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INSIDE

Clozapine for Dyskinesias in Parkinson's Disease

ABSTRACT & COMMENTARY

Source: Durif F, et al. Clozapine improves dyskinesias in Parkinson disease: A double-blind, placebo-controlled study. *Neurology*. 2004;62:381-388.

LEVODOPA-INDUCED DYSKINESIAS ARE ONE OF THE MOST COMMON motor complications of Parkinson's disease (PD), typically occurring after 5-7 years of illness. These involuntary movements often affect young patients, and they can be disabling. Dyskinesias typically activate when patients use their limbs; they often interfere with basic activities of daily living, and can even be dangerous—for example, choreic dyskinesias of the neck may accelerate cervical spondylosis and even produce cord compression.

Although there are no approved medications to treat levodopa-induced dyskinesias, several strategies are commonly used. Reducing the interval and amount of each dose of levodopa, maximizing the dose of dopamine agonists, and even liquefying the daily levodopa and giving it in small hourly increments are useful in selected patients. One in 3 PD patients will derive benefit in dyskinesia control from treatment with amantadine. However, psychosis and leg edema often limit the usefulness of this drug. For patients with severe motor fluctuations and dyskinesias, bilateral subthalamic nucleus stimulation offers the only definitive treatment, but the procedure requires a patient who is a good surgical candidate and accepts the operative risks.

Recent interest has focused on clozapine, the gold-standard atypical neuroleptic, as a treatment for levodopa-induced dyskinesias. The drug possesses antagonist activity at the D1 and D2 receptors and agonist activity at striatal 5HT1 receptors. The present study evaluates clozapine in a double-blind, placebo-controlled trial as a treatment for levodopa-induced dyskinesias.

Fifty nondemented PD patients with disabling dyskinesias (defined by the commonly used rating items of the Unified Parkinson Disease Rating Scale) were randomized to receive either clozapine or placebo for a period of 8 weeks. The dose of clozapine was titrated according to the clinician and patient's judgment, up to a maximum of 75 mg/d. Patients with dyskinesias were evaluated prior to enroll-

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ment and throughout the trial using a clinical rating scale to measure with dyskinesias and time "off." Patients were also asked to rate the severity of their dyskinesias every 2 weeks and were videotaped so that the severity of levodopa-induced dyskinesias could be rated in blinded fashion. In addition, patients were given an oral levodopa challenge at the beginning and end of the study, and the severity of dyskinesias were rated every 5 minutes for the duration of action of the challenge dose.

At the completion of the study, the mean dose of clozapine was 39 mg/d. There was a significant reduction in the duration of "on" periods with dyskinesias in the clozapine group: 5.7 hours per day vs 4.0 hours per day ($P = .003$ relative to the placebo group). There was a significant reduction in dyskinesias as the clozapine dose was increased, with benefit observed by the fourth week of the trial. No increase in "off" time or other deterioration in parkinsonism was observed. Levodopa-induced dyskinesias (as rated by the blinded videotaped analysis) following the levodopa challenge were also improved when patients were examined at rest. Activation-induced dyskinesias were not significantly different between the 2 groups. Somnolence and hypersalivation were more common in the clozapine group. Three patients taking clozapine developed hypereosinophilia, which resolved when the drug was discontinued.

■ **COMMENTARY**

This is one of the first trials to use a combination of patient self-rating, blinded videotape review, and levodopa challenge to measure the severity of dyskinesias. Durif and associates demonstrated that clozapine did not worsen parkinsonism and that it decreased the severity of dyskinesias. The drug was reasonably well tolerated for the duration of the trial.

The question facing neurologists in practice is whether clozapine should be used in patients with PD who develop significant levodopa-induced dyskinesias. Arguments against the use of clozapine include the trouble and expense of subjecting patients to a weekly blood draw for 6 months (followed by biweekly blood draw) to monitor the white blood cell count, the rare risk of myocarditis, the recently identified risk of inducing diabetes, and the known side effects of sedation, hypersalivation, and lowered seizure threshold that accompany the drug's use.

In my opinion, the risks inherent with clozapine preclude its use as an antidyskinetic agent unless dyskinesias are disabling. They do not improve with standard anti-PD management strategies, and the patient obtains no benefit from amantadine. It would appear reasonable to consider treating this challenging group of patients with clozapine prior to consideration of deep-brain stimulation. — **STEVEN FRUCHT**

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Antibiotics for Alzheimer's?

