, then Schindler et al will have made a significant contribution to the well being and recovery of stroke patients.

— **JOHN J. CARONNA**

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2. Rubens AB. *Neurology*. 1985;35:1019-1024.
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4. Frassinetti F, et al. *Brain*. 2002;125:608-623.

CME Questions

16. New treatment for spatial neglect following right hemisphere stroke include:

a. right neck muscle stimulation.
b. ice water irrigation of the right ear.
c. warm water irrigation of the right ear.
d. ice water irrigation of the left ear.
e. left neck muscle stimulation.

17. The Clock Drawing Test offers all of the following *except*:

a. rapid administration.
b. quantitative scoring.
c. good inter-rater reliability.
d. sensitivity to very mild dementia.

18. Painful diabetic neuropathy appears *not* to be associated with:

a. response to valproate.
b. more frequency glucose excursions.
c. higher mean glucose value.
d. women more than men.
e. None of the above

In Future Issues:

Phantom Sensations from Congenitally Absent Limbs

PHARMACOLOGY WATCH

FDA Approves Generic Version of AstraZeneca's Prilosec

The FDA has approved the first generic version of AstraZeneca plc's blockbuster drug, omeprazole (Prilosec). KUDCO, a subsidiary of Germany's Schwartz Pharma was granted the approval in a court ruling in mid-October. The FDA has cleared a number of other generic versions of the drug; however, this is the first, in the eyes of the courts, that does not infringe on patents held by AstraZeneca. In a complicated set of deals, KUDCO is partnering with Andrix Pharmaceuticals and Genpharm Inc to bring the drug to market by early 2003. Prilosec, with worldwide sales of more than $4 billion a year, has been the focus of intense legal wrangling as AstraZeneca has pulled all the stops to prevent marketing of generic forms of the drug. Meanwhile, consumer groups hoping to bring down the cost of prescription medications have been urging the Bush administration to speed generics, such as omeprazole, to market. The FDA has approved omeprazole for over-the-counter use but is still working with AstraZeneca on labeling language. Consumers can expect OTC Prilosec in the second quarter of next year.

Pegasys Approved To Treat Hepatitis C

A second pegylated interferon has been approved for the treatment of chronic hepatitis C infection. F. Hoffmann-La Roche Ltd's peginterferon alfa-2a (Pegasys) will compete with Schering-Plough's peginterferon alfa 2-b (PegIntron) for this indication. It is estimated that nearly 4 million Americans have evidence of infection with hepatitis C, of which nearly 3 million have chronic hepatitis C infection. In the last few years, standard treatment has become interferon either standard or pegylated, alone or in combination with ribavirin. Standard interferon must be given 3 times a week. Adding polyethylene glycol (PEG) to the interferon molecule increases the elimination half-life, allowing for less-frequent dosing, generally once a week. Pegasys is approved only as monotherapy; however, Schering-Plough has applied for approval of combination therapy with Pegasys and ribavirin. The FDA has fast-tracked the application, with final approval expected before the end of year.

HRT Reduces Alzheimer's Risk, Study Says

Yet another study has weighed in on the issue of hormone replacement therapy and the risk of Alzheimer's disease (AD). This study of a population of older adults in Cache County, Utah showed that 10 years or more of HRT significantly reduced the risk of Alzheimer's disease. Importantly, the study also showed that once women are in the early stages of Alzheimer's disease, it is too late for HRT to have any benefit. The rate of AD was evaluated in 1357 men (median age, 73.2 years) and 1889 women (mean age, 74.5 years). After a 3-year follow-up, women who formerly used HRT or women who are currently using HRT for longer than 10 years had a statistically significant reduction in the rate of AD (HRT users represented 26 cases/1066 women, non

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HRT users represented 58 cases/800 women [adjusted HR, 0.59; 95% CI, 0.36-0.96]). Almost all the HRT-related reduction in the incidence of AD was among women who had formerly used HRT. A related editorial suggests that there may be a critical period soon after menopause, which is characterized by rapid estrogen depletion, where HRT may provide the most neuroprotective benefit for women (*JAMA*. 2002;288:2123-2129, 2170-2173). In mid-October officials from the National Institutes of Health announced that they would continue to study the effects of HRT or conditions such as osteoporosis and AD. This announcement was important in light of the early termination of the Women's Health Initiative study on hormone replacement in July. Currently, the National Institute on Aging is funding 3 studies that will compare how well HRT combination therapy or estrogen alone helps prevent memory loss and loss of cognitive function in women older than 65.

