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INSIDE

A Novel Treatment for Parkinson's Disease With Remarkable Results

ABSTRACT & COMMENTARY

Source: Gill SS, et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. *Nature Medicine* advance online publication. www.nature.com.

A NUMBER OF NEUROTROPHIC FACTORS HAVE GREAT PROMISE for the treatment of neurologic diseases. Prior work showed that a number of neurotrophic factors appeared to have promise for treating ALS, as well as peripheral neuropathy. Unfortunately, the initial trials with several factors failed in ALS, and a trial of nerve growth factor in diabetic neuropathy also was unsuccessful. The present trial describes the effects of glial cell-line derived neurotrophic factor (GDNF) in 5 Parkinson's patients. The rational for examining glial neurotrophic factor is that it is one of the most potent growth factors that supports dopaminergic neurons. A large body of preclinical evidence had demonstrated that glial-derived neurotrophic factor will exert both neuroprotective effects, as well as neurorestorative effects, in animal models of Parkinson's disease. Neuro-restoration refers to regrowth of dopaminergic terminals, thereby restoring function by enhancing the function of the residual neurons. GDNF has been previously administered both in rodents and primates. In particular, a trial studying the effects of lentivirus-delivered GDNF showed marked neuroprotective effects in the model of Parkinson's disease in primates.

A previous trial used GDNF administered intraventricularly in Parkinson's disease patients; it was unsuccessful. Patients also had significant side effects, and there was no evidence of restoration of dopamine fibers in the striatum in 1 subject studied post-mortem. It was theorized that this lack of efficacy was because of an insufficient concentration of GDNF reaching the relevant structures. In the present study, the direct effects of infusion of GDNF into the putamen of 5 Parkinson's patients was therefore studied in a phase 1 safety trial. Gill and associates demonstrate remarkable improvement. The drug was infused by means of a catheter localized to the dorsal lateral putamen, which is the site that shows the greatest loss of dopaminergic fibers in Parkinson's disease. In several patients there was increased T2 signal around the tip of the catheter. This was dis-

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sipated following a reduction in the infusion rate. There were no other serious side effects. There was no nausea, anorexia, vomiting, or weight loss, which had been seen in the previous intraventricular trial. The only consistent side effect was Lhermitte's phenomenon, consisting of tingling passing from the neck down to the arms and sometimes to the trunk.

The patients were examined at 3, 6, and 12 months after the infusions. Periods of severe immobility that had occupied approximately 20% of the waking day before surgery were eliminated completely after 6 months of GDNF infusion. The overall improvement of the UPDRS scale, a widely used and validated scale for assessing functional changes in Parkinson's disease, showed a 39% improvement in the motor subscore after 1 year. There was a 61% improvement in the activities of daily living subscore. The improvement persisted throughout the trial. Another remarkable effect in the trial was that dyskinesias improved markedly in 4 patients. There were no increases in dyskinesias in the patients when they were off medication, which contrasts with the fetal transplant studies. Timed motor tests were improved in both the off- and on-medication states. An unexplained finding was an improvement in smell and taste. There were no effects on cognitive function. Gill et al also examined [^{18}F]dopamine PET scan changes. They observed that immediately surrounding the catheter there was a 28% increase in putamen dopamine storage after 18 months, whereas in the remaining putamen there was a continuing decline in dopamine.

COMMENTARY

This is an extraordinary report and extremely exciting finding. The results in such a small number of patients are phenomenally good. It suggests that GDNF may have neuroprotective and neurorestorative effects in Parkinson's disease patients. This raises the possibility that this type of strategy may be applicable to other neurodegenerative diseases. It is also possible that GDNF or other growth factors could be administered by gene therapy or by transplantation of neural-stem cells secreting GDNF. In fact, one of the authors is presently evaluating this strategy. In summary, this is one of the most exciting recent reports on potential novel treatments for an otherwise inexorably progressive neurodegenerative illness.

— M. FLINT BEAL

Memantine for Advanced Alzheimer's Disease

ABSTRACT & COMMENTARY

Source: Reisberg B, et al. Memantine for advanced Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341.

CURRENTLY, THERE ARE NO MEDICATIONS SPECIFICALLY approved in the United States for treatment of the advanced stages of Alzheimer's disease (AD). Results of the first US large-scale, prospective, double-blind study of memantine in the treatment of moderate-to-severe AD indicate that memantine-treated advanced AD patients fare better than those who received placebo, with no significant treatment-related side effects.