ABSTRACT & COMMENTARY

Source: Loeb MB, et al. A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. *J Am Geriatr Soc*. 2004;52:381-387.

ALTHOUGH INFECTIOUS AGENTS ARE NOT WIDELY believed to be the primary cause of Alzheimer's disease (AD), some evidence implicates certain neurotrophic viruses and bacteria as possible contributing factors. Canadian investigators Loeb and colleagues suggest that *Chlamydia pneumonia* infection might play a role in AD. They carried out a randomized, blinded, and placebo-controlled trial testing whether antichlamydial antibiotics (rifampin/doxycycline) could serve as a potential therapy for patients with mild-to-moderate AD.

In this multicenter study, 51 mild-to-moderate AD patients were randomized to receive 3 months of treatment with rifampin 300 mg daily plus doxycycline 200 mg daily. Fifty other age- and severity-matched AD patients received a placebo. The primary outcome mea-

sure was the standardized form of the ADAS-Cog, a test commonly used in AD drug trials. Additional measures of cognition, behavior, and daily function were obtained at 3 months, 6 months, and 12 months from the start of therapy. The majority of patients in the trial were on stable doses of cholinesterase inhibitors during the study period. Blood tests for *C pneumonia*, including PCR and immunoglobulins, were evaluated before and after antibiotic treatment.

Approximately 84% of the subjects completed the trial, with relatively equal numbers of dropouts from the treatment and placebo arms. There was no significant difference in adverse events between groups. The primary outcome variable measured was ADAS-Cog. There was no significant difference between antibiotic-treated patients and placebo controls at 3 or 12 months. However, there was a statistically significant effect favoring antibiotic treatment at 6 months. A significant difference favoring antibiotic treatment was found on the Mini-Mental State Examination at 12 months and measures of function, behavior, and mood at 3 months.

The PCR and immunoglobin tests did not indicate irradication of *C pneumonia* infection in those treated with antibiotics. Loeb et al suggested that the putative beneficial effects of these antibiotics observed in this trial were probably not mediated through any action against chlamydia. Instead, they postulate an anti-amyloid effect based on in vitro studies using antibiotics such as rifampin. Since amyloid levels were not measured in this study, this hypothesis could not be confirmed.

■ COMMENTARY

The successful treatment of some forms of peptic ulcer disease (PUD) with antibiotics after the realization that *Helicobacter pylori* played a role in the pathogenesis of PUD provides a rationale for examining whether other diseases once thought to be unrelated to infection can be treated more effectively through antimicrobial therapies. However, the evidence supporting bacterial infection as a cause of AD is considerably less convincing than the associations between *H pylori* and PUD. If chlamydial infection does promote AD, however, relatively little is known about the mechanism. This lack of knowledge undoubtedly handicapped Loeb et al, whose study was otherwise well designed and executed despite the uncertainties inherent in a first attempt to use antibiotics to treat a neurodegenerative dementia. An attractive feature of the experimental design was the assessment of outcome several months after completing a 3-month treatment period. This reduces the likelihood that the effects observed were mediated through treatment of acute infections that are common in dementia patients, such as UTIs and pneumonias.

In this study, the primary cognitive outcome measure at 12 months was negative, although results at an interim time point (6 months) suggested possible benefit with antibiotic treatment. Positive results in other domains, such as behavior and function, did not temporally correlate with improvement in cognition. This study, therefore, neither proves nor disproves a role for antimicrobial therapy in the treatment of AD. Before additional trials with antimicrobials are undertaken, more research should be carried out examining the possible association between infections and AD, including studies of the mechanisms involved and their relationship to known aspects of the AD pathogenesis. **— NORMAN R. RELKIN**

A Treatment for Creutzfeldt-Jakob Disease?

ABSTRACT & COMMENTARY

Source: Otto M, et al. Efficacy of flupirtine on cognitive function in patients with CJD: A double-blind study. *Neurology*. 2004;62:714-718.

