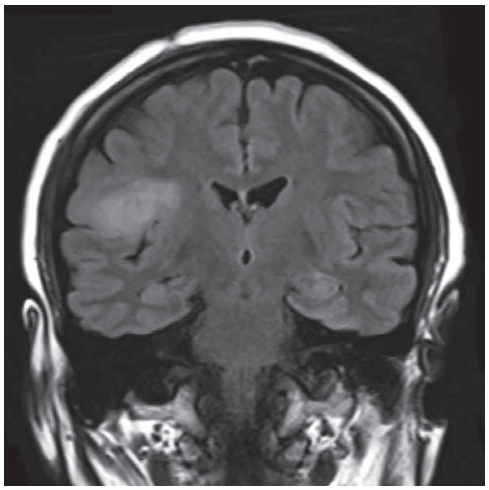
Pharmacologic Unmasking of Neurologic Deficits

A Stress Test for the Brain

Phillip E. Vlisides, M.D., George A. Mashour, M.D., Ph.D.

Neuroplasticity remains one of the most intriguing aspects of modern neuroscience and is of clinical relevance to anesthesiology. Indeed, the brain possesses a remarkable ability to adapt to various perturbations *via* structural and functional alterations. For example, patients who have experienced stroke demonstrate signs of adaptation by regaining neurologic function after injury, without regeneration of the original lesion *per se*. However, such adaptations can be reversed pharmacologically, with relative selectivity by agents that potentiate the transmission of γ-aminobutyric acid (GABA) compared with agents that antagonize the cholinergic system.[1] Understanding the interactions of brain dysfunction, adaptive changes, and pharmacology is important for the field of anesthesiology. Studying the effects of our drugs on neurologic function in surgical patients may provide a unique window into previous neurologic injury, subsequent neuroplastic changes, and associated clinical vulnerability, particularly in those with known or suspected neuropathology.



"A [γ-aminobutyric acid–mediated] sedation strategy may serve as a neurologic stress test…[to] strip away neural reserve to reveal subclinical brain vulnerability."

In this issue of Anesthesiology, Lin *et al.*[2] report midazolam-induced upper limb motor deficits in patients with supratentorial gliomas. This aligns with previous work demonstrating that sedation unmasks neurologic deficits in patients with brain tumors or cerebrovascular disease.[1,3,4] What is unique in the current study by Lin *et al.*[2] is the demonstration that flumazenil reverses these pharmacologically induced deficits, supporting a specific GABAergic mechanism. Interestingly, motor dysfunction was not restricted to the contralateral limb in this study; ipsilateral motor dysfunction was observed as well, and flumazenil restored baseline function bilaterally. Ipsilateral upper limb motor dysfunction was also more significantly reduced after midazolam administration compared with the dominant hand of control patients. As described in the article,[2] this may reflect the infiltration of the tumor with consequent interruption of neural function and structure beyond the epicenter of the lesion.

Like all studies, this one has limitations, which are well described by the investigators. The control group was, on average, approximately 11 yr older compared with the surgical group, which is an important caveat. Nonetheless, the effects of midazolam and flumazenil appeared comparatively robust in the surgical group, supporting the original hypothesis. The study was conducted in a limited patient population (*i.e.*, those with supratentorial gliomas in eloquent areas of the brain). As such, more work is required to test the generalizability of these findings in other patient populations. Additionally, postoperative recovery profiles and neurologic outcomes were not examined in this study.

Despite study limitations, the clinical implications of these findings have the potential to be impactful and wide-ranging. The authors present an accessible, practical method for probing neural vulnerability both anatomically and functionally. In patients with neurosurgical malignancies, GABAergic drug administration may help identify and classify the extent of covert disease not otherwise apparent from clinical examination or certain neuroimaging modalities. This may be particularly useful after tumor resection if disease has spread beyond surgical margins. Whether such ongoing dysfunction might reflect residual disease presence *versus* persistent injury after tumor removal is unclear, but this would open an interesting line of investigation.

Image: J. P. Rathmell.

This editorial accompanies the article on p. 36 and has a related Infographic on p. 17A.

