Midazolam-induced unexpected monoparesis: Not contraindicated for ambulatory general anesthesia

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Abstract

Midazolam has been used widely at premedication to general anesthesia without many complications, but reemergence of the transient ischemic attacks (TIAs) in patients with previous TIA or stroke have been reported. We found similar cases of self-limiting transient hemiplegia with midazolam use in patients without previous history of TIA or stroke, and the self-limiting effects did not recur after proceeding with general anesthesia. We believe that midazolam-induced TIAs is not a contraindication to ambulatory general anesthesia.

Keywords: midazolam, general anesthesia, transient ischemic attack, unilateral events.

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Introduction

Midazolam has been used widely as a premedication to general anesthesia because of its favorable safety profile, and rapid anxiolytic effect [1]. Re-emergence of stroke deficits [2] and transient ischaemic attacks (TIAs) with midazolam challenge has been reported [3]; however, midazolam induced unexpected (without previous history) monoparesis has not. We report two patients who demonstrated unexpected and transient unilateral events after intravenous (IV) midazolam injection not contraindicated for ambulatory general anesthesia. We review the literature and discuss the rationale behind these findings. Informed consents were obtained from these patients.

Patient 1

A 45-year-old female, 84 kg, and 167 cm was scheduled for an ambulatory hysteroscopy and endometrial ablation. She smoked 2 packs per day for 20 years and received a coronary bypass surgery 4 years ago; however, she denied any history of neurological diseases. Physical examination, laboratory tests, and ECG results were unremarkable. She was cleared for surgery by an internist. After 2 mg IV midazolam injection was given as a premedication to ease her anxiety, she described: "only the left side of her body was relaxed" and requested some more for the right side. An immediate neurological consultation was arranged which revealed a normal neurological examination and a normal computed tomography (CT) image. The operation continued with endotracheal general anesthesia uneventfully, induced by 150 mg IV propofol and maintained with sevoflurane/nitrous oxide/oxygen mixture and 100 mcg fentanyl throughout the 40-minute procedure. Forty-five minutes later when the patient had been fully awake and alert in the post-anesthesia care unit, repeated neurological examination revealed no detectable abnormality. She was discharged home. A phone follow-up 24 hours later revealed no neurological sequelae.

Patient 2

A 72-year-old female, 100 kg, and 163 cm underwent wide excisions of lesions and skin grafts on her right arm. She had a history of diabetes, heavy smoking, and coronary artery bypass surgery 1 year ago but denied any previous neurologic disorder. Her daily activities and walking were well tolerated. She too was medically cleared for surgery. After 2mg IV midazolam injection, she responded: "It works more on the left side than the right side of my body." A close neurological examination showed an apparent left handgrip weakness (30% or less by estimation). An old right focal lesion was noted by CT scans (Figure 1). Diffusion-weighted imaging (DWI) revealed no new findings. The patient reported symptoms improving in the next 2 hours and a full recovery in 3 hours. The operation was rescheduled. One week later the patient underwent endotracheal general anesthesia induced by 150 mg IV propofol and maintained with sevoflurane/nitrous oxide/oxygen mixture and 100 mcg fentanyl. Left-hand monoparesis did not recur. She was

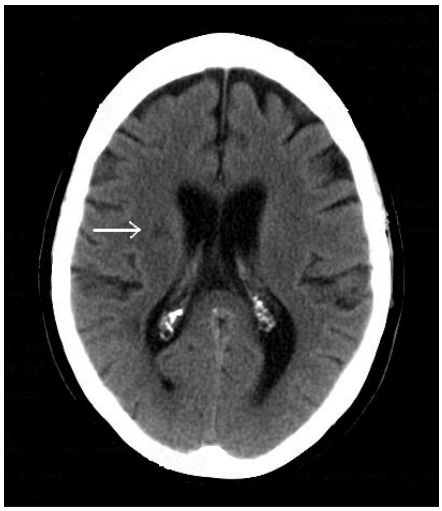

Figure 1 The CT scan of Patient 2, old ischaemic lesion, right side (arrowed).

discharged home, and a phone follow-up 24 hours later showed no complications.

Discussion

The unusual features of these 2 cases were the transient "unilateral effects" following IV midazolam injection in the ambulatory surgical setting. They had no clear neurological histories. In case 1, the patient described a subjective unilateral sensory effect, whereas in case 2 a post-sedation unilateral motor deficit was found. Further neurological exams and neuroimaging revealed old brain lesions in cases 2, but not in case 1. However, when endotracheal general anesthesia proceeded, there was no re-emergence of the neurological deficits previously induced by midazolam. We reviewed the literature and try to conceptualize the main reasons behind these unusual findings.