Memantine is an inhibitor of the postsynaptic N-methyl-D-aspartate (NMDA) receptor, which modulates calcium transport into neurons. Overstimulation of NMDA receptors by the excitatory neurotransmitter glutamate may cause excitotoxic damage to neurons and has been implicated in the pathogenesis of various degenerative disorders, including AD. Memantine reportedly limits glutamate-mediated excitotoxic damage, while permitting lower levels of NMDA activity that facilitate memory processes. These effects provided a biological rationale for the study of memantine as a potential treatment for AD.

The 32-center US trial enrolled 252 AD patients with

Neurology Alert, ISSN 0741-4234, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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a mean age of 76 years in a 28-week study comparing 10 mg b.i.d. of memantine to placebo. Primary outcome measures included a clinician/caregiver estimate of global response (CIBIC-plus) and an assessment of capacity to carry out daily activities (ADCS-ADL). Several secondary measures of cognitive function and behavior were examined using test instruments appropriate to the advanced stages of AD. Safety, as well as efficacy of treatment, was examined.

Of the 252 patients enrolled, 181 (72%) completed the trial, with fewer dropouts occurring from the memantine group (29) than among the controls (42). The most robust primary treatment response was seen on the measure of daily function (ADCS-ADL), which showed significantly better outcome in the memantine-treated patients than controls. A trend toward better outcome ($P = .06$) on the global outcome measure (CIBIC-plus) was seen in an intend-to-treat type analysis, which reached significance ($P = .03$) when the analysis was restricted to those who actually completed the study. Among the secondary outcome measures, the cognitive assessment instrument (SIB) and a measure of the stage of disease (FAST) showed a significant benefits in association with memantine treatment. Other measures, such as the Minimental State Exam, Global Deterioration Scale and the Neuropsychiatric Inventory were not significantly different between memantine and placebo groups.

As in other studies carried out in the elderly AD population, a majority of patients (85%) had 1 or more adverse events during the study. However, there were no significant differences in the frequencies of adverse events in the memantine group (106) vs placebo (109). Likewise, there were no serious adverse events related to memantine treatment.

COMMENTARY

Memantine is not a new treatment for AD. It has been approved in Germany for treatment of dementia for more than a decade and throughout the European Union since May 2002. It is marketed in Germany under the trade name "Axura" and throughout the rest of Europe as "Ebixa." In Germany, where experience with memantine is the most extensive, this agent is used to treat all stages of AD, as well as a variety of other forms of dementia.

The value of using a medication that brings about only a mild symptomatic improvement to treat advanced stages of AD is controversial. A handful of studies have suggested that patients with moderate-to-severe AD (and their caregivers) may benefit from treatment with cholinesterase inhibitors. It is more difficult to establish efficacy in advanced AD than milder stages because more severely affected patients often perform at the floor of the measures traditionally used for AD pharmacological studies, such as the ADAS-cog. The memantine trial used measures such as the SIB that are normed for severely impaired patients, to some extent circumventing this difficulty. The 0.3 point difference on the CIBIC-plus observed between memantine and placebo approached statistical significance but may not be clinically significant. Improvements on the Severe Impairment Battery and the ADCS-ADL functional scale are numerically more impressive and suggest that memantine may provide meaningful benefits in the treatment of advanced AD.

In the United States, the mainstay of treatment for AD are the acetylcholinesterase inhibitors (AchEIs). Since memantine acts via a completely different mechanism than AChEIs, combined use of memantine and cholinesterase inhibitors is under study. Preliminary results of a study recently presented at the 2003 American Academy of Neurology meeting (Farlow, et al. 48.003) suggested good safety and added efficacy when memantine is used in combination with the cholinesterase inhibitor donepezil.

Memantine is now under consideration by the FDA for approval in the United States as a monotherapy for AD. Since there are no approved therapies for advanced AD in the United States, memantine could gain a strong foothold in the AD pharmaceutical market if it receives the FDA's nod for this indication. It seems likely based on the European experience that use in mild-to-moderate AD, as well as in combination with cholinesterase inhibitors, would quickly follow. With its relatively benign side effect profile and long-standing track record of successful use in Germany, this agent has excellent potential for approval as the next treatment for AD in North America. — **NORMAN R. RELKIN**

Predictors of Disability in MS

ABSTRACT & COMMENTARY

Source: Confavreux C, et al. Early clinical predictors and progression of irreversible disability in multiple sclerosis: An amnesic process. *Brain*. 2003;126:770-782.

