Total Intravenous Anesthesia Using N-Methyl-D-Aspartate (NMDA) Receptor-Sparing Drugs in a Patient with Anti-NMDA Receptor Encephalitis

Daniel K. Broderick, MD, Douglas E. Raines, MD, and Karen C. Nanji, MD, MPH

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a recently identified syndrome characterized by psychosis and dysautonomia. Treatment includes resection of the underlying tumor. While the pathologic mechanism involves disruption of NMDA function by anti-NMDA receptor autoantibodies, there are few descriptions of the perioperative management or anesthetic approach for such patients. We report a classic presentation of anti-NMDA receptor encephalitis and describe the use of total IV anesthesia with NMDA receptor-sparing drugs. Modest postoperative analgesic requirements, not reported in prior cases, are also described in our report. (A&A Case Reports. 2014;2:83–5.)

Since its first report in the medical literature in 2007,[1] anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has gained attention as a significant cause of acute paraneoplastic encephalitis in young adults and is the second most common cause of noninfectious encephalitis.[2] While anti-NMDA receptor encephalitis may have important considerations for perioperative management, the anesthesia literature examining its implications is sparse.[3–6]

Anti-NMDA receptor encephalitis is caused by the disruption of NMDA function by anti-NMDA autoantibodies.[7] In more than half of cases, these antibodies are associated with an underlying tumor, most commonly an ovarian teratoma.[7] Patients present with a flu-like prodrome followed by rapid development of psychosis, seizures, dyskinesias, and catatonia. Left untreated, autonomic instability, cardiac arrhythmias, and hypoventilation may occur, leading to death in severe cases.[1]

This case report describes the anesthetic management of a woman presenting to our hospital with anti-NMDA receptor encephalitis. Our report provides a detailed account of the use of total IV anesthesia (TIVA) as a technique to avoid further disruption of the NMDA receptor in these critically ill patients. Notably, while we put forth a theoretical framework for the use of an NMDA-sparing approach, there are no experimental data suggesting that alternatives like volatile anesthetics are harmful in such cases.

We obtained written consent from the patient to include the details outlined in the case description.

CASE DESCRIPTION

Our case is a 38-year-old, 86 kg, previously healthy woman who experienced 1 week of headaches, insomnia, and auditory hallucinations. She subsequently had witnessed seizure-like episode and was admitted to an outside hospital neurology service, where a lumbar puncture, magnetic resonance imaging study of the brain, and electroencephalogram were all normal. The patient was discharged but continued to demonstrate increasing psychosis, marked by perseverative behaviors and auditory hallucinations, which prompted readmission to the outside hospital. She was initially treated with olanzapine but developed profound neuropsychiatric deterioration, demonstrating unpredictable, nonsensical, and aggressive behavior. An abdominal computer tomography scan was obtained to exclude paraneoplastic syndrome, and it revealed an ovarian teratoma. The patient was transferred to our center for subsequent management.

On arrival, her temperature was 36.6°C (98.0°F), heart rate 95 bpm, arterial blood pressure 126/81 mm Hg, and hemoglobin oxygen saturation 99% while breathing room air. Routine laboratory tests, including a complete blood count, chemistry panel, renal, and liver function tests were normal. The paraneoplastic workup was completed with serum and cerebrospinal fluid (CSF) autoantibody panels, and she was treated empirically with high-dose corticosteroids.

On hospital day 3, the patient was scheduled to undergo laparoscopic salpingo-oophorectomy. Preoperative physical examination revealed a catatonic woman who was unresponsive to questioning and refusing airway examination. Her vital signs were similar to those on hospital admission. Anesthesia was induced with fentanyl (200 mcg) and propofol (200 mg). Neuromuscular blockade was achieved with cisatracurium (10 mg), and tracheal intubation was uneventful. Known NMDA antagonists such as nitrous oxide (N_2O), volatile anesthetics, and ketamine were avoided, and a TIVA technique was used with continuous infusions of propofol (initial rate 100 mcg/kg/min, titrated to 50 mcg/kg/min, total dose 10.9 mg/kg) and remifentanil (initial rate 0.1 mcg/kg/min, titrated to 0.05 mcg/kg/min, total dose 6 mcg/kg) to maintain anesthesia during the 90-minute surgical period. Analgesia was supplemented with 0.6 mg hydromorphone, divided into 2 doses, 0.4 mg at 30 minutes and 0.2 mg at 90 minutes after anesthetic induction (total dose 7 mcg/kg). The surgeons were successful in removing the ovarian teratoma.