THIS REPORT DESCRIBED THE RESULTS OF A DOUBLE-blind, placebo-controlled study of flupirtine maleate (FLU), a triaminopyridine compound in patients with Creutzfeldt-Jakob disease (CJD). Twenty-eight patients were randomized oral treatment with either flupirtine (n = 13) or matching placebo (n = 15). The patients had to achieve at least 50% in 2 of the subscales of the dementia tests employed for inclusion in the study. Otto and colleagues used standardized questionnaires to monitor the progression of the disease. The main outcome variable was the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog). Otto et al used the difference between the baseline and the best score under treatment as the primary efficacy variable. They also examined 2 other cognitive tests and survival. The patients were well matched at the time of randomization. The patients with flupirtine showed significantly less deterioration in the dementia tests than the patients treated with placebo. The mean change in the ADAS-Cog (baseline to best) was 8.4 in the flupirtine group and 20.6 in the placebo group ($P < .02$). Otto et al concluded that flupirtine has beneficial effects on cognitive function in patients with CJD.

■ **COMMENTARY**

This is the first treatment that has shown any clinical benefits in patients with CJD in a double-blind trial. Flupirtine maleate is a centrally acting non-opioid analgesic that has been in clinical use since 1986. In addition to its analgesic and muscle relaxant properties, flupirtine has been shown to be a drug with an intriguing spectrum of effects relevant to neuroprotection. To date, there is evidence for at least 3 mechanisms of action that suggest the neuroprotective potential of flupirtine: 1) it has antioxidant properties; 2) it is involved in protection against glutamate-mediated excitotoxicity; and 3) it interferes with apoptotic pathways.

The rationale for carrying out the trial was based on in vitro studies, which have shown the neurotoxicity caused by the PrP106-126 fragment was greatly reduced following coincubation with flupirtine. It was demonstrated that flupirtine increased Bcl-2, which has effects in preventing apoptosis, and glutathione levels, which can prevent oxidative damage. A number of other studies have shown that flupirtine has anti-apoptotic effects. This has been particularly shown recently in in vitro cell models of Batten disease. In vitro, it also shows beneficial effects in blocking b-amyloid toxicity. Flupirtine has effects in blocking excitotoxicity in vitro, too.

The results of the neuropsychological evaluations in the present study were based on relatively short durations of treatment. The median treatment time for the flupirtine group was 29 days for the intention-to-treat cohort, and the median for the placebo group was 20.5 days. As noted, there was less of deterioration in the ADAS-Cog with flupirtine treatment. In addition, there were trends for improvement in the Mini-Mental Status Examinations (MMSE) score. The 2 groups started with MMSE scores of 19.2 in the flupirtine group and 20.5 in the placebo group. The decrease in MMSE score was 3.3 points in the flupirtine group and 8.0 points in the placebo group ($P = .07$). A similar result was obtained for another cognitive test. In the cognitive part of the Kessler Dementia Scale, there was a significant difference in deterioration with flupirtine. The survival analysis showed that the mean survival in the flupirtine group was 141 days vs 97 days in the placebo group. This, however, did not reach significance with a $P = .19$ using standard Kaplan-Meir survival analysis.

These results appear promising. As noted, this is the first test of any agent that has shown any efficacy in CJD. The present results must be interpreted with caution due to the marked variability in CJD, as well as the small number of patients examined. It is possible that this is a symptomatic effect. There are excellent rodent models of CJD. CJD can be reliably transmitted to certain transgenic mice. It would, therefore, be extremely valuable to test flupirtine in these models. If a benefit were demonstrated in these models, it would be valuable to pursue other studies with flupirtine in CJD. **— M. FLINT BEAL**

Ropinirole for Restless Legs

ABSTRACT & COMMENTARY

Source: Trenkwalder C, et al. Ropinirole in the treatment of restless legs syndrome: Results from the TREAT RLS 1 study, a 12-week, randomized, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry*. 2004; 75:92-97.

MEN AND WOMEN WITH RESTLESS LEGS SYNDROME (RLS), aged 18-79 years, were included in this randomized, 12-week, double-blind, placebo-controlled study conducted at 43 centers in 10 European countries, designed to assess the efficacy of ropinirole, a dopamine agonist, in the treatment of RLS. Diagnosis was made using International RLS Study Group (IRLSSG) diagnostic criteria, and an IRLSSG score of 15 or more was needed for inclusion. Exclusionary criteria included other movement or sleep disorders: renal failure, iron deficiency anemia, pregnancy, alcoholism, drug abuse, or dopamine agonist intolerance. Ropinirole was begun at 0.25 mg/d with upward titration over 7 weeks to a maximum of 4.0 mg/d, after which it was held constant until week 12. Mean change in IRLSSG score at 12 weeks was the primary end point. Secondary end point measures included general improvement assessment using the clinical global impression-global improvement (CGI-I) scale, improvement in quality of sleep, work and other activities, and quality of life, work productivity, and activity impairment questionnaires. Analyses of covariance, logistic regression, and Cox's regression model provided statistical analysis.

