Midazolam Challenge Reinduces Neurological Deficits After Transient Ischemic Attack

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Background and Purpose—A transient ischemic attack (TIA) in the brain is classically considered a syndrome lasting <24 hours. Having previously shown that an experimental challenge with the GABA A agonist midazolam in recovered stroke patients can reinduce the acute clinical state, we determined whether TIA patients would demonstrate a similar effect.

Methods—Four right-handed patients participated: 3 with clinical TIA presumed to have affected the left hemisphere within the previous 24 to 72 hours and no evidence of a new lesion on diffusion-weighted and fluid-attenuated inversion recovery imaging, and 1 patient with an asymptomatic temporal arteriovenous malformation. The TIA duration ranged from 30 minutes to 3 hours. Each patient underwent baseline testing for motor function and aphasia, after which intravenous midazolam was delivered until mild drowsiness was detected. Patients were tested during the peak drug effect and again after 2 hours when sedation had dissipated.

Results—No patient showed weakness or aphasia at baseline. After administration of midazolam, all 3 TIA patients demonstrated re-emergence of features that characterized their recent transient neurological syndromes (right-sided weakness and/or aphasia) but no left-sided findings. The arteriovenous malformation patient who had never been symptomatic showed no drug effect. Two hours later, all TIA patients returned to their normal clinical state.

Conclusions—Patients who had suffered recent transient cerebral ischemic episodes and were neurologically intact with negative diffusion-weighted imaging showed re-emergence of prior focal deficits after administration of a benzodiazepine in a dose that produces light sedation. These findings suggest that presumed TIA may produce neuronal dysfunction beyond the symptomatic period. (Stroke. 2003;34:794-796.)

Key Words: cerebral ischemia, transient ■ GABA ■ magnetic resonance imaging, diffusion-weighted ■ midazolam

The conventional definition of a transient ischemic attack (TIA) in the brain is an acute neurological syndrome of presumed ischemic origin with a duration of <24 hours. It has long been presumed in these cases that the resolution of symptoms indicates the absence of brain dysfunction. We present here the use of a pharmacological challenge that is capable of demonstrating a re-emergence of an image-negative, transient syndrome that we infer to represent residual cerebral dysfunction after “TIA.”

An experimental challenge with the sedative midazolam has shown temporary re-emergence of many of the elements of a clinical syndrome that had been precipitated in the acute state after a focal brain infarct but had undergone considerable remission in the days to years thereafter. Patients who had clinically “recovered” from a prior left cerebral stroke thus demonstrated aphasia and right-sided weakness, and patients with prior right cerebral infarction demonstrated temporary left-sided weakness and left visual-field neglect but no aphasia or right-sided weakness in response to the challenge. Midazolam, a nonselective benzodiazepine, was chosen for such testing because of its frequent clinical use, ease of administration, and brevity of clinical effect and because it potentiates the activity of GABA at the GABA A receptor, the predominant central nervous system inhibitory neurotransmitter. We sought here to determine whether patients clinically diagnosed as having TIA would demonstrate a similar effect with this agent and thus show that, despite the brief nature of symptoms, there was still brain dysfunction.

Subjects and Methods

After signing the institutional-approved consent form, 4 right-handed patients participated in this study. Three had experienced a transient neurological syndrome of presumed ischemic origin thought to have affected the left hemisphere within the previous 24 to 72 hours with no evidence of a new lesion on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery imaging at 24 hours. Patient 1 had experienced inability to read and had difficulty speaking with no weakness; Patient 2 presented with right hemiplegia and aphasia. The aphasia fully resolved within 45 minutes, but because she had residual weakness, she was given recombinant tissue plasminogen activator. Her workup revealed cardiac disease and an ulcerated aortic arch plaque. Patient 3 had several episodes of right-sided weakness and dysarthria and was found to have an occluded left internal carotid artery at its origin. Because the aphasia or dysarthria was transient in each of these cases, there were no quantitative...
analyses of their language deficits. There were no prior ischemic lesions on imaging. Patient 4 had no TIA but had an asymptomatic left mid to superior temporal arteriovenous malformation (AVM), discovered incidentally, in a location where an acute stroke would likely have produced a major sensory aphasia. We tested this patient to determine whether the presence of a left cerebral brain lesion per se would be sufficient to produce deficits during the drug state.

