Sodium valproate vs phenytoin in status epilepticus: A pilot study

To the Editor: Misra et al. should be commended for performing a randomized study comparing the treatment of status epilepticus with phenytoin (PHT) and valproic acid (VPA).¹ Very few trials have addressed this issue and all of them investigated the first-line treatment, mainly with benzodiazepines.

However, there are some concerns. First, although VPA or PHT are generally used as second-line treatment according to most recent guidelines,² in the current study they were prescribed as first-line agents. This does not reflect clinical practice. Secondly, the sample size calculation appears peculiar: running the calculation with the same data, with a two-sided test and a relative difference in efficacy of 20%, one is given a result of 807 subjects.³ The use of a two-sided test is mandatory in this setting, as the authors cannot predict a priori which treatment will be superior to the other. This is also true for the analysis of the primary outcome: a two-sided Fisher exact test gives a p of 0.088.⁴

Under these conditions, it appears misleading to state that the study shows that VPA was more effective than PHT.¹ A more correct interpretation might be that, considering that the study was underpowered, a tendency towards better efficacy of VPA was found. Finally, as a tolerability measure, it may be interesting to add the incidence of VPA encephalopathy.⁵

These considerations illustrate the difficulty of recruiting a suitable sample size to study the pharmacologic treatment of status epilepticus, and reinforce the need for a large, collaborative multicenter trial.

Andrea O. Rossetti, *Lausanne, Switzerland*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We appreciate Dr. Rossetti's comments. Our choice of reference and study drugs was based on the possibility of drugs not only in aborting status epilepticus (SE) but also to continue the same drug as maintenance therapy for preventing seizure recurrence.

Regarding the sample size and statistical power of the study, we agree that our sample size is rather small; therefore we have used one-sided p values. Our preliminary results are suggestive of better efficacy of VPA than PHT. Because of this limitation, we designated this as a pilot study and have concluded that our results need confirmation in a larger study.

It is ironic that there is no sufficiently large randomized controlled trial (RCT) to evaluate the role of VPA in SE in spite of approval of intravenous VPA by the Food and Drug Administration in 1996. This is probably due to lack of interest of pharmaceutical companies and sponsoring agencies. Under these

circumstances, small, well-conducted studies should be published and results subjected to meta-analysis to obtain valid conclusions.

The efficacy of all the drugs used in SE is limited by their side effects. Phenytoin results in hypotension in 27%, cardiac arrhythmias in 6.9%, and hypoventilation in 9.9% in patients with convulsive SE. The frequency of these side effects is similar to those following lorazepam.⁶ In contrast, VPA has better tolerability and safety. In 318 patients receiving about 2,200 doses of VPA, there were no cardiovascular or respiratory complications.⁷ We found one patient had hypoventilation and three had raised transaminase levels but none had VPA encephalopathy.

VPA encephalopathy is a concern because of several case reports and short series of encephalopathy following VPA, especially in conjunction with topiramate.⁸ Children with carnitine deficiency and those with urea cycle enzyme defects are more prone to VPA encephalopathy and need close monitoring. No case of VPA encephalopathy was reported in various prospective and retrospective studies on children⁹ or adults¹⁰ with SE receiving intravenous VPA. However, patients receiving VPA, if consciousness is not improved after cessation of SE, should be carefully monitored clinically and biochemically for possible continued subtle SE and VPA encephalopathy.

U.K. Misra, J. Kalita, R. Patel, *Lucknow, India*

Disclosure: The authors report no conflicts of interest.

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Neuroprotective agents for clinical trials in ALS: A systematic assessment

To the Editor: In their article on neuroprotective agents for amyotrophic lateral sclerosis (ALS), Traynor et al.¹ list 24 potential neuroprotective drugs for patients with ALS. Taxol is not mentioned. However, two cell death mechanisms postulated to underlie neuronal death in ALS, defective axonal transport² and calcium-mediated toxicity,³ are reversed by Taxol in vitro⁴ and in vivo.⁵

In vitro at an optimum concentration, Taxol blocks the toxicity of the calcium ionophore A23187.⁴ Similarly, glutamate, through activation of ionotropic receptors, allows calcium influx into neurons and potentiates toxicity of mutant superoxide dismutase in motor neurons by a calcium-dependent mechanism.⁶

Riluzole, the only effective treatment for ALS, blocks glutamate release and thus could be inhibiting this calcium-mediated cell death mechanism. The two cell death mechanisms may not be entirely independent because calcium inhibits the formation of the microtubule transport system. In a transgenic (Tg) mouse model of degeneration of spinal motor neurons, Zhang et al. show that

Taxol improves fast axonal transport, protects against axonal degeneration of spinal motor neurons, and improves mobility in Tg mice treated with Taxol compared to controls.⁵

There are two potential problems with use of Taxol. It produces a painful mainly sensory neuropathy in 50% to 60% of patients taking it for various forms of cancer. Brain concentrations are very low after intravenous injection. However, both of these problems have potential solutions. First, there are symptomatic and potentially protective treatments for Taxol-induced sensory neuropathy.⁷ Second, chemical modifications of Taxol decrease its affinity for the multidrug resistance protein, P-glycoprotein, and enhance Taxol permeation across the blood–brain barrier.⁸ These modifications should make Taxol more effective in clinical trials if it shows promise in in vitro and in vivo models of ALS.