First, a neurotransmitter mechanism is inferred for these self-limiting unilateral effects following midazolam injection. Midazolam (2,3) is a gamma-aminobutyric acid type A (GABAa) receptor agonist that potentiates the activities of GABA, the predominant central nervous system inhibitory neurotransmitter at the GABAa receptors that are widely distributed throughout the brain. Lazar et al. find that patients with histories of TIA or stroke show reemergence of TIA after administration of midazolam in a dose that produces light sedation and all recover within 2 hours [2,3]. However, our cases are unexpected, without neurological history. Thal et al. [4] report 54 patients with previous TIA in whom briefly unmasked focal motor deficits are found when sedated with midazolam or fentanyl. These findings suggest that the reemergence of TIA phenomenon is not specifically from a particular class of sedative but a general property of centrally acting compounds (diazepam, (5) sufentanil, (6) fentanyl, (4) midazolam (2,3)).

Second, the patient may have a previous silent stroke (infarcts on CT scan but no symptoms [7] that remained unnoticed as in case 2 (Figure 1), since she too has increased risks for stroke [8] such as cigarette smoking, hypertension, diabetes mellitus, ischemic heart diseases, obesity, and cardiac surgery and since silent stroke is observed in just 13% of patients with TIA or minor ischemic stroke and has no residual deficit after the qualifying event [7]. The second possibility is that the presumed lesion remained undetected by imaging as in case 1; diffusion MRI reveals clinically relevant focal abnormalities in just 48% of TIA's [9]. Furthermore, it is also possible that one may suffer from a brand new perioperative stroke lesion; up to 45% of the patients after cardiac surgery acquire new ischemic brain lesions that are sub-clinical [10]. Table 1 summarizes perioperative brain ischemia risks with sedation or general anesthesia. Patients with previous strokes undergo general anesthesia increase brain ischemia rate to 1.5 – 2.9% [11]. The incidence of perioperative TIA is as high as 100% (2-4) when challenged previous TIA or stroke patients with midazolam or fentanyl for sedation.

Third, the diseased hemisphere may be more sensitive to midazolam per se during hypercapnia. During hypercapnia, specifically as a result of midazolam induced poor-ventilation [22] during premedication in these 2 cases, the brain's GABAergic activities are prone to changes in CO2 levels [13].

Fourth, we find that explanation by hypoventilation [12] and reduced cerebral blood flow to hypercapnia [14] of corresponding cerebral territories can not be excluded. When the subclinically diseased/injured/degenerated hemisphere [2–4] affected by hypoventilation and hypercapnia during respiratory depression following midazolam injection, [12] there is a subsequent unbalanced reduction of cerebral blood flow on the diseased side resulting in "differential effect" between the 2 hemispheres [15,16]. Normally, the addition of CO_2 to the inhaled anesthetic mixture is followed by cerebral vasodilation and increased cerebral blood flow in a non-diseased brain. However, using positron emission tomography, Levine et al. are able to demonstrate in TIA patients that the cerebral blood flows on injured hemispheres become significantly lower than the normal side possibly due to a steal phenomenon [14]. Although the findings in these two cases cannot be explained merely by effects of general sedation [2], they imply "improved ventilation" under general anesthesia somehow relieves the hypoventilation related hypercapnia and thus mitigates the brain's differential hypoperfusion response.

Table 1 Summary of reported perioperative risks of TIA.

Sedation	Reported risk rate
11 patients studied by Lazar et al.: midazolam challenge the transient revelation of resolved prior motor deficit (2,3)	100%
54 patients studied by Thal et al.: midazolam or fentanyl challenge the transient revelation of resolved prior motor deficit (4)	73%
General Anesthesia	Reported Risk Rate
Cardiac surgery (7)	45%
Advanced age, over 80 for surgery (8)	3.2%
General surgery with a history of previous stroke (11)	2.9%
General anesthesia with a history of previous brain ischemia (11)	1.5-2.9%
History of diabetes, hypertension, and smoking (8)	Increased
General anesthesia for non-vascular surgery (8)	0.08-0.7%

The main limitation of this report is a paucity of cases, especially patients with previously unnoticed or undetectable (silent) stroke. Nevertheless, this report sheds light to clinicians to conceptualize how these unexpected and self-limiting situations occur and manage them accordingly.

Conclusion

We describe 2 patients in whom there were no previous histories of neurological deficits, yet they developed monoparesis following IV midazolam injection and without reemergence after subsequent endotracheal general anesthesia. We believe that the decreased cerebral blood flow due to sedation-related hypercapnia and increased sensitivity to midazolam on the injured hemisphere play roles in these unilateral events. Good ventilation and hydration are essential to mitigate these unilateral effects. The transient pharmacological effect should resolve over time. A thorough exclusion of new neurological lesions is crucial since these patients are at increased risk for recurrent TIA or major stroke in the future.

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Conflict of interest: None.

Ethical standards: The authors confirm that the patients in these case reports gave their informed consent.

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