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What is more exciting to consider is how a pharmacologic sedation strategy may serve as a neurologic stress test for neurologically vulnerable patients beyond the neurosurgical population. Just as a treadmill or certain cardioactive drugs can strip away cardiac reserve to reveal subclinical heart vulnerability, so too might sedatives strip away neural reserve to reveal subclinical brain vulnerability. This pharmacologic testing may not serve as a stress test in the conventional vascular sense but rather as a way of characterizing neural function and reserve in those with overt—or covert—neuropathology. Midazolam sedation, and reversal, could be tested in additional patient populations (*i.e.*, those with cerebrovascular disease) for identifying pre-existing neuropathology and adaptive neural compensation that may be present. Motor function testing could also be paired with cognitive assessment after pharmacologic sedation, and results can be correlated with perioperative outcomes (*e.g.*, delirium, stroke) to complete the neural stress test paradigm. For example, patients who become heavily sedated or obtunded after midazolam may be prone to hypoactive delirium postoperatively; such associations can be formally tested. Indeed, preoperative electrocardiogram and cardiac stress tests are routine for high-risk cardiovascular patients, but there is no corollary strategy for testing neural vulnerability during analogous periods of stress in surgical patients. Pharmacologic sedation, with the GABAergic-based method described, may induce the altered brain states required to unmask pre-existing neurologic deficits and associated vulnerabilities. Furthermore, recovery from general anesthesia, a state that is typically induced by drugs that potentiate GABA transmission, might reveal underlying neurologic compromise, which could be manifest in the perioperative period as delirium. Indeed, it is becoming clearer that the brain's response to general anesthetics—for example, the neurophysiologic state of burst suppression—might be more diagnostic of neural vulnerability rather than a causal etiology.[5]

Preoperative evaluation and risk stratification can be challenging for neurologic outcomes, as predictive models are often constructed indirectly and without measuring key and standardized variables in the target end-organ of interest (*i.e.*, the brain). However, Lin *et al.* have presented a compelling strategy for identifying subclinical neurologic deficits in surgical patients *via* GABAergic sedation. The extent to which these latent deficits portend adverse perioperative outcomes is unclear, but such relationships can now be formally studied. Cognitive reserve can also potentially be analyzed with this strategy, and results could be correlated with altered perioperative brain states (*e.g.*, emergence excitation, postoperative delirium). Anesthesiologists are well positioned to lead the required scientific and clinical investigations, and results may lead to novel methods for identifying neurologic risk in surgical patients or screening for neurologic vulnerability that would otherwise be undetected until clinical manifestation.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Vlisides: pvliside@med.umich.edu

References

1. Lazar RM, Berman MF, Festa JR, Geller AE, Matejovsky TG, Marshall RS: GABAergic but not anti-cholinergic agents re-induce clinical deficits after stroke. J Neurol Sci 2010; 292:72–6
2. Lin N, Han R, Hui X, Zhang K, Gelb AW: Midazolam sedation induces upper limb coordination deficits that are reversed by flumazenil in patients with eloquent area gliomas. Anesthesiology 2019; 131:36–45
3. Lin N, Han R, Zhou J, Gelb AW: Mild sedation exacerbates or unmasks focal neurologic dysfunction in neurosurgical patients with supratentorial brain mass lesions in a drug-specific manner. Anesthesiology 2016; 124:598–607
4. Thal GD, Szabo MD, Lopez-Bresnahan M, Crosby G: Exacerbation or unmasking of focal neurologic deficits by sedatives. Anesthesiology 1996; 85:21–5; discussion 29A–30A
5. Wildes TS, Mickle AM, Ben Abdallah A, Maybrier HR, Oberhaus J, Budelier TP, Kronzer A, McKinnon SL, Park D, Torres BA, Graetz TJ, Emmert DA, Palanca BJ, Goswami S, Jordan K, Lin N, Fritz BA, Stevens TW, Jacobsohn E, Schmitt EM, Inouye SK, Stark S, Lenze EJ, Avidan MS; ENGAGES Research Group: Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: The ENGAGES randomized clinical trial. JAMA 2019; 321:473–83