Taxol is currently being evaluated in animal models as a potential therapy for Alzheimer disease.⁵ It deserves consideration for trials in in vitro and in vivo models of ALS.

William J. Burke, *St. Louis, MO*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We thank Dr. Burke for his comments concerning the possible role of Taxol as a treatment for ALS. The purpose of our article is to facilitate development of a systematic and rational selection process to determine which candidate agents should be prioritized for clinical trials in patients with ALS and to stimulate debate on this issue among the ALS research community.

The priority list outlined in our article is dynamic and will be updated annually as additional data on both existing and novel neuroprotective agents becomes available.¹ Therefore, we look forward to evaluating Taxol as well as other agents that have a potentially beneficial effect on disease progression in ALS.

B.J. Traynor, L. Bruijn, R. Conwit, F. Beal, G. O'Neill, S.C. Fagan, M.E. Cudkowicz, *Bethesda, MD*

Disclosure: The authors report no conflicts of interest.

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Mortality of stroke patients treated with thrombolysis: Analysis of nationwide inpatient sample

To the Editor: Dubinsky and Lai found a 1.9-fold increase in the relative risk (RR) of mortality associated with treatment with tissue-type plasminogen activator (tPA) among patients with ischemic stroke.¹ Several methodologic issues impact the interpretation of the results.

First, Dubinsky and Lai could not adjust for the confounding effect of stroke severity, which may partly have overestimated the association between tPA and mortality.^{2,3} Moreover, they did not account for the individual hospital's experience in treating stroke patients with tPA. The number of thrombolysees performed at a hospital is inversely related to in-hospital mortality.³

Second, to report a single RR for the association between tPA and mortality across a very heterogeneous patient population is problematic. In our analyses of a German stroke registry, there was a subgroup of patients with very poor prognosis in whom tPA appeared to have been given as a last resort, and in whom tPA was associated with a poor outcome. The estimated RR of mortality associated with tPA changed dramatically when different adjustment methods were used that did or did not account for the tPA treatment effect among patients with poor prognosis.⁴

For example, we found an 11-fold increased risk in mortality when we estimated what would have happened had every ischemic stroke patient been treated with tPA versus none. In contrast, the comparison between the experience of tPA-treated patients and the calculated outcomes had those same patients not been treated showed no association with mortality. Dubinsky and Lai present a RR that was estimated from a logistic regression that did not specify a covariate-treatment interaction term.¹ We also found an intermediate effect estimate (RR = 1.93) when we used a similar logistic regression model.⁴

Because the effect of tPA on mortality varies so much between different patient groups, reporting a single RR from a logistic regression model does not produce a clinically meaningful result for this particular example.

A recent study utilized the same database as Dubinsky and Lai and found similar mortality and intracerebral hemorrhage rates.² The authors come to a divergent conclusion that the observed rates are similar to the rates reported from prospective trials and large observational studies^{3,5} and that thrombolysis has a safety profile similar to that observed in large clinical trials.²

Tobias Kurth, Peter U. Heuschmann, Alexander M. Walker, Klaus Berger, *Boston, MA*

Disclosure: Dr. Kurth has received investigator-initiated grants from Bayer AG, McNeil Consumer & Specialty Pharmaceuticals, and Wyeth Consumer HealthCare for studies evaluating the risk and benefit of analgesics. He is a consultant to i3 Drug Safety and has received an honorarium from Organon for contributing to an

expert panel. Dr. Heuschmann has received an honorarium for a lecture from Solvay. Dr. Walker's drug safety group has conducted sponsored research for every major pharmaceutical manufacturer over the past decade. Dr. Berger has received an investigator-initiated research grant for an epidemiologic migraine study from a consortium formed by Allmiral, Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Boots Healthcare, Glaxo-Smith-Kline, Janssen, McNeil, MSD Sharp & Dohme, and Pfizer, and has received a research grant to study quality of life in Parkinson Disease from Hoffmann-LaRoche.

To the Editor: We disagree with the conclusions of the recent report by Drs. Dubinsky and Lai on mortality and hemorrhage risk after thrombolysis for acute ischemic stroke.¹

The authors used the Charlson Index to adjust for medical comorbidities among stroke patients identified in the National Inpatient Sample (NIS) but they could not adjust for stroke severity, likely the most important factor influencing outcome after stroke.⁶ The landmark NINDS rt-PA Stroke Trial demonstrated a reduction in morbidity but not in mortality among patients treated with thrombolysis.⁷ However, patients treated with rt-PA have (on average) more severe strokes than patients not treated with thrombolysis.⁸ (This effect is also documented in our unpublished, population-based data.) Mild or rapidly improving stroke symptoms are often cited by clinicians as reasons rt-PA is not administered. Without an index of stroke severity, mortality rates for NIS patients receiving thrombolysis cannot be meaningfully compared to NIS patients not receiving thrombolysis, nor to other randomized studies, cohort studies, or population-based reports.

