Host: Welcome to the *Anesthesiology* journal podcast, an audio interview of study authors and editorialists.

Dr. James P. Rathmell: Hello, I’m Jim Rathmell, Professor of Anesthesia at Harvard Medical School and Chair of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women’s Hospital in Boston. I’m one of the Executive Editors for *Anesthesiology* and you’re listening to an *Anesthesiology* podcast that we’ve designed for physicians and scientists interested in the research that appears in the journal.

Today we’re going to talk with the lead author of an original research article and an accompanying editorial view that appear in the July 2019 issue. With us today is Dr. Adrian Gelb. Dr. Gelb is Professor Emeritus in the Department of Anesthesia and Perioperative Care at the University of California San Francisco. He’s the senior author on an article that appears in the July 2019 issue of the journal titled “Midazolam Sedation Induces Upper Limb Coordination Deficits that Are Reversed by Flumazenil in Patients with Eloquent Area Gliomas.” Dr. Gelb, thank you for joining us.

Dr. Adrian W. Gelb: My pleasure, Jim. Thank you very much for the honor and the privilege of this podcast.

Dr. James P. Rathmell: Also with us today is Dr. Phil Vlisides. Dr. Vlisides is an Assistant Professor of Anesthesiology who works in the Center for Consciousness Science in the Department of Anesthesiology at the University of Michigan Medical School in Ann Arbor. Dr. Vlisides wrote an editorial view together with Dr. George Mashour that accompanies Dr. Gelb’s research article in the July 2019 issue of the journal and it’s titled “Pharmacologic Unmasking of Neurologic Deficits: A Stress Test for the Brain.” Dr. Vlisides, thank you for joining us.

Dr. Phillip E. Vlisides: Hi; Dr. Rathmell. It’s great to be here with you both. Thanks for having me.

Dr. James P. Rathmell: Dr. Gelb, what a phenomenal career you’ve had contributing to so many areas in our field and at an international level. Congratulations on all you’ve done and on the publication of this new study. Can you set the stage for us? What were the observations that led you to conduct this study?

Dr. Adrian W. Gelb: Thanks, Jim. It is really capitalizing on comments that our surgical colleagues make—in this case neurosurgeons—when I would comment to them when dropping the patient in the PACU or the ICU that they seemed neurologically worse than expected. Often neurosurgeons, like other surgeons, would say, “Oh, it’s probably just the anesthesia. They’ll be much better tomorrow or the day after.” And that seemed to me like a testable hypothesis. So, that’s really what we set out to test: Do some of the medications that we use really worsen neurologic signs and symptomology in our patients?

Dr. James P. Rathmell: So, you observed and then you published your observations that patients with gliomas in some areas of the brain have no apparent neurologic deficits or minimal neurologic deficits but develop worsened deficits when they’re sedated. The specific regions of the brain are often called “eloquent areas.” Can you explain what that means?

Dr. Adrian W. Gelb: So, eloquent areas of the brain are areas that are devoted to specific but very important functions in our lives: motor function, ability to move hands, legs, sensory functions, hearing, vision are most commonly referred to as being controlled by eloquent areas.

Dr. James P. Rathmell: So, what was the hypothesis you tested with this new study?

Dr. Adrian W. Gelb: So, just to jump back to the original study, the hypothesis there was, is the effect of the medications we use simply a nonspecific sedation effect or is it in some way receptor-specific? And for that original study, my colleagues Nan Lin in Beijing; and for this recent study, Nan again and Kaiying Zhang who’s now at UT Houston, we started off sedating patients very lightly. So, they sedated to the level where they’ll respond to voice. And we looked at midazolam, propofol, dexmedetomidine and fentanyl and we found fentanyl and dexmedetomidine had very little effect whereas propofol had some effect and midazolam a profound effect. So, we could conclude that this is not a nonspecific sedation effect.

One of the questions was, is this specific to the benzodiazepine receptor and secondly—and most importantly for our patients—is it reversible? So, in the current study we looked only at midazolam, sedated patients again very lightly all with supratentorial brain tumors and we had them do fairly simple tests, the sort of thing one has two- and three-year-old children do: pick up a little peg, put it in a hole in the board, do it as fast as you can and then take the pegs out as fast as you can.

And we had them do that without any sedation, with a very small dose of midazolam, and then reversed with flumazenil. And what we found was, once again, that midazolam had a profound, very significant unmasking or worsening of neurologic function of the hands and that this was reversed with flumazenil, pointing to the fact that this is probably a very specific benzodiazepine receptor effect.

Dr. James P. Rathmell: So, you tested 32 patients in total, 15 in the glioma group and 17 in the control group, and they all performed this standardized test and you described it where they’re timed to place nine pegs in holes on a board and that test has been very well-validated to detect subtle neurologic deficits.

This same test was repeated after administration of midazolam and then administration of flumazenil. So, what’s the take-home message from this, particularly for anesthesiologists who routinely care for patients having awake craniotomies?

Dr. Adrian W. Gelb: Well, I would say that the potential take-home message actually extends beyond just awake craniotomies. It pertains to any patient with a brain tumor who is receiving midazolam in the ICU, in the PACU, preoperatively or intraoperatively, that the midazolam may worsen the neurologic effects. And if that does happen, you need to be aware that midazolam can produce this, that it’s reversible by flumazenil and that one shouldn’t launch off on discussions or investigations suggesting that the patient has deteriorated in a significant fashion.

Dr. James P. Rathmell: What you’re suggesting is this may even obviate the need for imaging or prevent use of imaging in these situations. Have you seen people go off and get imaging and then find out later it was just a – this midazolam effect?