Confavreux and colleagues studied 1844 multiple sclerosis (MS) patients enrolled in a large European database up until 1997. Clinical variables were identified early in the course of the disease, and their continued prognostic significance was determined after the first stages of irreversible neurological disability. They used 3 scores on the Kurtzke Disability Status

Scale as benchmarks of accumulated disability: EDSS 4 (limited walking but without cane); 6 (walking with unilateral aid); 7 (wheelchair restricted). Median times from onset of MS to assignment of a score of 4, 6, and 7 were significantly influenced by gender, age, symptoms, course (relapsing-remitting or progressive), time of onset of disease, degree of recovery after the first relapse, time to a second neurological episode, and the number of relapses in the first 5 years of disease. The median time from onset of MS to assignment of a score of 4, 6, and 7 was 8.4 years, 20.1 years, and 29.9 years, respectively. The median interval to reach landmarks of disability was significantly longer in females than males and inpatients with a younger age of onset. The interval was also longer in those with an initial relapsing-remitting course (85% of the patient cohort) vs a progressive one (15%); those with a complete rather than incomplete recovery; and those with a longer time from onset of MS to a second neurological event.

Times to assignment of a score of 6 or 7 were also influenced by the time interval from onset of MS to a score of 4. Those with a slower progression to 4 showed a delayed progression to 6 or 7. The median intervals to progression were longer in cases presenting initially with isolated optic neuritis, intermediate in cases presenting with isolated brainstem dysfunction, and shorter in patients presenting with dysfunction of long tracts. None of the assessable clinical variables substantially affected the time from a score of 4 to 6 or 7, or from a score of 6 to 7. Thus, the early clinical variables significantly influenced the time from the onset of MS to the assignment of a disability score of 4 but not the subsequent progression of disability to 6 and 7. Similarly, the total number of relapses in the first 5 years did not appear to affect the intervals to later progression to scores of 6 and 7.

Approximately half of the 1844 patients in the cohort received immunosuppressive drugs at some time in their disease course for at least 6 months, usually in the relapsing phase but not before the third relapse (mean of 6.2 years from onset of MS). The most widely used treatment was azathioprine (804 patients), followed by cytoxan (78), interferon beta (72), methotrexate (60), and mitoxantrone (18). Only azathioprine had a minor benefit in increasing the interval from onset of MS to assignment of a score of 4 but not subsequent scores of 6 or 7.

COMMENTARY

The long-term clinical disability information generated from the large cohort in this MS database is consistent with other studies and our own clinical impressions about disease progression in MS. Thus, Confavreux and colleagues verify prior studies that have consistently shown it takes longer to reach landmarks of irreversible disability in younger female patients with relapsing disease, patients presenting with optic neuritis, and patients with fewer relapses in the first years of disease. Their original contribution is that determining that these same good prognostic clinical variables up to an EDSS of 4 did not seem to remain predictive of the time course of disability past 4 to landmarks of 6 and 7. Their data support the concept that disability progression in MS may be a 2-stage process, the initial phase of variable duration occurring in the relapsing period of the disease that is influenced by the above clinical phenotypes, and a second phase that is more invariant to these baseline parameters at the onset of the disease. The time period from onset to a score of 4 takes place mainly in the relapsing phase, whereas subsequent accumulation of irreversible disability develops during the progressive phase. There is undoubtedly a biological explanation for the invariant course of later disability: Relapses represent recurrent focal inflammation, whereas progression signals a more chronic, diffuse neurodegeneration. One limitation of this study is that all of the data were generated prior to the more widespread use of interferon beta after 1997, which has been shown to favorably modify the natural history of disease. Nonetheless, their findings have implications for the design of future therapies targeting the later stages of disease that may signal progressive cell death in the central nervous system and inexorable disability. — **BRIAN R. APATOFF**

A Negative Trial of Creatine in ALS

ABSTRACT & COMMENTARY

Source: Jan Groeneveld G, et al. A randomized sequential trial of creatine in amyotrophic lateral sclerosis. *Ann Neurol*. 2003;53:437-445.

