Correspondence

EFFICACY AND TOLERABILITY OF LEVETIRACETAM VERSUS PHENYTOIN AFTER SUPRATENTORIAL NEUROSURGERY

To the Editor: I read with interest the article by Milligan et al. comparing the efficacy and tolerability of levetiracetam to phenytoin after supratentorial neurosurgery. The authors provide valuable information regarding the efficacy of levetiracetam in preventing perioperative seizures.

Phenytoin is rarely, if ever, dosed according to body weight. In general, patients are given a gram and then put on maintenance (300 mg/day). Initially, this results in subtherapeutic serum levels, making patients prone to perioperative seizures.

One potential advantage of phenytoin over levetiracetam is that serum levels are standardized and can be readily checked. Rapid dose adjustments are possible in the setting of a breakthrough seizure while on phenytoin. In most centers, this is not possible with levetiracetam, which leads to physicians “blindly” increasing the maintenance dose.

This problem should be considered before levetiracetam replaces phenytoin as the drug of choice for seizure prophylaxis after supratentorial neurosurgery.

Nitin K. Sethi, New York, NY

Disclosure: The author reports no disclosures.

Reply from the Authors: We thank Dr. Sethi for his comments. We agree that phenytoin is rarely dosed according to body weight with respect to perioperative prophylaxis and that this practice may result in subtherapeutic phenytoin levels. Furthermore, phenytoin may not be given a fair chance to show its full potential in seizure prophylaxis.

However, the incidence of seizures was lower (4%) than the incidence of adverse drug reactions (18%) in the patients receiving phenytoin. In addition, most of our patients had levels within the usual therapeutic range, although at the lower end. Targeting higher levels is unlikely to mitigate this problem and may lead to an increase in adverse drug reactions.

The potential difficulty in obtaining levetiracetam levels is not a clear drawback to its use as prophylaxis in the perioperative period. In this study, we most commonly used a dose of 500 mg levetiracetam twice daily. This dose has been effective in preventing seizures in other clinical situations and most studies have not shown a clear dose-response relationship across individuals.

In addition, levetiracetam is pharmacokinetically more predictable than phenytoin, so there is a reduced need to monitor levels. If a breakthrough seizure does occur while the patient is receiving levetiracetam, the decision to increase the dose is usually made without obtaining a level. This occurs in various clinical situations.

We do not think this is a decision made “blindly,” but rather one made with consideration of the patient, drug, dosage, and other clinical factors.

Tracey A. Milligan, Shelley Hurwitz, Edward B. Bromfield, Boston, MA

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PRONOUNCING BRAIN DEATH: CONTEMPORARY PRACTICE AND SAFETY OF THE APNEA TEST

To the Editor: I read with interest the article by Wijdicks et al. describing the need to abort apnea testing in only 3% of patients examined. An additional 7% did not undergo apnea testing due to medical instability as judged by the examining physician, although precise criteria and blood pressure cutoffs are not specified.

We conducted a large study of apnea testing and used the same technique as Wijdicks et al. We found that 39% of patients developed marked hypotension.
(defined as at least 15% drop in mean arterial pressure) or need for vasopressor manipulation during
the test. Wijdicks et al. do not mention how frequently vasopressors were adjusted during their apnea
testing.

One difference between the two studies is that all of the patients in the Wijdicks et al. study were on
vasopressors or inotropes. In our study, 87% were on inotropes and 42% on vasopressors. We also found
that the use of dopamine and vasopressin was not significantly different between the patients with sta-
ble blood pressure and hypotension.

Dr. Wijdicks has previously opined that ”hypotension develops during apnea testing in certain pa-
tients who otherwise fulfill the clinical criteria of brain death.” The most recent study was an opportu-
nity to determine precise guidelines to delineate the significance of the often seen hypotension and guide
future apnea testing. Their article does not fully address this. Precise numerical cutoffs are necessary to
guide safe performance of apnea testing.

**Joseph S. Jeret, Rockville Centre, NY**

*Disclosure: The author reports no disclosures.

**Reply from the Authors:** Dr. Jeret urges obtaining precise cutoffs in order to properly conduct safe ap-
nea testing.

We are investigating definitive cutoffs yet good predictors are difficult to establish because apnea tests are
performed in patients under different circumstances (e.g., polytrauma vs destructive ganglionic hematoma).
When hypotension or deoxygenation occurs, it appears rapidly after disconnection from the ventilator and we
have not waited for critical values to appear.