Among 284 patients, 146 treated with ropinirole and 138 with placebo, 112 (76.7%) and 109 (79%), respectively, completed the study. Ropinirole significantly improved IRLSSG score at 12 weeks compared to placebo, with benefit evident even at week 1. Secondary end points also were significantly improved by ropinirole, including the CGI-I scale, sleep adequacy and quantity, reduction of daytime somnolence and sleep disturbance, and quality-of-life questionnaire. Nausea and headache were the most frequent side effects, but

only 6 patients withdrew due to nausea, and no serious adverse event (urinary tract infection, fever, syncope, abdominal pain) was attributed to active medication. Ropinirole is a safe and effective alternative for treatment of RLS.

■ **COMMENTARY**

Mandatory diagnostic criteria for RLS include (1) a subjective urge to move the legs, which (2) worsens with rest and inactivity, as well as (3) at night, and (4) improves with movement. Given the nocturnal worsening, circadian rhythms have been touted as possibly modulating RLS. To test this hypothesis, 7 RLS patients and 7 healthy age- and sex-matched controls were monitored over a continuous 28-hour period while assessing circadian variations in leg discomfort, periodic leg movements, core body temperature, and salivary melatonin.[1] None had medical conditions associated with RLS such as renal failure or anemia or other neurological or psychiatric illness, and none had traveled across the international dateline in the preceding 6 months. Surprisingly, both groups (more so the RLS group) demonstrated a significant circadian variation in leg discomfort and periodic leg movements that correlated with core body temperature and salivary melatonin. However, only changes in melatonin secretion preceded motor and sensory symptoms in RLS patients, with a 2-hour lag time until symptoms were at their worst. These findings clearly demonstrate a circadian rhythm in RLS and implicate melatonin in the nocturnal worsening, possibly by inhibiting central dopamine secretion. **— MICHAEL RUBIN**

Reference

1. Michaud M, et al. *Ann Neurol*. 2004;55:372-380.

Thalidomide Neuropathy

ABSTRACT & COMMENTARY

Source: Isoardo G, et al. Thalidomide neuropathy: Clinical, electrophysiological and neuroradiological features. *Acta Neurol Scand*. 2004;109:188-193.

Six patients are the focus of this report defining the neuropathic side effects of thalidomide treatment in multiple myeloma. All subjects underwent evaluation prior to commencing thalidomide treatment, including neurological examination focusing on motor and sensory function, nerve conduction studies of bilateral median, ulnar, peroneal, and tibial motor, and median, ulnar, and sural sensory nerves, and somatosensory evoked potential studies of the median and tibial nerves. Blood studies included glucose, thyroid, liver, and renal function tests, vitamin E, B12, cryoglobulins, hepatitis B and C, HIV, multiple antibody studies, Shirmer testing, and fat and bone marrow biopsy. MRI of the cervical and thoracic spine was performed using a 1-Tesla magnet.

All patients developed a pure or predominant sensory polyneuropathy while on thalidomide. Family history excluded hereditary neuropathy in all, and none had spinal cord compression. Symptoms included pain, paresthesiae, and imbalance, and examination demonstrated distal impairment of touch, vibration, and pain sensitivity, distal or total areflexia, Romberg sign, and gait ataxia. Electrophysiological studies were consistent with a sensory axonal neuropathy or neuronopathy, with decreased or absent sensory responses, mild loss of motor amplitudes, and normal or mildly decreased conduction velocity not into the demyelinating range. MRI demonstrated posterior column high-signal intensity on T2-weighted sequences in the cervical region in only 1 patient. With discontinuation or lowering of thalidomide dosage from 200 mg/d to 100 mg/d or 50 mg/d, symptoms improved or resolved in 3 of 6 patients, although the clinical examination did not change by 6 months. Thalidomide can induce an axonal sensory neuropathy or, infrequently, a ganglionopathy. Discontinuation of medication does not guarantee reversibility.