This is the first reported clinical trial of the effects of creatine in sporadic ALS patients. The trial was carried out in The Netherlands. The rationale for the trial was based on work done by my laboratory. We demonstrated that creatine had significant effects in improving survival and preventing loss of motor neurons in a transgenic mouse model of ALS, in which human mutated Cu,Zn-superoxide dismutase (mSOD1) is overexpressed. In that animal study, administration of creatine starting at 50 days of age prolonged survival by 26 days, which was markedly better than the effects of riluzole. The

present clinical trial was a double-blind, placebo-controlled, sequential clinical trial. The primary end points were death, persistent assisted ventilation, or tracheotomy. Secondary outcome measurements were the rate of decline in isometric arm muscle strength, forced vital capacity, functional status, and quality of life. The trial was terminated when 34 patients had died and the sequential monitoring of the statistics suggested that there was no difference in the null hypothesis between the 2 treatment arms. Jan Groeneveld and associates did observe a slightly slower decline in arm strength and in vital capacity at 1 month. Otherwise, no significant benefits occurred. There were no significant adverse effects. The dose used was 10 g daily. This is consistent with the doses that were effective when used in mice. These doses were 1 or 2% creatine in the diet, which correspond to 6-12 g daily in humans.

COMMENTARY

These results are extremely disappointing. The results with creatine in the transgenic mouse model have been replicated by numerous groups. This suggests that studying this transgenic mouse model, which represents mutations found in a small percentage of familial ALS patients, may not be predictive of clinical efficacy in sporadic ALS patients. Whether this conclusion is generally valid remains to be proven. At present, trials of minocycline, as well as Celebrex®, in sporadic ALS are ongoing. Both of these agents have been shown to have significant therapeutic benefits in the transgenic mouse model of ALS. There are also 2 further trials of creatine under way in the United States, and it will be interesting to see the outcome of these efforts. The present results, however, suggest that caution is needed in extrapolating results in certain transgenic mouse models caused by mutations that occur in a very small proportion of ALS patients. One expects that this will not be the case with other transgenic mouse models, such as Huntington's disease, where a common genetic defect occurs in all patients. **— M. FLINT BEAL**

Silent Strokes Predispose to Dementia

ABSTRACT & COMMENTARY

Source: Vermeer SE, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348: 1215-1222.

THERE IS LITTLE DOUBT THAT CEREBROVASCULAR disease is a major contributor to cognitive decline in the elderly. Recurrent symptomatic strokes affecting cortical or subcortical function inevitably result in a stepwise burden of accumulating damage and disability. Less clear, however, is a possible relationship between silent brain infarcts as diagnosed incidentally on MRI and a risk for the subsequent development of dementia.

In the Rotterdam Scan Study, 1015 elderly participants were followed prospectively over a 4-year period to correlate the presence of ischemic brain injury on an initial MRI with their subsequent risk of developing dementia. All participants were free of dementia at baseline, and any patient with a known history of stroke was excluded. The entire cohort was analyzed for the development of dementia, but only 75% were available for subsequent detailed mental status examination and/or MRI primarily due to the death or institutionalization of more than 100 enrollees.

Thirty participants developed dementia; of these, 14 had 1 or more silent infarcts on initial MRI scan, and 7 had multiple infarcts. The presence of silent brain infarcts at baseline increased the risk of dementia more than 2-fold (hazard ratio, 2.26), even when controlling for other MRI findings, such as periventricular or subcortical white matter lesions or brain atrophy. White matter disease also predicted dementia, although less powerfully, with a hazard ratio of 1.59 for periventricular and 1.21 for subcortical disease.

Among those participants who underwent a follow-up MRI scan, strokes appeared in 7/30 (23%) who became demented (3 symptomatic, 4 silent) compared with 79/618 (12%) who did not develop dementia (1 symptomatic, 71 silent). Documented decline in memory as measured by neuropsychiatric testing was restricted to patients with new infarcts, whether they had baseline silent strokes or not. Strokes in the thalamus were more likely to produce cognitive effects than in other locations. Dementia was diagnosed as Alzheimer's disease (AD) in the majority (26/30), while vascular dementia was only identified in 2/30.

As Vermeer and colleagues note, this study did not focus on subtypes of dementia, but rather an overall association between silent vascular disease and cognitive loss. They postulate that there may be a direct association between ischemia and the development of Alzheimer's pathology (plaques and neurofibrillary tangles) or alternatively, ischemia may unmask otherwise mild cases of AD.