From the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Accepted for publication September 30, 2013.

Funding: None.

The authors declare no conflicts of interest.

Address correspondence to Karen C. Nanji, MD, MPH, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114. Address e-mail to knanji@partners.org.

DOI: 10.1213/XAA.0000000000000003

At the time of surgical closure, all sedative-hypnotics were discontinued. The patient had 1 twitch on train-of-four testing with a 50 mA current, and her heart rate was 83 bpm. Neuromuscular blockade was reversed with neostigmine (4 mg) and glycopyrrolate (0.4 mg), after which train-of-four testing was measured to be 4 of 4 twitches. There was difficulty establishing a consistent pattern of ventilation. Thirty minutes after surgical closure, naloxone (2 doses of 40 mcg) was given for presumed narcosis, and the patient resumed spontaneous ventilation, and her trachea was extubated.

The patient was given 10 mg oxycodone in the postanesthesia care unit, in addition to IV ketorolac (30 mg). On postoperative day (POD) 1, the patient's pain was treated only with ketorolac; she required no analgesics on POD 2 and 3. On POD 4, 5, and 6, she was given 30, 20, and 10 mg oxycodone, respectively. The patient never required IV opioids for breakthrough pain in the postoperative period.

The patient's erratic behavior and auditory hallucinations resolved by day 6 after surgery, and she was discharged home with family support. Pathology confirmed a teratoma, and CSF testing was positive for anti-NMDA receptor antibodies. Within 4 weeks of her admission, the patient had returned to normal daily life with her husband.

DISCUSSION

It is understood that anti-NMDA antibodies cause receptor deactivation by binding and internalization of the NMDA receptor,[7,8] but the precise way this process causes encephalitis is not clear. It has been speculated that the disease course of anti-NMDA receptor encephalitis parallels the spectrum of behavioral effects of NMDA antagonists such as ketamine.[7] Given at subanesthetic IV doses (<1.0 mg/kg), ketamine inhibits memory formation, causes attention impairment, and induces bizarre thought content.[9] When ketamine is used alone for procedural sedation (1.5–2.5 mg/kg IV), it causes dissociative anesthesia while preserving or increasing arterial blood pressure and heart rate.[10] Dysphoria (27%–56%), vivid hallucinations (6%–10%), and unpleasant dreams (10%) can also occur at these doses.[10] Purposeless movements and tonic-clonic muscle activity have been observed. While the incidence is rare, ketamine overdoses cause respiratory depression starting 2 minutes after administration, coinciding with peak brain concentrations.[11] This spectrum of ketamine's effects is analogous to reports showing an association between higher titers of CSF NMDA autoantibodies and disease severity; those with mild disease had lower titers, and those who died had the highest.[8] As patients recover, their antibody titers begin to decrease.

Other commonly used anesthetic drugs also cause NMDA receptor inhibition. Desflurane, isoflurane, and sevoflurane all antagonize NMDA receptors as a component of their effect on a wide range of targets throughout the brain.[12] N_2O also disrupts NMDA receptors at anesthetic concentrations.[13] While propofol's primary effect is mediated through direct activation of γ-aminobutyric acid type A receptors, studies involving neuronal protection from NMDA-mediated glutamate excitotoxicity have generated conflicting evidence as to the effect it has on NMDA receptors,[14] and this is an area for future research.

Given what is known about anti-NMDA receptor encephalitis and the effects of NMDA antagonism, our patient's preoperative catatonia was suggestive of continued secretion of anti-NMDA antibodies and ongoing disruption of NMDA receptor function. We chose anesthetic drugs that would avoid further exacerbation of her encephalopathic state, specifically fentanyl, remifentanil, cisatracurium, and hydromorphone. We also used propofol although its relationship with the NMDA receptor remains to be fully understood. We avoided ketamine, volatile anesthetics, and N_2O as these are known NMDA antagonists.