Heparin Plus Alteplase More Effective

Patients with submassive pulmonary emboli (PE) will fare better treated with heparin plus alteplase compared to heparin alone, according to a new study. Alteplase, a thrombolytic agent, is commonly used in the treatment of massive PE. This study seeks to define the drug's role in submassive PE in hemodynamically stable patients. Two hundred fifty-six patients with PE and pulmonary hypertension or RV dysfunction but without arterial hypertension or shock were evaluated. One hundred thirty-eight received heparin plus alteplase 100 mg and 118 received heparin plus placebo. The primary end point was in-hospital death or treatment escalation (pressors, repeat thrombolysis, intubation, CPR, or emergency embolectomy). The primary end point occurred nearly 3 times as often in the heparin plus placebo group, all due to treatment escalation. In-hospital death was nonsignificantly higher in the heparin group, 3.4%, vs 2.2% for the alteplase group ($P = .71$). However, 30-day event-free survival was higher with heparin vs alteplase ($P = .005$). The authors conclude that thrombolytic therapy with alteplase plus heparin should be considered in patients with submassive PE (*N Engl J Med*. 2002;347:1143-1150).

Digoxin Effects Differ By Sex

Digoxin should be used with caution in women with heart failure and may even be associated with an increase in mortality, according to a new study. The Digitalis Investigation Group looked at 6800 patients on digoxin therapy with the primary end point being mortality from any cause. While there was no increased mortality in men on digoxin, women on the drug had a higher rate of death compared to the placebo group (33.1% vs 28.9%, respectively; 95% CI,-0.5-8.8). The authors conclude that the effect of digoxin therapy differs between men and women. Women with congestive heart failure of a higher mortality rate associated with use of the drug, while the same is not seen with men (*N Engl J Med*. 2002;347:1403-1411).

McClellan Named FDA Commissioner

The Food and Drug Administration finally has a commissioner, after 2 years of vacancy in the position. The new commissioner, Mark McClellan, MD, was approved quickly and unanamously. He has a background in both medicine and economics, and has been an advisor to both Presidents Clinton and Bush. He has most recently been a professor of medicine and economics at Stanford University. Dr. McClellan joins the FDA at a time of unprecedented change and turmoil. There is high turnover at the agency, and criticism from consumer groups that drug approvals take too long on the one hand, and are too cursory on the other. President Bush has recently backed removing legal obstacles to the approval of generic drugs, a move meant to reduce prices for consumers, and a move that is not popular with Pharma.

FDA Actions

The FDA has approved 2 formulations of buprenorphine, a new schedule III narcotic for treatment of patients with narcotic addiction. Buprenorphine will be marketed as Subutrex by Reckitt Benckiser pharmaceuticals, while the second preparation, which combines buprenorphine with naloxone, will be marketed by the same company as Suboxone. The combination with naloxone is intended for maintenance therapy since naloxone will safeguard against intravenous abuse. The FDA took the unusual step of putting buprenorphine into the schedule III category rather than schedule II to allow easier prescribing in compliance with recent congressional legislation making maintenance narcotics more available to patients.

Bristol-Myers has received approval to market Metaglip, a new combination drug for treatment type 2 diabetes. Metaglip combines gliptizide and metformin in a single tablet for initial therapy of type 2 diabetes. ■

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The essential monthly primary care update

By Louis Kuritzky, MD

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Daily Vitamin E and Multivitamin-Mineral Supplementation and Acute RTI in Elderly Persons

Source: Graat JM, et al. *JAMA*. 2002;288:715-721.