■ **COMMENTARY**

Given its anti-inflammatory, anti-angiogenic, and immunomodulatory properties, thalidomide is finding ever-increasing indications.[1] Its mechanism of action remains uncertain but may include inhibition of tumor necrosis factor-alpha production and interference with leukocyte integrin membrane receptor expression. Dermatologic conditions, including erythema nodosum leprosum, pyoderma gangrenosum, aphthous stomatitis, and Behcet disease, as well as non-dermatologic conditions encompassing systemic lupus erythematosus, graft-vs-host disease, multiple myeloma, myelofibrosis, and Rasmussen encephalitis, have responded to thalidomide, warranting that its neurological complications should be familiar to all neurologists. **— MICHAEL RUBIN**

Reference

1. Nasca MR, et al. *Ann Pharmacother*. 2003;37: 1307-1320.

Magnetoencephalography: Tie-breaker vs Confounding Data for Epilepsy Localization

ABSTRACT & COMMENTARY

Source: Pataraia E, et al. Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? *Neurology*. 2004;62:943-948.

MEDICATION RESISTANCE IS A FACT OF LIFE FOR 30-40% of patients with epilepsy. Non-pharmacologic treatment options include resective epilepsy surgery, vagal nerve stimulation, the ketogenic diet, and experimental protocols. Of these, epilepsy surgery offers the greatest chance of curing the patient's epilepsy. To achieve this degree of success, it is critical to localize the epileptogenic zone as accurately as possible. Pataraia and colleagues attempt to evaluate the use of MEG in evaluating patients for epilepsy surgery.

Pataraia et al analyzed the data from 82 of 113 consecutive patients evaluated for epilepsy surgery. All patients underwent video-EEG (vEEG) monitoring and eventually proceeded to surgery. Each patient had a 30-minute recording session in which both MEG and EEG were recorded simultaneously. The sensitivity of MEG in detecting epileptiform discharges was 79%. Localizing data from interictal and ictal vEEG and interictal MEG were compared with the area of resection and classified as completely overlapping, partially overlapping, and nonoverlapping. Using such criteria, MEG and vEEG results were equivalent 32% of the time. Pataraia et al also estimate that MEG provided additional localizing information in 40% of their patients.

■ COMMENTARY

MEG detects the magnetic currents induced by the electrical field potentials of the dendritic arbor. The chief advantage of the method vs EEG is that the meninges, skull, and scalp are all "transparent" relative to the magnetic field (ie, there is no distortion of the signal by these tissues). The mathematical modeling of the source of the magnetic field is, therefore, much simpler (but does not yield a unique "inverse solution"). The magnitude of the brain's magnetic currents is in the femtotesla range, making this a very expensive technique because one needs to have the MEG machine housed in a magnetically shielded room. Further disadvantages of MEG involve characteristics of the equivalent current dipole: deep sources are difficult to detect, and radial dipoles are completely undetectable.

One confusing part of Pataraia et al's analysis is that they do not provide information regarding why the resection zone did not completely overlap with the ictal vEEG results. There are at least 3 potential reasons for such a discrepancy: 1) Interictal EEG data that were discordant with ictal EEG were compelling enough to warrant extending the resection zone; 2) Ictal EEG was nonlocalizing; and 3) The resection had to be tailored to avoid eloquent cortex. Without having details of these cases, it is difficult to interpret the sensitivity and specificity data.

Another criticism of this study involves the fact that there is only cursory information regarding the outcome of epilepsy surgery. The use of any localization technique should be discussed in the context of the gold standard of seizure-free outcome. If one diagnostic test localizes the epileptogenic zone to the same area as another method, is it because they are both equally good or equally bad? To determine whether one method is superior to another, or at least qualifies as a "tie-breaker" when data conflict, it is preferable to gauge the localization relative to seizure outcome.

MEG is not yet a fully mature technology in localizing the epileptogenic zone in patients undergoing evaluation for epilepsy surgery. Pataraia et al do bring us closer to the routine use of MEG by providing preliminary sensitivity and specificity information on the largest number of patients thus far studied. — **ANDY DEAN**

Cerebral Venous Sinus Thrombosis: Favorable Outcome with Heparin Therapy

ABSTRACT & COMMENTARY

Source: Ferro JM, et al, for the ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis. *Stroke*. 2004;35:664-670.

