Seize the Chance to Save a Life: Local Anesthetic Systemic Toxicity

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Stem Case and Key Questions Content
A 33-year old female with right wrist fracture presents for open reduction and internal fixation. She arrives in your preoperative area from home on the day of surgery. She is planned for admission post-operatively. Her past medical history includes seizure disorder, chronic back pain, and tobacco use (1.5 ppd for 10 years).

Vital signs include: height 63 inches, weight 65 kg, BP 131/72, HR 73, SpO2 100% RA, Temp 36.5, RR 16. Her current medications include: Dilantin, Oxycontin BID, and Oxycodone PRN.

1. What additional information do you want regarding her seizure disorder? Does she have epilepsy?

2. Does the timing of her most recent seizure affect your anesthetic plan?

3. The patient is very concerned about post-operative pain control due to her long-standing history of chronic pain and opioid use, and asks what the options are for pain management. You discuss regional versus general anesthesia options for anesthetic management and a regional block for post-operative pain. Does her seizure history contraindicate regional anesthesia?

4. Is she at increased risk for local anesthetic systemic toxicity? If you proceed with regional anesthetic technique, should you modify any aspects of your planned block?

5. Do you need to see anti-epileptic drug levels prior to surgery?

6. The case is planned for 2 hours, and after talking with both the patient and the surgeon, you decide on a regional anesthetic with MAC, and plan to place a supraclavicular block and catheter under ultrasound guidance to maximize her post-operative pain relief. The block is placed with negative aspiration throughout with total dose of 25ml of 0.5% Ropivacaine (125mg) with epinephrine at
1:400,000. Additionally, because of her degree of opioid tolerance, she was given 60mg of propofol for sedation during the block/catheter placement. As you are securing the catheter, she becomes unresponsive and begins seizing. Your treatment? Should you give her Dilantin?

7. Should you feel reassured that you performed the block under ultrasound guidance?

8. Should you consider Intralipid? If so, how do you administer it?

9. The seizure stops and she is now stable in a post-ictal state. Possible seizure etiologies?

10. Are you concerned about the dose of local administered? What is the toxic dose of Ropivacaine with/without epinephrine? What is LAST? Why may she likely have had no early signs of LAST prior to the seizure?

11. What is the prevalence of seizure disorder? What is the incidence of seizure due to local anesthetic toxicity with regional anesthesia (epidural, caudal, peripheral nerve block)?

12. Do you proceed with the case, or cancel?

13. If you elect to proceed, would you change your plan to a general anesthetic? Do you dose her regional catheter post-operatively with local?

14. Once she is fully awake and recovered, what do you tell her about future regional anesthetics should she require surgery again in the future?

Model Discussion Content
Seizure Disorder
Epilepsy is the most common of serious neurological disorders, with a prevalence of 0.5-1% of the population (1-3). Epilepsy is the tendency to have recurrent unprovoked seizures. Therefore, all patients that have epilepsy have seizures, but not all patients with a history of seizures have a diagnosis of epilepsy. Patients with epilepsy often require non-neurological surgery, and many anesthetic agents affect the seizure threshold, in both patients with epilepsy and in those with no prior history of seizure (1,2). In those patients whose seizures have been well-controlled, anesthesia providers should advise patients to continue taking their medications in the perioperative period, and stress the need to avoid missing a dose of their anti-epileptic medications if possible (1). If only one dose is likely to be missed, an attempt should be made to administer it as soon as possible after surgery (1). Generally, routine drug level monitoring is not required perioperatively since anesthetic agents do not cause significant alterations to the pharmacokinetics of anti-epileptic drugs (1,2). In the
case of prolonged ICU stay however, changes in serum pH and albumin levels may affect the serum concentrations of anti-epileptic drugs, so assessment of drug levels may be warranted (1,2). Dilantin has unique pharmacokinetic properties which typically necessitate daily serum concentrations to guide dosing (1).

Perioperative seizure incidence in 2005 was identified as 3.1 per 10,100 patients, and in this population 30% were directly associated with anesthesia (2). A retrospective study of 6-years of medical records of 641 patients with a pre-existing seizure disorder showed that among those patients, 3.4% experienced perioperative seizures (2). Patients at increased risk for perioperative seizures had more frequent seizures at baseline, a shorter length of time between the last seizure and hospital admission, and sub-therapeutic levels of anti-epileptic drugs (2,4). The perioperative period has many implications for seizure development including changes in anti-epileptic medication regimen due to NPO status, lack of patient adherence to preoperative medication recommendations, sleep deprivation, stress, surgical pain, and adverse drug reactions (2,5). It is important that inpatient anti-epileptic drug regimens are as close to the outpatient regimen as possible to maintain adequate blood levels (2).

Local Anesthetic Systemic Toxicity (LAST)
Local anesthetic systemic toxicity is a major source of morbidity and mortality in the practice of regional anesthesia (6). American Society of Anesthesiologists Closed Claims data noted that LAST accounted for one-third of claims for death or brain damage associated with regional anesthesia (6). LAST can occur after administration of an excessive dose, with rapid absorption, or as a result of an inadvertent intravenous injection (7). The time-to-peak plasma levels after a single local anesthetic bolus ranges from 15 to 120 minutes in previous studies, depending on anatomic location (4,8,9). Estimated overall incidence of perioperative seizures related to local anesthetic toxicity is 120 per 10,000 (2). Systemic toxicity typically manifests as central nervous system (CNS) toxicity (tinnitus, disorientation, and seizures) or cardiovascular toxicity (hypotension, dysrhythmias, and cardiac arrest) (7). Although the dose causing CNS symptoms is typically lower than the dose and concentration resulting in cardiovascular toxicity, as the CNS is more susceptible to local anesthetic toxicity than the cardiovascular system (7).