Vitamin supplementation has been shown to improve cellular immune parameters, but whether vitamin E or multivitamins/minerals (MVIM) have an effect on clinical events has not been clearly elucidated. Since respiratory tract infections (RTI) may become especially consequential for senior citizens, the question of whether vitamin E or MVIM alter the frequency, severity, or duration or such infections is of great clinical relevance.

Graat and associates studied the effect of MVIM, containing traditional RDA levels of multiple vitamins and minerals, including zinc, selenium, iron, magnesium, copper, iodine, calcium, manganese, chromium, molybdenum, and silicium, as well as a separate vitamin E supplement of 200 mg. Study subjects (n = 652) were comprised of noninstitutionalized persons older than age 60 who were followed for 15 months. At baseline, a very small proportion of individuals had suboptimal serum levels of either ascorbic acid (6%) or alpha-tocopherol (1.3%).

MVIM supplementation demonstrated no clinically or statistically significant effect upon RTI incidence, severity, duration, number of symp toms, or restriction of activity. Vitamin E supplementation demonstrated worse outcomes than placebo in reference to illness severity, duration, symptoms, fever, and restriction of activity. Graat et al caution that not only do their data discourage employment of MVIM due to lack of efficacy, but also due to a deleterious effect of vitamin E. ■

B-Type Natriuretic Peptide Levels and Outcome in Patients with Heart Failure

Source: Bettencourt P, et al. *Am J Med*. 2002;113:215-219.

Brain natriuretic peptide (BNP) levels reflect the degree of cardiac ventricular wall stress and are useful to diagnose chronic heart failure (CHF), as well as differentiate other dyspnea syndromes (in which BNP levels are not elevated) from CHF. BNP levels correlate with severity of CHF, hence, in any one episode of CHF, their degree of elevation might provide prognostic information. Bettencourt and colleagues examined the relationship between hospital BNP levels (on admission and discharge) in persons with acute decompensation of CHF, and subsequent hospital CHF readmission or death.

All subjects (n = 43) received "standard" CHF treatment, including diuretics (furosemide, and in some cases, spironolactone) and ACE inhibitors. Subjects were followed for 6 months.

When patients were hospitalized for CHF, BNP levels typically decreased with treatment. After hospital discharge, in the group that remained event free during follow-up, the decline in BNP during hospitalization (47%) was much more substantial than the decline in persons who required readmission (17%). Patients whose BNP increased during the index admission were more than 3 times more likely to require readmission or die during follow-up. BNP, and its response to treatment, provides important prognostic information in persons with CHF. ■

Companion Influence During Primary Care Medical Encounters

Source: Schilling LM, et al. *J Fam Pract*. 2002;51:685-690.

It is commonplace in primary care settings for patients to be accompanied by family, friends, or caretakers in the examining room during some portion or all of the clinician-patient interaction. The effect of the "third person" (3P) has received little literature scrutiny. Schilling and colleagues studied 226 adult medical encounters, approximately half of which included another accompanying adult who spent any portion of the visit in the examining room. Patients, companions, and clinicians rated the influence of the companion upon the visit. Aspects of the clinical encounter that were monitored included physician understanding, patient understanding, counseling time, length of visit, treatment, referrals, and number of tests ordered.

Physicians reported that having a companion present generally was either neutral to or increased physician and patient understanding. Almost universally, physicians perceived no effect upon treatments, referrals, or number of tests ordered whether a companion was present. On the other hand, 25-32% of physicians felt that the 3P caused an increase

in the length of visit or time spent counseling. Although overall the presence of an adult companion may enhance physician and patient understanding, it appears to be potentially at the expense of greater time required for counseling and the visit itself. ■

Efficacy of Handrubbing with Alcohol-Based Solution vs. Standard Handwashing with Antiseptic Soap: Randomized Clinical Trial

Source: Girou E, et al. *BMJ*. 2002; 325:362-365.