IN CONTRAST TO ARTERIAL THROMBO-EMBOLIC ISCHEMIC stroke, cerebral venous sinus thrombosis (CVST) is unique in its clinical presentation and treatment algorithm. CVST often presents with headache as a result of increased intracranial pressure (ICP) and frequently produces a hemorrhagic component with seizures. CVST is also benign in comparison with ischemic stroke. As

reported by Ferro and associates on behalf of the multicenter international ISCVT study, venous stroke, typically treated with heparin, has a good outcome in the vast majority of cases.

Ferro et al report on 624 cases of CVST. Patients were analyzed for the presence of thrombophilia and for risk factors such as malignancy, pregnancy, and oral contraceptive use. Many patients (43.6%) had more than one risk factor. Diagnoses were made by MR venography in the majority of patients, with many undergoing formal angiography as well. Lumbar puncture was done in 224 patients, with 83.5% showing an elevated opening pressure (> 180 mm H20). There was evidence of an infarct on CT or MRI in 46.5% of patients, with findings of a hemorrhage in 39.3%. Either intravenous or low-molecular-weight heparin was given in 83.3% of patients. Local endovascular thrombolysis was performed in only 2.1% of patients. Anti-epileptic drugs were used in 44.4%.

Outcome analysis was based on a follow-up of 16 months (median time). On average, patients were kept on anti-coagulation for 7.7 months. The majority of patients (57.1%) had a Modified Rankin Scale of zero (no symptoms or signs) at final follow-up, with 22% having minor residual symptoms. Small numbers of patients were left with severe impairments (2.2%), and the total mortality was 8.3%. Roughly half of the deaths were not related to the CVST but rather to an underlying condition, such as cancer. Multivariate predictors of death or disability were age older than 37 years, male sex, coma, hemorrhage on admission CT scan, thrombosis of the deep cerebral venous system, central nervous system infection, and cancer.

Not surprisingly, patients with a syndrome of isolated intracranial hypertension, without focal neurological signs, had the best outcomes. There was a trend in favor of those patients treated with therapeutic doses of anticoagulation in the acute phase, but this did not reach statistical significance. In cases of CVST related to pregnancy (n = 77), 8 women went on to have uncomplicated births.

■ COMMENTARY

This large study confirms that heparin should be the standard of care for patients with CVST. Treated appropriately, the majority of patients have an excellent outcome, often producing no permanent neurologic deficits. The presence of clinical features such as coma or deep-vein involvement predict more serious outcomes. While such high-risk findings may suggest a need for more aggressive management, such as endovascular thrombolysis, data from randomized studies would be needed to validate their efficacy. Finally, identification of risk factors (which may often be multiple) is important in identifying those patients at risk for CVST recurrence. **— ALAN Z. SEGAL**

rt-PA Stroke Trials: Pooled Analysis and Opinion

ABSTRACTS & COMMENTARY

Sources: The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768-774; Caplan LR. Thrombolysis 2004: The good, the bad, and the ugly. *Reviews in Neurological Diseases*. 2004;1:16-26.

THROMBOLYSIS WITH INTRAVENOUS RT-PA (IVRT-PA) is an effective treatment for strokes due to acute cerebral ischemia. Six large, multicenter, randomized, placebo-controlled trials tested the benefits of IVrt-PA for acute stroke within 6 hours of onset (NINDS stroke trial parts 1 and 2, ECASS I and II, and ATLANTIS A and B). The investigators used similar doses of IVrt-PA and had common outcome measures, but the maximum time allowed from stroke onset to start of treatment (OTT) ranged from 3 to 6 hours. The 2 NINDS trials allowed a 3-hour window for treatment and the 2 ECASS trials a 6-hour window; ATLANTIS part A allowed a 6-hour window and part B a 5-hour window. A subsequent analysis of the NINDS trial data indicated that the chance of benefit from IVrt-PA diminished as time elapsed during the first 3 hours after stroke onset.[1]

In order to determine whether time-to-treatment with IVrt-PA is a critical predictor of therapeutic benefit, the authors pooled common data from the 6 randomized stroke trials. Using multivariable logistic regression, they assessed the relation of OTT on favorable 3-month outcome and the occurrence of clinically relevant cerebral hemorrhage.

