Reemergence of Stroke Deficits With Midazolam Challenge

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Background and Purpose—Patients who have sustained a neurological injury and then improved may experience transient reemergence of their syndromes when given benzodiazepines. As a step toward assessing whether neurotransmitter systems underlie poststroke clinical improvement, we selected midazolam, a γ-aminobutyric acid (GABA) agonist, for systemic administration to measure general or stroke-specific effects in patients.

Methods—Eight patients with image-verified stroke (5 with left-sided and 3 with right-sided cerebral lesions) participated. The strokes had occurred from 7 days to 6 years earlier, with patients showing clinical improvement from their initial syndromes. Each patient underwent baseline testing for motor function, aphasia, and left hemispatial neglect, after which intravenous midazolam was delivered until mild drowsiness was detected. Patients were tested during this period and again after 2 hours when sedation had dissipated.

Results—After the administration of midazolam, the 5 patients with left hemisphere stroke demonstrated reemergence of worsening of their initial right hemiparesis and aphasia but showed no left neglect. The 3 patients with right cerebral stroke showed reemergence of left hemiparesis and left visual field neglect but no aphasia. All patients returned to baseline after 2 hours.

Conclusions—Under conditions of light sedation, patients whose initial stroke syndrome had substantially improved clinically showed transient reemergence of their initial focal syndrome. These data suggest a possible role for GABA-A-mediated neurochemical mechanisms in poststroke improvement and sensitivity to medication effects. (Stroke. 2002;33:283-285.)

Key Words: cognition ■ GABA ■ midazolam ■ stroke outcome

Investigations with functional imaging to study motor and language recovery after stroke have shown new regions of brain activity.1–4 The mechanisms by which such regions assume these new roles are largely unknown. One method of investigation might be to probe neurotransmitter systems that may underlie functional recovery.

Some patients who have sustained neurological deficits and then improved demonstrate a transient reemergence of syndromes after administration of anesthesia.5–7 To determine whether a sedative would transiently reinstate former stroke deficits, we selected midazolam, a nonselective benzodiazepine that potentiates γ-aminobutyric acid (GABA), the predominant central nervous system inhibitory neurotransmitter.

Subjects and Methods

Eight right-handed individuals with first-ever, image-verified stroke were enrolled. Informed consent was obtained from all patients as approved by the Columbia-Presbyterian institutional review board.

Study Measures

Three tasks assessed language (presumably left hemisphere) function, and 2 tested visual-spatial (presumably right hemisphere) skills; strength was assessed on both sides of the body. The consensus of 3 examiners was required for a patient’s response to be judged an error or abnormal. The order of tasks was varied across patients.

All behavioral tasks were administered on a Macintosh computer. The aphasia battery assessed naming, comprehension, and repetition. During the baseline evaluation, patients underwent the Boston Naming Test8 and the Dictated Commands and Repetition of Phrases subtests of the Boston Diagnostic Aphasia Examination (BDAE).9

Line bisection consisted of the individual presentation of 9 horizontal black lines on the computer screen. The patient’s instruction was to touch the center of the line. The perceived midpoint was calculated by averaging the percent deviations from the true midpoint on a scale from −100% (left end of the line) to +100% (right end of the line).10 Letter cancellation consisted of 72 black letters in a nonlinear array with 12 A’s in the left and right visual fields, respectively, and 24 distractive elements in each field. The patient was instructed to touch each letter A.

We assessed motor weakness in the upper extremities by testing drift, rapid alternating movements, and distal and proximal arm strength using the Medical Research Council rating scale.

Midazolam was then administered to patients as an intravenous bolus, titrated in 0.5-mg aliquots until they were unable to count backward. The aphasia battery for the drug phase was shortened to fit into the 4- to 5-minute period of maximum sedation. For the Boston Naming Test, we took 15 items. For repetition, we derived 5
sentences from the BDAE. Comprehension involved 15 new items for the patient to manipulate. The line bisection task remained unchanged except for line presentation order. Target cancellation involved the identification of the 12 A’s in each field but with new target locations within the field. The assessment of motor strength was unchanged.

We defined a change in language function as a loss of /H113502 points on a test (of 15 on naming, 15 on comprehension, and 5 on repetition) after drug administration compared with the patient’s baseline. Letter cancellation was abnormal with /H113502 A’s not detected in a visual field or the patient shifted to a right-to-left selection pattern. For line bisection, the development of visual neglect was defined via $t$ test as a statistically significant shift to the right or left in the patient’s perception of the midline during the medicated state compared with the patient’s baseline. A decline in motor strength was defined as the emergence of a definite pronator drift, a finger-tapping asymmetry, or a 1-point drop in the Medical Research Council scale.

Patients with dyslexia or visual field defect after stroke received a test of reading and confrontation testing of visual fields. Trials began with a 4-letter word in the center of the screen. As patients read aloud each word, a colored square was then presented for 100 ms in 1 of the 4 visual quadrants on the screen. Shown red, green, and blue, patients were required to respond with 1 of the 3 color names.