COMMENTARY

Dementia nomenclature can be confusing, especially as it relates to cerebrovascular disease. Patients with vascular damage may be diagnosed as suffering from strate-

gic infarct dementia, multi-infarct dementia, or merely vascular dementia. Those with severe hypertension might be labeled as Binswanger's disease or may be thought to have white matter changes consistent with "leukoariosis." Additional overlap between these vascular diagnoses and AD pathology further muddies these classifications. From a practical therapeutic standpoint, however, acetylcholinesterase inhibitors, such as donepezil, should be considered for all patients regardless of subtype. Given the likely heterogeneous factors at work, it is not surprising that these agents appear to improve memory in patients thought to have AD, vascular-type disease, or some mixture of the 2.

Middle-aged and elderly patients who undergo MRI not for dementia, but often for unrelated reasons, are frequently discovered to have ischemic-type disease, whether lacunar strokes in deep gray matter structures or more nonspecific white matter hyperintensities. While such findings are still not cause for alarm in the majority of patients, the Rotterdam study reminds us that they are not benign and should motivate a comprehensive program of vascular risk factor reduction (including, but not limited to, control of lipid and blood pressure, and smoking cessation) as well as antiplatelet therapy such as daily baby aspirin. — **ALAN Z. SEGAL**

Perioperative Ulnar Neuropathy: Fact or Fiction?

ABSTRACT & COMMENTARY

Source: Stewart JD, Shantz SH. Perioperative ulnar neuropathies: A medicolegal review. *Can J Neurol Sci*. 2003;30:15-19.

CONSIDER THIS ALL-TOO-FAMILIAR SCENARIO. PATIENT X awakens from otherwise uneventful abdominal surgery and complains of ulnar nerve distribution weakness or tingling, or both. Ulnar neuropathy at the elbow (UNE) is documented, litigation ensues, and large sums of money exchange hands. Who is guilty and of what?

In a thoughtful and thorough review of the medicolegal literature, Stewart and associates highlight several important facts, often overlooked, concerning the above hypothetical. First and foremost, despite widespread adherence to decades-old wisdom and recommendations for preoperative positioning intended to prevent UNE, its incidence has not declined, suggesting that prepositioning does not protect the ulnar nerve. Secondly, among 22 peri-operative UNE patients, only 5 were aware of their symptoms on waking from anesthesia, with another 3 noting the problem on postoperative day 1.[1] Most noted the onset during the first week (n = 10) or 2-4 weeks later (n = 4). Retrospective analysis of surgical cases at the Mayo Clinic (n = > 1.1 million) found UNE in 414 patients (0.04%) with most symptoms beginning > 24 hours post-operatively.[2] Persistent UNE was seen mostly in men (70%), with other risk factors being diabetes, older age, > 2 weeks of hospitalization, and either a very thin or obese body habitus. Strikingly, neither duration of surgery or anesthesia nor patient position was associated with UNE. Complete recovery was seen in 53% by 1 year. In a prospective follow-up study,[3] Warner et al studied 1502 adult surgical patients, excluding those with prior history of UNE or those undergoing cardiac surgery, the latter to prevent confusion with brachial plexopathy, a known complication of cardiac surgery. Only 7 (0.5%) developed UNE, and male gender was found to be the only risk factor. None experienced symptoms prior to postoperative day 2, and all began during the first week. Six were mild and purely sensory. Significantly, all had been padded for prevention of UNE. These findings indicate that peri-operative UNE may be postoperative in nature and related to convalescing in the recumbent position with leaning on the elbows. This possibility was underscored when Warner et al similarly found 2 UNE among 990 nonsurgical hospitalized medical patients.[4] And do not presume that postoperative patients are sedated and thus unable to report UNE early on. Among 991 patients with postsurgical lower limb neuropathy, symptoms were reported within 4 hours of completing anesthesia,[5] indicating that the late(r) reporting of UNE is due not to surgery but to its onset and causation during the recovery period. Judges should throw out lawsuits brought against surgeons for a presumed intraoperative UNE complication.

COMMENTARY

Electrodiagnosis of UNE may itself be a challenging exercise. Guidelines were recently developed by the Quality Assurance Committee of the American Academy of Electrodiagnostic Medicine and the Quality Standards Subcommittee of the American Academy of Neurology (AAN) and endorsed by the AAN and the American Academy of Physical Medicine and Rehabilitation, to address this issue.[6] These included:

Electrodiagnosis of UNE may be made on the basis of one or more of the following:

1. Slowed conduction velocity across the elbow to below 50 m/s;
2. Slowed conduction velocity across the elbow by more than 10 m/s compared to the below elbow segment;

3. A > 20% drop in compound muscle action potential (CMAP) amplitude across the elbow (remember to exclude a Martin-Gruber anastomosis); or
4. A significant change in CMAP configuration across the elbow (but note that significant is not defined).