**General Design**

While being monitored for blood pressure, heart rate, and \( O_2 \) saturation, all patients underwent baseline testing (see the Figure) of language (comprehension, repetition, and naming) by means of a computerized assessment battery described previously\(^2\) and motor function (upper extremities, rapid alternating movements, and distal and proximal arm strength) using the Medical Research Council rating scale. Then, midazolam was administered in an intravenous bolus titrated in 0.5-mg aliquots to mild sedation as assessed by errors in counting backward from 20 to 1. The language (aphasia) battery and motor assessment were readministered over the 4-minute period of maximum drug sedation. Two hours after drug infusion, when the effects of the medication were judged fully dissipated, the language and motor tests were given again. Changes in function in language were predefined by a loss of \( \pm 2 \) points in aphasia testing (out of 15 in naming, 15 in comprehension, and 5 on repetition), which was based on preestablished criteria\(^2\)–\(^4\) and used in previous studies of superselective Wada testing.\(^5\) 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. The entire study was videotaped, and 3 judges had to agree as to whether medication had induced any effects in motor function or in oral responses by patients.

**Results**

Three men and 1 woman ranging in age from 36 to 75 years (see the Table) participated. The duration of TIAs ranged from 30 minutes to 3 hours. Patient 4 had the asymptomatic AVM.

At baseline (predrug) and 2 hours after the drug had been given, all TIA patients were clinically intact, showing normal skills in language and motor function. After administration of midazolam (2 to 3 mg), both patients 1 and 2 redeveloped an aphasia, and patient 2 developed a right hemiparesis. Patient 3 demonstrated re-emergence of his right hemiparesis. None of these 3 patients evidenced any weakness on the left side. Patient 4, who had never experienced any prior neurological deficits associated with the AVM, did not show any functional deficits at baseline or during or after sedation.

The deficits induced by the administration of midazolam were always less severe than those at the time of the clinical event, and there appeared to be no correlation between the severity of the clinical event and the degree of return under midazolam. In all cases, the peak effect of midazolam occurred within minutes of the final aliquot. The sedative effect of the agent was fully dissipated about 1 hour after the last dose was given. Blood pressure, which was continuously monitored, was not affected by the drug. No patient was able to later report any details of the relationship between the original clinical syndrome and the deficits elicited by midazolam.

**Discussion**

Our study represents the first pharmacological challenge in patients whose history was typical for TIA, demonstrating symptomatic relapse of clinical elements resembling their brief neurological syndromes. Although the definition of a TIA is made on a clinical basis, we made our inclusion criteria more stringent by requiring negative DWI imaging.\(^6\)

Our results show that administration of midazolam, a GABA-ergic sedating agent, can unmask former transient, focal neurological deficits. The original clinical syndromes were presumed to be the result of a brief ischemic event in the left cerebral hemisphere, and after midazolam had been given to each of our patients, all demonstrated deficits specifically associated with abnormality in the left side of the brain. Patient 4, who never had any symptoms, showed that the presence of a cerebral lesion is not, in and of itself, sufficient to produce drug-induced effects in our testing procedures.

Before the use of CT and MRI, the diagnosis of TIA was made purely on clinical grounds, but neuroimaging has altered thinking about the presence of brain injury when ischemic syndromes are brief. Standard MRI has demon-
strated neuroanatomically relevant infarcts in 31% of cases of presumed TIA.7 More recently, DWI and apparent diffusion coefficient imaging revealed clinically relevant focal abnormalities in 48% of a TIA series.8 In our TIA patients, none had abnormality on DWI, yet all showed re-emergence of their syndromic deficits with the drug challenge.

Our data suggest that measuring sensorimotor and cognitive function during a brief pharmacological challenge may increase sensitivity to the presence of brain injury. Although we studied only a small number of patients and other TIA patients may not show the same degree of symptom re-emergence, these findings nevertheless provide support for the notion that a functional challenge could prove helpful in the identification of brain injury beyond the brief symptomatic period. Unfortunately, the very nature of a transient clinical syndrome made it difficult to obtain a full quantitative assessment of deficits.

Future prospective, drug-blinded studies with larger numbers of patients may determine the time course of the persistence of subclinical neuronal dysfunction after transient ischemic events and the severity of deficits later elicited by GABA-ergic compared with other sedating agents. Although the study of neurologically normal subjects would validate further the specificity of these neurochemical effects, the experimental design of the present study allowed patients to serve as their own controls because each patient was evaluated on the full test battery. In this fashion, we have been able to demonstrate that prior deficits re-emerge corresponding only to the injured hemisphere, and to date, neither this study nor our prior work2 has shown medication-induced effects from the presumably unaffected side of the brain.

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References
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