Dr. Adrian W. Gelb: Yes; in fact, very commonly because the easy access to CT scanning makes it available. So, a patient in the PACU or the ICU seems worse than a surgeon would expect, they get a CT scan and often the report is it just looks like a normal expected CT scan.

And in some of those patients when one looks back, one sees that they were agitated, somebody gave them some midazolam; and, in retrospect, it was probably the midazolam that made them look neurologically worse.

Dr. James P. Rathmell: An enormous, enormous impact directly to those patients. Dr. Vlisides, I want to turn to your editorial view. It’s titled “Pharmacologic Unmasking of Neurologic Deficits: A Stress Test for the Brain” and you coauthored it with Dr. George Mashour in your institution.

You do a nice job of pointing directly to the unique findings of Dr. Gelb’s study. Can you go over your take on what’s new and interesting about the study and the implications of the new findings from your point of view?

Dr. Phillip E. Vlisides: Sure. And first I’d really like to compliment Drs. Gelb and Lin and their team on a wonderful study. To me, the study wasn’t as simple as giving patients midazolam and observing for all the reduced neurologic deficits. It seems worse than a surgeon would expect, they get a CT scan and often the report is it just looks like a normal expected CT scan.

And in some of those patients when one looks back, one sees that they were agitated, somebody gave them some midazolam; and, in retrospect, it was probably the midazolam that made them look neurologically worse.

Dr. James P. Rathmell: Congratulations on all you’ve done and on the publication of this new journal and it’s titled “Pharmacologic Unmasking of Neurologic Deficits: A Stress Test for the Brain” and you coauthored it with Dr. George Mashour in your institution.

You do a nice job of pointing directly to the unique findings of Dr. Gelb’s study. Can you go over your take on what’s new and interesting about the study and the implications of the new findings from your point of view?
Dr. James P. Rathmell: Well, you point out some limitations of the study. What are the limitations you saw?

Dr. Phillip E. Vlisides: Well, I think it’s important to keep in mind that, of course, this is a focused study involving a subset of neurosurgical patients with a distinct type of neurosurgical pathology. So, I’m really curious to see how this type of sedation strategy might unmask neurologic deficits in other populations as well, of course.

The control group was a little bit younger than the neurosurgical group, but the effects of both midazolam and flumazenil seemed to be pretty robust in patients with the neurosurgical pathology, as Dr. Gelb said. And so, I think the findings are still quite compelling.

Dr. James P. Rathmell: In your editorial you go on to tell us that the authors present an accessible, practical method for probing neural vulnerability, both anatomically and functionally. Can you elaborate? How might this test prove useful in the future?

Dr. Phillip E. Vlisides: Right. So, I think this is very interesting: midazolam, this is a drug we use every day perioperatively and to me the study suggests that we might be able to leverage the GABAergic properties of midazolam to unmask neurologic deficits by potentially interfering with adaptive neural mechanisms that, at the least, seem to be modulated by GABA.

So, for example, maybe there are similar adaptive properties involving cognitive function and arousal in certain patients and maybe those adaptive processes might be neutralized from midazolam.

And I’ve had many patients, I’m sure you both have as well, who receive perhaps a small dose of midazolam and then pretty readily it becomes inaudible or obtunded and I wonder if those patients might be more prone to things like hypoxic delirium postoperatively and other altered arousal states.

So, can that sensitivity to midazolam tell us something about neural cognitive vulnerability and so on? And in that context, is there potentially a therapeutic role for flumazenil as well? So, I think these are questions we can certainly ask and test and I think the strategy could potentially be used to test for these types of associations clinically and I think that’s an exciting possibility.

Dr. James P. Rathmell: Fantastic. Dr. Gelb, what comes next for you and your research group?

Dr. Adrian W. Gelb: Well, I’d just like to add a comment about one of our findings which amazed us and that was the fact that not only was the expected hand disabled significantly, but we actually found the normal side, the ipsilateral hand, also manifested dysfunction with this small dose of midazolam and this really speaks to the extensive connectivity in the brain.

I think we in anesthesia tend to have very simple ways of thinking about neurologic function. But I think what we’ve unmasked here is this very extensive but often latent connectivity within the brain broadly across from one side to the other.

And this seemed most prominent in patients who had the most malignant lesions, perhaps reflecting the fact that whatever compensatory mechanisms developed are less mature than they are in those with slow-growing tumors.

So, to Phil’s comment about using it as a test, this may be an opportunity to actually pretest the maturity and the lack of vulnerability of those compensatory mechanisms.

To your question on what’s next, we’re interested in looking at those connections within the brain and there are some phenomenal imaging techniques now that allow one to explore functional connectivity and we see that as the next step of interest to us that we’ve embarked on.

But the suggestions in the editorial—which, quite honestly, we have not ever thought about this as a test—are very exciting as well and I think is an opportunity for us to look at that relationship between pretesting and postoperative outcome.

Dr. James P. Rathmell: Terrific. I hope today’s discussion will lead many of you listening to read this new article and the editorial view that appear in the July 2019 issue of Anesthesiology. You can learn more about how sedation with midazolam induces limb motor coordination deficits that are reversed by flumazenil in patients with gliomas.

Dr. Jon Wanderer from Vanderbilt and I also created an infographic that appears in the same issue titled “A Stress Test for the Brain: Sedation-Induced Deficits” where we aim to explain this study in simple and clear terms.

Drs. Gelb and Vlisides, thank you for joining me today and for the terrific explanations.

Dr. Adrian W. Gelb: You’re welcome. Thank you very much, Jim, for inviting us.

Dr. Phillip E. Vlisides: Thank you both very much. Greatly appreciate it.

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