When the diagnosis remains uncertain:

1. Record from the first dorsal interosseous (FDI) muscle;
2. Use the inching technique to look for latency, CMAP amplitude, and configuration changes;
3. Compare conduction velocity across the elbow to that between axilla and elbow; and
4. When desperate, try recording from forearm ulnar muscles.

Remember to use needle electromyography, if warranted, to exclude a more widespread, or second, lesion. — **MICHAEL RUBIN**

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NSAIDS: Not Associated With Cerebral Hemorrhage but not Protective vs Ischemic Stroke

ABSTRACTS & COMMENTARY

Sources: Bak S, et al. Risk of stroke associated with nonsteroidal anti-inflammatory drugs. *Stroke*. 2003;34:379-386; Johnsen SP, et al. Nonaspirin nonsteroidal anti-inflammatory drugs and risk of hospitalization for intracerebral hemorrhage. *Stroke*. 2003;34:387-391.

Inhibition of thromboxane A2 synthesis by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) underlies the risk of bleeding complications associated with their use. Aspirin use is associated with a reduced risk of thrombotic events and possibly an increased risk for intracerebral hemorrhage (ICH).[1] Therefore, exposure to NSAIDs also might increase the risk of ICH and decrease the risk of ischemic stroke.

Bak and colleagues used a population-based patient registry to identify all patients with a hospital discharge diagnosis of first stroke in 1 county in Denmark. They compared the use of NSAIDs in patients (659 with ICH, 208 with subarachnoid hemorrhage [SAH], 2717 with ischemic stroke) and in 40,000 controls randomly selected from the same county. Information regarding use of NSAIDs and other medications was determined from the prescription registry. The analysis was adjusted for potential confounding medical conditions including hypertension, diabetes mellitus, and hyperlipidemia.

Current exposure to NSAIDs did not increase the risk of ICH or SAH and offered no protection against first-ever ischemic stroke.

In another unrelated Danish study, Johnsen and associates used data from a county hospital patient register to identify 912 cases of first ICH and 9059 sex- and age-matched population-based controls. All prescriptions for NSAIDs before the date of admission for ICH were identified through a prescription registry. Analysis was adjusted for potential confounding factors including medical diagnoses and medications. Patients prescribed nonaspirin NSAIDs were not at an increased risk of being hospitalized for ICH. This finding was true for all subgroups, including the elderly and patients with a previous discharge diagnosis of hypertension.

COMMENTARY

The studies of Bak and Johnsen support the findings of previous studies. Thrift and associates[1] examined the association between the use of aspirin and other NSAIDs and ICH. Low-dose aspirin or other NSAID use was not associated with ICH. Aspirin in doses greater than 1225 mg/wk (175 mg/d), however, was associated with an increased risk for ICH. Saloheimo and colleagues reported similar results.[2]

Therefore, based on present evidence, NSAIDs other than aspirin can be prescribed for patients without increasing their risk of ICH.

The failure of NSAIDs to protect against ischemic stroke is not surprising. In contrast to even low-dose aspirin, conventional NSAIDs inhibit cyclo-oxygenase (COX)-1 in an incomplete and reversible fashion, which may not be sufficient to effectively inhibit thromboxane A2 biosynthesis. Through their effect on COX-2, NSAIDs also inhibit the biosynthesis of prostacyclin I2, a platelet inhibitor and vasodilator. It is not known, however, whether the absent antithrombotic effect of NSAIDs is due to the incomplete inhibition of COX-1 or to the concomitant inhibition of COX-2.

Clinicians have been aware that an interaction between aspirin and NSAIDs exists[3] and that when used in combination, NSAIDs may antagonize the protective

effects of aspirin in patients with established cardio- or cerebrovascular disease. MacDonald and Wei[4] found an increased mortality in patients with a hospital discharge diagnosis of cardiovascular disease who used aspirin plus ibuprofen compared with users of aspirin alone. They did not adjust for potentially confounding medical conditions, which renders their results inconclusive but still of cautionary value. Based on present information, clinicians should advise their patients taking aspirin for secondary protection to limit their use of NSAIDs or avoid them altogether. — **JOHN J. CARONNA**

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CME Questions

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13. All of the following are true about memantine *except*:
a. it is a selective NMDA agonist.
b. it improves cognition and function in advanced AD.
c. it has very few side effects.
d. it has a different mechanism of action that cholinesterase inhibitors.