The patient's postoperative opioid requirements were modest, especially during the first 3 PODs. Typical opioid use after laparoscopic pelvic surgery ranges from 14 to 19 mg of oxycodone (or morphine equivalent) on POD 0 to a low of 1 to 6 mg oxycodone on POD 3.[15,16] Through POD 3, our patient required a total of 10 mg oxycodone, in addition to IV ketorolac. This observation is consistent with laboratory and clinical evidence that suggest that NMDA antagonists attenuate pain intensity and decrease postoperative opioid use.[17] These analgesic effects may reflect the continued circulation of anti-NMDA antibodies in the perioperative period.

Few case reports in the existing literature describe anesthetic techniques used in patients with anti-NMDA receptor encephalitis.[3–6] A variety of techniques have been used, including the avoidance of N_2O and ketamine. Our report provides both a detailed description and a theoretical framework for the use of TIVA in such patients. Importantly, no major complications are described in the literature. Because the literature is sparse on the use of NMDA antagonists in patients with this disease, it is unknown to what degree anesthetic selection affects the outcome of such cases. An anesthetic approach should be chosen with consideration of other important variables such as case urgency, hemodynamics, anesthetizing location, drug availability, and cost.

In conclusion, anti-NMDA receptor encephalitis is a recently identified cause of a rapidly debilitating and potentially life-threatening psychosis, where a primary therapeutic modality is surgery. This case outlines a classic presentation of the disease and important considerations for anesthetic management, including a detailed report of TIVA for a patient with anti-NMDA receptor encephalitis.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36
2. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, Ward KN, Lunn MP, Irani SR, Vincent A, Brown DW, Crowcroft NS; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 2010;10:835–44
3. Pryzbylkowski PG, Dunkman WJ, Liu R, Chen L. Anti-N-methyl-D-aspartate receptor encephalitis and its anesthetic implications. Anesth Analg 2011;113:1188–91
4. Pascual-Ramírez J, Muñoz-Torrero JJ, Bacci L, Trujillo SG, García-Serrano N. Anesthetic management of ovarian teratoma

excision associated with anti-N-methyl-D-aspartate receptor encephalitis. Int J Gynaecol Obstet 2011;115:291–2
5. Kawano H, Hamaguchi E, Kawahito S, Tsutsumi YM, Tanaka K, Kitahata H, Oshita S. Anaesthesia for a patient with paraneoplastic limbic encephalitis with ovarian teratoma: relationship to anti-N-methyl-D-aspartate receptor antibodies. Anaesthesia 2011;66:515–8
6. Splinter WM, Eipe N. Anti-NMDA receptor antibodies encephalitis. Paediatr Anaesth 2009;19:911–3
7. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, Parsons TD, Lynch DR, Dalmau J, Balice-Gordon RJ. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 2010;30:5866–75
8. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8
9. Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996;14:301–7
10. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med 2009;27:512
11. Green SM, Clark R, Hostetler MA, Cohen M, Carlson D, Rothrock SG. Inadvertent ketamine overdose in children: clinical manifestations and outcome. Ann Emerg Med 1999;34:492–7
12. Solt K, Eger EI 2nd, Raines DE. Differential modulation of human N-methyl-D-aspartate receptors by structurally diverse general anesthetics. Anesth Analg 2006;102:1407–11
13. Jevtović-Todorović V, Todorović SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumski CF, Olney JW. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 1998;4:460–3
14. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. The experimental and clinical pharmacology of propofol, an anaesthetic agent with neuroprotective properties. CNS Neuroscience & Therapeutics 2008;14:95–106
15. Turunen P, Carpelan-Holmström M, Kairaluoma P, Wikström H, Kruuna O, Pere P, Bachmann M, Sarna S, Scheinin T. Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. Surg Endosc 2009;23:31–7
16. El Hachem L, Acholonu UC Jr, Nezhat FR. Postoperative pain and recovery after conventional laparoscopy compared with robotically assisted laparoscopy. Obstet Gynecol 2013;121:547–53
17. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. Anesth Analg 2003;97:1730–9