Two hours after drug infusion, the battery was readministered.

Results

Six men and 2 women participated, aged 37 to 76 years (Table 1). Five patients had left hemisphere stroke, and 3 patients had right hemisphere stroke. The time from clinical presentation to drug challenge ranged from 7 days to 6 years. Of the 8 patients, 5 had almost complete resolution of their stroke syndromes; 3 were neurologically normal.

All patients performed at the same functional level at baseline and 2 hours after drug administration. Table 2 shows the nature of the initial poststroke syndrome and the corresponding effects of the drug for each patient. All patients demonstrated relapse of a syndrome during the medicated state that resembled the deficits described by prior observers or seen at the time of stroke admission. Among individuals who suffered left hemisphere stroke, patients 1 and 2 redeveloped aphasia, and patients 1 and 3 became weaker on the right. The Figure shows that patient 4 demonstrated the reemergence of alexia; patient 5 had reappearance of her right upper quadrantal field defect but no alexia. No patient with a left hemisphere injury showed left-sided weakness or left visual neglect.

The individuals with right hemisphere stroke showed reemergence or worsening of left-sided weakness during the medicated state or neglect to the left. No patient with a right hemisphere lesion showed aphasia or right-sided weakness.

### TABLE 1. Patient Characteristics, Time From Clinical Event to Drug Challenge, and Clinical State at Time of Study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/Sex</th>
<th>Radiological Diagnosis</th>
<th>Time to Midazolam Challenge</th>
<th>Clinical State at Time of Midazolam Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75/M</td>
<td>L subinsular infarct</td>
<td>19 d</td>
<td>R pronation</td>
</tr>
<tr>
<td>2</td>
<td>59/M</td>
<td>L posterior temporoparietal hemorrhage</td>
<td>2 y, 6 mo</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>76/M</td>
<td>L capsular and corona radiata infarct</td>
<td>6 mo</td>
<td>Dystonic R hemiparesis</td>
</tr>
<tr>
<td>4</td>
<td>53/F</td>
<td>L temporo-occipital infarct</td>
<td>9 mo</td>
<td>Mild alexia</td>
</tr>
<tr>
<td>5</td>
<td>64/M</td>
<td>L posterior MCA infarct</td>
<td>6 mo</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>62/M</td>
<td>R frontal MCA infarct</td>
<td>7 d</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>69/M</td>
<td>R medial temporo-occipital, R posterior parietal, R thalamic infarct</td>
<td>2 y</td>
<td>Mild distal L arm weakness</td>
</tr>
<tr>
<td>8</td>
<td>37/F</td>
<td>R frontal lobe/basal ganglia infarct</td>
<td>6 y</td>
<td>Dystonic L hemiparesis</td>
</tr>
</tbody>
</table>

L indicates left; R, right; and MCA, middle cerebral artery.

### TABLE 2. Test Outcomes After Administration of Midazolam

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Stroke Location (Hemisphere)</th>
<th>Initial Clinical Syndrome</th>
<th>Outcomes After Midazolam Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left-Sided Weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aphasia</td>
</tr>
<tr>
<td>1</td>
<td>L</td>
<td>Aphasia; R hemiparesis</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>L</td>
<td>Aphasia</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>L</td>
<td>R hemiparesis</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>L</td>
<td>Alexia</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>L</td>
<td>Alexia; R upper quadrantanopia</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>L hemineglect; L hemiparesis</td>
<td>−</td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>L hemiparesis</td>
<td>−</td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>L hemiparesis</td>
<td>−</td>
</tr>
</tbody>
</table>

R indicates right; L, left.

*Not tested.
After receiving a short-acting sedative, patients whose stroke syndromes had subsided or who had recovered demonstrated the transient reemergence of their former deficits. Those with left cerebral injury demonstrated aphasia, right-sided weakness, or alexia but never left-sided weakness or neglect. Conversely, patients with a right cerebral stroke demonstrated temporary left-sided weakness and/or neglect but no aphasia or right-sided weakness. None of the relapsed findings were qualitatively new or affected neurological systems not affected in the original stroke.

Thal et al,11 who studied the effects of sedation on motor function by giving patients with mass lesions or carotid disease either fentanyl or midazolam, found reemergence of prior symptoms. Our results confirm this work for brain lesions in general and extend it to the study of stroke, providing an experimental methodology that may prove useful in the study of inferred neurotransmitter mechanisms.

The exacerbation or recurrence of previous stroke deficits with midazolam in our series suggests a vulnerability of the recovered brain to GABA_A-mediated inhibition. The findings, however, cannot be explained merely by effects of general sedation. The reemergence of focal deficits here indicates that the poststroke brain was not sensitive as a whole, providing additional support for the notion of transmitter-specific neural networks involved in poststroke improvement.12 Future prospective studies with larger numbers of patients may determine the relationship between the extent of deficit at stroke onset, the kinetics of stroke recovery, and the severity of deficits later elicited by GABAergic and possibly other sedating agents.

Acknowledgments

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References

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