14. Good prognostic indicators at the onset of multiple sclerosis to delay the time to EDSS 4 include the following *except*:
a. female sex.
b. degree of recovery from the first attack.
c. optic neuritis.
d. fewer attacks in the first 5 years.
e. long tract signs.

15. Which of the following contribute to the development of dementia?
a. Lacunar stroke
b. Subcortical white matter disease
c. Periventricular white matter disease
d. Neurofibrillary plaques and tangles
e. All of the above

16. Ulnar neuropathy at the elbow in the postoperative patient:
a. occurs more often in women than men.
b. is almost never seen in the obese who have a lot of "natural padding."
c. is more likely due to a postoperative, rather than an intra-operative, etiology.
d. All the above are true
e. All the above are false

17. Which of the following statements is true? NSAIDs:
a. increase the risk of ICH.
b. reduce the risk of ICH.
c. increase the risk of ischemic stroke.
d. reduce the risk of ischemic stroke.
e. None of the above

Answers: 13(a); 14(e); 15(e); 16(c); 17(e)

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **At the end of the testing period, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a certificate of completion.** When your evaluation is received, a certificate will be mailed to you.

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Neurology Alert*. Send your questions to: Christie Messina—Reader Questions, *Neurology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■

In Future Issues: **Machado-Joseph, Muscle Cramps, and Mexiletine**

PHARMACOLOGY WATCH

Counterfeit Procrit Uncovered by FDA Surveillance

In one of the more bizarre stories of the year, the FDA has uncovered files of counterfeit Procrit (epoetin alfa—Johnson & Johnson) in routine surveillance. To make matters worse, the fake vials have been contaminated with bacteria and many contain no active ingredient. Johnson & Johnson is sending out a "Dear Doctor" letter to warn health care professionals about the counterfeit vials including the lot numbers of the suspected counterfeits. Fake Procrit was also discovered last summer in United States. At that time, counterfeiters apparently purchased 2000 U/mL vials and labeled them as the higher priced 40,000 U/mL vials. More information is available at the Johnson & Johnson/Ortho Biotech web site including pictures of the counterfeit vials.

Pharmaceutical Marketing Campaigns in Full Swing

Love 'em or hate 'em, direct-to-consumer (DTC) advertisements of pharmaceuticals are big business. The Kaiser Family foundation reports that spending on DTC ads increased nearly 10-fold in 10 years, from $260 million to $2.5 billion in 2000. More than 80% of respondents report seeing or hearing a drug ad in the last 3 months according to an FDA survey, and the Kaiser study reports that one third of patients have asked their doctor about an ad they saw on TV or in print. Unfortunately, drug ads are increasingly unregulated. The FDA is tasked with reviewing DTC ads for false or misleading statements, but according to a recent review in *Consumer Reports*, the agency has only 30 reviewers to handle 30,000 submissions each year. By the time false or misleading ads are pulled from the airways, they have often run their lifespan, with new ads appearing in their place. But are the pharmaceutical companies getting $2.5 billion of value from these ads? Apparently. A recent FDA survey of physicians revealed that when patients initiate a discussion about a prescription drug they've seen advertised, they asked for a prescription more than 50% of the time. Some 66% of physicians said they were not pressured to prescribe a drug in that situation. However, when a specific brand name drug was requested, physicians felt pressured to prescribe it more than 50% of the time. Despite this, physicians are split on the effect of DTC ads on their patients and practice, with 32% feeling negative about the ads, 40% feeling positive, and 28% feeling that DTC advertising has no effect on the practice (www.fda.gov/cder/ddmac/presentations.htm).