We are further puzzled by the concluding statement of Drs. Dubinsky and Lai's abstract: "US community experience in the use of thrombolysis has higher rates of complications and mortality than in controlled clinical trials."¹ The intracranial hemorrhage rate among rt-PA treated patients from the NIS was lower than among rt-PA treated patients in the NINDS rt-PA Stroke Trial (4.2% vs 6.4%).^{1,7} The mortality rate was also lower in the NIS although the time frame reported was not comparable (in-hospital mortality of 10.1% in the NIS vs 3-month mortality of 17% in the NINDS rt-PA Stroke Trial).^{1,7} A meta-analysis of open-label studies of rt-PA administered using the NINDS rt-PA Stroke Trial protocol showed hemorrhage rates and mortality comparable to the trial data.⁵ Patients in the meta-analysis had a median baseline NIH Stroke Scale score equivalent to patients in the NINDS rt-PA Stroke Trial.^{145,7}

Finally, the use of procedure code 99.10 to identify patients treated with rt-PA is suspect. Because this code provided no additional revenue to hospitals before approval of the new DRG 559, it was sporadically used in rt-PA treated patients (showing a sensitivity of only 50% in one study), and it cannot be assumed that its application was randomly distributed among patients.⁸

We agree that the translation of results from clinical trials to

clinical practice is important but methodologic issues make the study by Dubinsky and Lai unhelpful.

Matthew L. Flaherty, Brett Kissela, Pooja Khatri,
Cincinnati, OH

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We appreciate the comments of Dr. Kurth et al. and Dr. Flaherty et al. The purpose of our study was to determine the community-wide utilization of thrombolysis and in-hospital mortality.¹ The main limitation of our study was the lack of a measure of stroke severity and we acknowledged that this has a major effect on the decision to use thrombolysis and on survival. However, the rate of utilization of thrombolysis, morbidity, and mortality in this nationwide sample are important to determine the utilization and potential benefit. Comorbidities (including those due to atherosclerosis) were controlled for by the Charlson Index, a validated tool used to examine mortality in similar datasets.⁹

The mortality associated with thrombolysis varies between community studies and controlled clinical trials and is dependent on the length of follow-up. In a meta-analysis of controlled trials the mortality was 8.6% within 7 to 10 days, which is lower than what we have reported with a similar follow-up.¹⁰ Our report of a ~20% sample of all US hospitalizations found a rate similar to that reported in Germany¹¹ but less than what was reported in community hospitals in Cleveland.¹²

We did not control for hospital experience, due to changes in hospitals selected for the NIS from year to year. A recent study, using the NIS, controlled for hospital volume of strokes and of thrombolysis, reported that these did not predict mortality.² Their results were similar to ours.

Case ascertainment is a major source of bias in community studies. There is a potential for under- and for over-reporting. In the only study comparing chart abstraction to an administrative database the specificity of thrombolysis was 50% (17/34 cases) while the sensitivity was 100%.⁸ However, the results of this study of convenience samples of 30 consecutive stroke admissions from 42 academic medical centers involved in a quality improvement project on stroke therapy cannot be generalized to judge the accuracy of the NIS. While we may have missed some cases, we eliminated many that were most likely miscoded, based on age, type of admission, and comorbidities. There is no reason to suspect that any missed cases would alter our results.

The recent implementation of a DRG for stroke thrombolysis will aid research in the effects of thrombolysis in community hos-

pitals. This will help to determine if the benefit seen in controlled clinical trials can be extended to community experience with thrombolysis.

Richard M. Dubinsky, Sue M. Lai, Kansas City, KS

Disclosure: The authors report no conflicts of interest.

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Corrections

Standard vs atraumatic Whitacre needle for diagnostic lumbar puncture: A randomized trial

In the Brief Communication “Standard vs atraumatic Whitacre needle for diagnostic lumbar puncture: A randomized trial” by R. Lavi et al. (*Neurology* 2006;67:1492–1494), the second author’s name is misspelled. The correct spelling is D. Yarnitsky. The authors regret the error.

Severe childhood SMA and axonal CMT due to anticodon binding domain mutations in the *GARS* gene

In the Brief Communication “Severe childhood SMA and axonal CMT due to anticodon binding domain mutations in the *GARS* gene” by P.A. James et al. (*Neurology* 2006;67:1710–1712), the table titled “Comparison of patients with *GARS* mutations” an incorrect mutation was noted. The mutation should read I280F and not I120F. The authors are grateful to Dr. Ricardo B.L. Gonçalves for pointing out this typographical error.

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Corrections

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