Treatment was started within 6 hours of stroke onset in almost 3000 patients randomly allocated to IVrt-PA or placebo. Median age was 68 years. Ethnic background was reported as white in 85%, black in 9%, Hispanic in 2%, Asian in 1%, and "other" or not recorded in 3%. Median baseline National Institute of Health Stroke Scale (NIHSS) score was 11. The median OTT was 243 minutes. Two-thirds of patients were treated more than 180 minutes after symptom onset.

Odds ratios for favorable outcome at 3 months by

OTT and NIHSS category were calculated with adjustment for age, baseline glucose concentration, baseline diastolic blood pressure, and previous hypertension. Odds of a favorable 3-month outcome significantly increased as OTT decreased. Odds were 2.8 for 0-90 min, 1.6 for 91-180 min, 1.4 for 181-270 min, and 1.2 for 271-360 min, in favor of the rt-PA group. The hazard ratio for death, adjusted for baseline NIHSS, was 1.0 for all intervals from 0 to 270 min. For the 271-360 min interval, it was 1.45. Cerebral hemorrhage was significantly more common in rt-PA patients (6%) than in controls (1%). Sixty percent of those with parenchymal hematoma died within 3 months (62% in the rt-PA group and 47% in the placebo group). Median age of patients with cerebral hemorrhage was 72 years; median OTT was 261 min (180-300 min) and median baseline NIHSS score was 12 (8-16). Hemorrhage was not associated with OTT or baseline NIHSS score but was significantly associated with rt-PA treatment and age.

This analysis of pooled data confirms that the sooner rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 minutes. The results suggest a potential benefit beyond 3 hours but with a potential for an increased risk of death.

In the inaugural issue of *Reviews in Neurological Diseases*, Louis Caplan reviews the investigations that preceded and follows the FDA approval and release of rt-PA for clinical use 8 years ago. He presents the current guidelines for the use of IV and intraarterial rt-PA, and in his role as a "2000-year-old" clinician offers his recommendations and sage advice for the acute treatment of ischemic stroke.

■ COMMENTARY

The pooled analysis of 6 trials of thrombolytic therapy helps to define the limits of the treatment window for rt-PT. Although the results suggest that the benefit of rt-PA could extend beyond 3 hours, it does not extend beyond 6 hours. The odds of a favorable outcome were not different from 1.0 at 360 min. The apparent reduction in benefit from rt-PA at later periods did not result from an increased rate of parenchymal hemorrhage. The investigators surmise that the progressive disappearance of the ischemic penumbra probably accounts for the declining benefit of thrombolytic treatment with time. Nevertheless, subgroups of patients who continue to have potentially viable ischemic brain tissue at later times might still have substantial benefits from treatment. The task of future studies will be to identify such patients who might respond to treatment at the later end or even beyond the suggested therapeutic window.
— JOHN J. CARONNA

Reference

1. Marler JR, et al. *Neurology*. 2000;55:1649-1655.

CME Questions

16. Restless legs syndrome (RLS):
a. is worse upon wakening.
b. may be improved by melatonin supplements.
c. may be related to inhibition of central dopamine secretion.
d. shows no benefit to ropinirole.
e. All the above are true or false

17. The rationale for testing antibiotics as a treatment for AD is:
a. related to their effects on urinary tract infections.
b. related to a reported association between chlamydial infection and AD.
c. related to their indirectly diminishing neurofibrillary tangles.
d. related to suppression of immune-mediated neuronal apoptosis.

18. Thalidomide causes:
a. drop out of anterior horn cells in the ventral horn.
b. predominantly motor neuropathy.
c. demyelinating sensory polyneuropathy.
d. predominantly sensory axonal neuropathy or ganglionopathy.
e. All or none of the above

19. Cerebral hemorrhage following IVrt-PA in acute stroke patients is significantly associated with:
a. baseline HIHSS score.
b. time from stroke onset to start of treatment.
c. male gender.
d. age.
e. previous history of hypertension.

Answers: 16(c); 17(b); 18(d); 19(d)

Correction

CME question number 16 was erroneously run in the April issue. The question is re-run in this issue with the corresponding article.

In Future Issues:

Myasthenia Gravis 2004