Handwashing (HWS) is generally recognized as the single most influential factor to reduce transmission of nosocomial infections. Unfortunately, studies indicate that half or less of clinicians comply with appropriate HWS recommendations. Despite interventions to increase adherence with handwashing (eg, more sinks, educational programs), results have been disappointing. Although handrubbing with alcohol (HRA) is suggested as an alternative to HWS, its acceptance has been impeded by lack of clinician confidence that an alcohol based, waterless hand antiseptic is sufficiently effective in reducing bacterial contamination.

Girou and associates performed a prospective, randomized, blinded trial in 3 intensive care units. Subjects (health professionals) were randomly assigned to chlorhexidine 4% (Hibiscrub) or handrubbing with an alcohol- based solution. Hand cultures were performed immediately before, and 1 minute after cleansing.

Both maneuvers were effective in reducing bacterial contamination, but HRA was substantially more effective (83% vs 58% reduction in contaminating bacteria). HWS and HRA occupied essentially the same mean amount of time (about 30 seconds). Previous in-vitro studies have shown that HRA is more effective than soap. Incorporation of HRA may enhance control of nosocomially transmitted infections but may require enhanced clinician education for endorsement. ■

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A Program To Prevent Functional Decline in Physically Frail, Elderly Persons Who Live at Home

Source: Gill TM, et al. *N Engl J Med*. 2002;347:1068-1074.

Most literature that addresses restoration of function in elders focuses upon rehabilitation of persons who have recently suffered a morbid event, such as a stroke or hip fracture. Whether other frail elders might benefit from 'prehabilitation' strategies is little studied. To that end, Gill and colleagues recruited a population (n = 188) of seniors (> age 75) who were defined as "frail" by means of a rapid-gait test and a mobility test (ability to rise from a chair with arms folded).

The intervention program included instructions in safe techniques for moving in bed and outdoors, gait training, removal of environmental hazards (eg, loose rugs, cords, clutter) and installation of adaptive equipment in bathrooms. Interventions were monitored for 16 visits over 6 months, with last follow-up at 12 months.

The recipients of the home intervention had significantly less disability and less admission to a nursing home. Interventions included the service of a physical therapist, but the entire mean cost of intervention, including equipment and supplies, was $1998 per participant. The subjects who suffered severe disability at baseline continued to experience deterioration over time, despite receiving the same interventions. Gill et al comment that though the frequency of physical therapy visits is in excess of that allowed for reimbursement by Medicare, the overall cost-per-patient is comparatively moderate. ■

Treatment of Chronic Painful Diabetic Neuropathy with Isosorbide Dinitrate Spray

Source: Yuen KCJ, et al. *Diabetes Care*. 2002;25(210):1699-1703.

Painful diabetic neuropathy (PDN) is a troublesome and often refractory clinical dilemma. Nitric oxide (NO) production is impaired in PDN and is suspected of playing a pathogenetic role in producing pain and burning. All clinical formulations of nitrates are NO donors. Based upon anecdotal observations that individual PDN patients reported a favorable effect of isosorbide dinitrate (ISDN) spray on pain symptoms, Yuen and colleagues initiated a formal clinical trial.

Patients (n = 22) had all suffered chronic PDN and had failed traditional treatments, such as acetaminophen, amitriptyline, or gabapentin, either due to lack of efficacy, intolerance, or both. The trial was structured such that patients received either 40% propylene glycol (placebo) or 30 mg isosorbide dinitrate (1 spray) QHS in a double-blind crossover fashion for 2 sessions of 4 weeks each, punctuated by a 2-week washout period.

Use of ISDN spray produced a statistically significant reduction in pain and burning. Side effects (transient headache) were mild. ISDN may be of value in treatment of PDN, perhaps through a mechanism of increased delivery of NO. ■