The high incidence of hypotension (40%) in the 1990–1992 study by Jeret and Benjamin of 70 ap-
nea tests is notable. Strict adherence to preconditions for the apnea test using the 1995 American Academy of
Neurology guidelines—and mostly neurointensivists performing the declaration of brain death—may have explained the low incidence of hypotension (7%) in our contemporary study of over 200
patients.

**Eelco F.M. Wijdicks, Rochester, MN**

*Disclosure: The author reports no disclosures.

1. Wijdicks EFM, Rabinstein AA, Manno EM, Atkinson JD. Pronouncing brain death: contemporary practice and
3. Wijdicks EFM. In search of a safe apnea test in brain death: is the procedure really more dangerous than we

**GASTROINTESTINAL BLEEDING AFTER
ACUTE ISCHEMIC STROKE**

**To the Editor:** We read with interest the article by O’Donnell et al., who describe 1.5% of patients
with ischemic stroke who developed gastric hemorrhage and gastric hemorrhage that was related to recur-
cence of stroke, myocardial infarction, and venous thromboembolism during hospital stay.

It is unclear whether gastric hemorrhage was due to stroke or to antithrombotic or anticoagulant ther-
apies which their patients might have received for myocardial infarction and venous thromboem-
bolism. The timing of gastric hemorrhage following stroke may provide a clue about the etiology.

In our study, 30% of patients with intracerebral hemorrhage developed gastric hemorrhage.2 In a pro-
spective study on intracerebral hemorrhage, 3.3% of patients had gastric hemorrhage within 48 hours,
9.8% within 3–5 days, and 20.8% after 5 days of stroke. Early bleeding is likely due to raised intracranial
pressure and stress ulcers, whereas later bleeding is likely due to septicemia or systemic inflammatory
response syndrome (SIRS).3

In a multivariate analysis in intracerebral hemorrhage, gastric hemorrhage was related to septicemia/
SIRS and size of hematoma.3 A combination of antiplatelets such as aspirin and clopidogrel is known
to produce high frequency of intracerebral hemorrhage.4 Did this combination increase the risk of gas-
tric hemorrhage and was the hemorrhage severe in the patients studied by O’Donnell et al.? In addition,
was it measured in a qualitative or quantitative way?

Another interesting difference was that 49% of the patients reported by O’Donnell et al. with gastric hem-
orrhage were women. We reported only 4.3% women in our study.3 The gender difference in stress ulcer has
not been investigated but peptic ulcer is more common in men than women (6.8% vs 2.8%).5

We encourage further evaluation of gender differences in gastric hemorrhage to determine potential
social, cultural, and genetic components.

**Usha K. Misra, Jayantee Kalita, Lucknow, India**

*Disclosure: The authors report no disclosures.

**Reply from the Authors:** We thank Drs. Misra and Kalita for their thoughtful comments. We agree that
there is an apparent discrepancy between the frequency of gastrointestinal bleeding reported in our
study and their previous studies.1,2

Two key considerations may account for this differ-
ence. First, the patient populations are different.
Patients with intracerebral hemorrhage are likely to be at greater risk of stress ulceration as they are more likely to be admitted to the intensive care unit, undergo major surgery, and more likely to have an underlying diathesis to bleeding compared to patients with ischemic stroke.2

Second, we included registry data obtained by screening patient records for clinically documented gastrointestinal bleeding which likely resulted in underreporting of bleeding episodes, particularly minor bleeds. The comparative frequency of the more serious gastrointestinal hemorrhages requiring transfusion (unlikely to be missed by chart review) was 36/6,853 (0.5%) in our study1 and 1/51 (2.0%) in the cohort study by Misra et al.2

Unfortunately, we were unable to comment on the etiologies of gastrointestinal bleeding since this information was not captured in our study.1 We agree that further research is required to explore a potential gender effect.

Martin J. O’Donnell, MB, PhD, Moira Kapral, MD, MSc, Frank Silver, MD, Hamilton, Ontario, Canada

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CORRECTION

The common BDNF polymorphism may be a modifier of disease severity in Rett syndrome

In the article “The common BDNF polymorphism may be a modifier of disease severity in Rett syndrome” by B. Ben Zeev et al. (Neurology® 2009;72: 1242–1247), an author’s name is misspelled. The seventh author is M. Vecsler. The authors regret the error.