Ambulatory Antibiotic Reduction: Take the Good with the Bad

The national campaign to reduce antibiotic use in ambulatory practice seems to be working, but there is good news and bad news. Researchers from UCSF and Harvard reviewed the rates of overall antibiotic use in the National Ambulatory Medical Care Survey between 1991-1992, and compared those rates to usage between 1998-1999. The use of antibiotics decreased in the latter time period especially for the treatment of respiratory tract infections such as the common cold and pharyngitis (visits with a

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prescription decreased from 13% to 10% in adults, and from 33% to 22% among children). The use of broad-spectrum antibiotics increased over the same time span; however, including the macrolides azithromycin and clarithromycin, quinolones, amoxicillin-clavulanate, and second- and third-generation cephalosporins. The use of these antibiotics increased from 24% to 48% of all antibiotic prescriptions among adults and from 23% to 40% among children. An accompanying editorial reiterates the CDC's Campaign for Appropriate Antibiotic Use in the Community, which encourages prescribing antimicrobials only when they are likely to be beneficial to the patient, selecting agents that will target the likely pathogen, and using these agents in the correct dose and for the proper duration. The editorial suggests that we have been effective at decreasing the overall use of antibiotics, but less successful at promoting targeted therapy, ie, using narrow spectrum antibiotics whenever appropriate to reduce the likelihood of resistance in a population (*Ann Intern Med*. 2003;138:525-533,605-606).

Nefazodone Under Attack Once Again

Public Citizen, the national nonprofit watchdog organization, has petitioned the FDA to remove the antidepressant nefazodone (Serzone—Bristol-Myers Squibb) from the US market. The petition is based on evidence of liver toxicity associated with the drug including liver failure and death. Nefazodone was recently pulled from the European market after reports of a worldwide total of 28 cases of liver failure of which 18 patients died. The move in Europe was voluntary on the part of Bristol-Myers Squibb because of the call for increased liver enzyme monitoring requirements in several European countries. In this country, the FDA has required a black box warning on nefazodone since January 2002. Despite these concerns, nefazodone, which is a SSRI antidepressant, continues to be relatively popular, with more than 4 million prescriptions written last year. Bristol-Myers Squibb has no plans to withdraw the drug in this country at present.

Lindane Receives Black Box Warning

The FDA has issued a Public Health Advisory concerning the use of lindane for the treatment of scabies and lice. The boxed warning is the result of concern of potential neurotoxicity especially in children. The new advisory states that lindane is a second-line treatment and updates information about its potential risk in children and adults who weigh less than 110 pounds. The advisory also states that reapplication of lindane lotion or shampoo is not appropriate even if itching continues after the single treatment. The FDA is also requiring package sizes to be limited to 1 and 2 oz in order to minimize the potential for product access in a single treatment. Lindane, also known as gamma benzene hexachloride, is an industrial pesticide, has been in use for decades, and has been banned in several countries. Neurologic side effects include dizziness, seizures, and even death. The drug is currently approved for the treatment of lice and scabies in patients who have failed or are intolerant of other therapies. First-line agents for scabies include permethrin cream (Nix, Elimite, Acticin) and malathion lotion (Ovide) and for lice pyrethrum with piperonyl butoxide shampoo and cream rinse permethrin cream rinse (Nix and Rid).

Aspirin Could Help Reduce Colorectal Adenomas

Two different studies in the same issue of the *New England Journal of Medicine* suggest that daily doses of aspirin reduce the risk of colorectal adenomas. In the first study, 635 patients with previous colorectal cancer were randomized to receive either 325 mg of aspirin per day or placebo. The study was terminated early when a significant reduction in colorectal adenomas was shown during the planned interim analysis. After an average of 12.8 months of follow-up, 1 or more adenomas were found in 17% of patients in the aspirin group and 27% patients in the placebo group ($P = 0.004$). The mean number of adenomas was lower in the aspirin group ($P = 0.003$) and the time to detection of the first adenoma was longer in the aspirin group than in the placebo group ($P = 0.022$). In the second study, 1121 patients with a recent history of adenomas were randomized to placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients). Follow-up colonoscopy was done approximately 3 years after randomization. The incidence of 1 or more adenomas was 47% placebo group, 38% in the 81 mg aspirin group, and 45% in the 325 mg aspirin group (global $P = 0.04$). The risk of larger polyps including adenomas measuring > 1 cm or with tubulovillous or villous, or severe dysplasia was also lowest in the 81 mg aspirin group. An accompanying editorial suggests that inhibition of COX-2 may prevent inflammation, increased cell proliferation and angiogenesis. The author also cautions that prophylactic aspirin is not a substitute for colorectal cancer screening (*N Engl J Med*. 2003; 348:883-890, 891-899,879-880). ■