The earliest signs of systemic toxicity are typically signs of excitation, including lightheadedness and dizziness, difficulty focusing, tinnitus, confusion, and circumoral numbness (7). One potential issue with sedation (particularly propofol) is that these early signs may be missed as the patient may be unable to report them (7). Premedication with benzodiazepine lowers the probability of seizures, but also can mask signs of early toxicity (7). Routine premedication with benzodiazepines continues to be extensively used, however, as the masking of toxicity is considered a theoretical concern (7). Prevention of LAST begins with setting up an environment capable of treating toxicity due to regional anesthesia, and to carefully select the type, dose, and concentration of local anesthetic (7).
Additionally, consideration needs to be given to the type of regional technique to be performed (7). Seizures associated with brachial plexus block (in particular the interscalene and supraclavicular approaches, where inadvertent injection of local anesthetic can enter the cerebral circulation via uptake by the carotid and/or vertebral arteries), were reported in up to 79 per 10,000 patients from a single institutional database (6). Moreover, local anesthetic should always be injected incrementally, with aspirations every 3-5 ml to monitor for accidental intravascular injection (regardless of whether or not epinephrine is used as a marker for intravascular injection) (7). Toxic doses of the more commonly used local anesthetics are: Ropivacaine 3mg/kg, Bupivacaine 2.5mg/kg plain and 3mg/kg with epinephrine, Lidocaine 4-5mg/kg plain and 7mg/kg with epinephrine, and Mepivacaine 4-5mg/kg plain and 7mg/kg with epinephrine (10). Additionally, patients should be monitored not only during the local injection, but also after as clinical toxicity can be delayed up to 30 minutes (11). Ultrasound guidance can potentially reduce the frequency of vascular puncture, but no randomized-controlled trials exist that can demonstrate or refute an actual reduction in LAST (6). Therefore, ASRA practice guidelines state that the best prevention of intravascular injection is the utilization of both ultrasound guidance and epinephrine test dosing (6).

Treatment of LAST begins with early recognition of the toxicity and discontinuation of the local anesthetic administration. The American Society of Regional Anesthesia and Pain Medicine (ASRA) has developed a “Checklist for Treatment of Local Anesthetic Systemic Toxicity” (11), and published a “Practice Advisory on Local Anesthetic Systemic Toxicity” (6). Per ASRA recommendations, the initial focus is on airway management, suppression of seizures with preferably benzodiazepines (though propofol can stop seizures, it should be avoided when signs of cardiovascular compromise are present) (6). Cardiac arrhythmias can be managed using ACLS, but may require medication adjustments. ASRA recommends avoidance of vasopressin, calcium channel blockers, beta blockers, or local anesthetics (11). Additionally, ASRA suggests reducing individual epinephrine doses to <1mcg/kg (11). Based on animal studies and case reports, lipid emulsion 20% (Intralipid) should also be considered if LAST suspected. The dosing of lipid emulsion is a 1.5mL/kg (lean body mass) bolus IV over one minute, followed by a continuous infusion at 0.25mL/kg/min (11). Bolus can be repeated once or twice for persistent cardiovascular collapse, and the infusion rate can be doubled to 0.5mL/kg/min if blood pressure remains low (11). Infusion should be continued for at least 10 minutes after circulatory stability is attained (11). The recommended upper limit of lipid emulsion dosing is approximately 10mL/kg over the first 30 minutes (11). ASRA allow recommends posting LAST events at www.lipidrescue.org and reporting use of lipid to www.lipidregistry.org (11). Of note, propofol is not a substitute for lipid emulsion (6).

Regional Anesthesia in Patients with Seizure Disorder
All patients undergoing regional anesthesia are at risk for LAST, particularly when large doses of local anesthetic are used (4). The incidence of CNS local anesthetic toxicity (seizure) has been previously published for various types of regional techniques in the general population (1.2 to 11 per 10,000 patients) (6).
epidural anesthetics, 1.3 to 69 per 10,000 caudal anesthetics, and 0 to 25.4 per 10,000 peripheral nerve blocks) (4). Prior work however, did not report the number of patients with a history of seizure disorder (4). A retrospective study reviewed patients with a documented seizure history who underwent epidural, caudal, or peripheral nerve block over a 14-year period (4). This study found that only 5 of 24 patients who experience post-operative seizure could potentially be related to local anesthetic toxicity; although the relationship between local anesthetic and seizure could not be conclusively demonstrated (4).

Currently, based on existing literature, regional anesthesia has not been concluded to be contraindicated in patients with a pre-existing seizure disorder (2,4,12). Recommendations however, for patients with a predisposition to seizures include using the lowest effective anesthetic dose, using local anesthetic agents with lower toxicity (such as lidocaine or mepivacaine), and providing post-operative analgesia with opioids (2,4). The incidence of any convulsive disorder has been shown to approach 10% in patients through 74 years of age (4,13). It is therefore, not unlikely to have patients with a seizure disorder diagnosis present for surgical procedures which are amenable to regional anesthesia (4). Moreover, data on the overall incidence of perioperative seizures in patients with pre-existing seizure disorder and the effect of anesthetic management on seizure risk are lacking (4).

References
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