Catching the Seizure Culprit: Drugs on the Differential

Melissa A. Nestor, PharmD; Melody Ryan, PharmD, MPH, BCPS, CGP, FCCP; Aaron M. Cook, PharmD, BCPS

Seizure activity occurring in hospitalized patients can be multifactorial, and discerning the underlying cause from a multitude of potential factors can pose a diagnostic dilemma. Seizure activity, although a rare complication, has been associated with commonly used medications. "Seizure activity occurring in hospitalized patients can be multifactorial, and discerning the underlying cause from a multitude of potential factors can pose a diagnostic dilemma. It is often difficult to point to a definite cause of seizure activity in surgical patients as multiple factors in the perioperative period can contribute such as drug therapy, underlying patient physiology, and nature of any injury. Orthopedic traumas can be secondary to seizure activity, either secondary to falls sustained during seizure activity or due to physiological strain caused by seizure activity."

Seizure activity, although a rare complication, has been associated with commonly used medications. Although drug-related seizures can present in patients with no known seizure history, extra care should be taken when treating a patient with a known seizure history. This article focuses on commonly used drug therapy agents with high potential for causing seizure activity in patients (Table 1), including antibiotic agents, opioid and nonopioid pain medications, and antidepressant agents, and identification of patients at high risk for developing drug-related seizures.

Antibiotics are among some of the most commonly used agents in hospitalized patients, both for prophylaxis and treatment of infection. Three classes of antibiotics that have been linked to seizure activity or other neurotoxicity include β-lactam agents, fluoroquinolones, and metronidazole (Table 2).

Penicillin was the first β-lactam agent to have a described association with seizure activity, with reports dating to the early clinical use of penicillin in the 1940s. It is believed that the penicillin-related seizure activity is due to interference with gamma-aminobutyric acid (GABA) transmitter activity. Other β-lactam agents, including the isoxazolyl penicillins (oxacillin, nafcillin), ureidopenicillins (piperaclillin), and amoxicillin/ampicillin have been associated with increased seizure activity. The cephalosporins also have been associated with seizure activity through the same mechanism as the penicillins.

Cefepime and ceftazidine are the agents most often reported with drug-associated seizures, but all agents within the class, including cefazolin, have been linked to drug-associated seizures. Likewise, the carbapenems have been linked to drug-related seizure activity with more reported cases of drug-related seizure with high dose imipenem/cilastatin as compared to other carbapenem agents.

Meropenem and ertapenem have an incidence of seizure activity comparable to that of cephalosporin agents while limited data are available for the newest carbapenem agent, doripenem, with respect to the incidence of drug-related seizure. The fluoroquinolone agents have the potential to precipi-
trovafoxacin have been associated with central nervous system adverse event rates ranging from 1% to 11% for erythromycin, levofloxacin, and clarithromycin. Other antibiotic agents associated with central nervous system toxicity include tetracyclines, sulfonamides, aminoglycosides, and rifampin. Pain medications are commonly used in the orthopedic patient populations and there is a risk of drug-related seizure with use of these agents. In particular, seizure has been associated with agents such as tramadol, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Table 1: Drugs Associated With Seizure Activity

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Antipsychotics</th>
<th>Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Clozapine</td>
<td>Meperidine</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Chlorpromazine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Haloperidol</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Anesthetics</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Propofol</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Sevoflurane</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Cyclosporine</td>
<td>Tricyclic antidepressants</td>
</tr>
</tbody>
</table>

It is unclear by what mechanism fluoroquinolones may induce seizure, but interference with gamma-aminobutyric acid receptors is suspected based on molecular side chain structure of individual fluoroquinolone agents. Of the commonly used systemic fluoroquinolone agents, ciprofloxacin is more likely to be associated with central nervous system toxicity, including seizure, than levofloxacin and moxifloxacin.

Other antibiotic agents, such as metronidazole, have been linked to drug-related seizure. The mechanism underlying the increased potential for seizure is unknown at this time. Metronidazole concentrations within the brain are known to be high after typical doses and it has been postulated that cumulative dose may be a factor.

With increased incidence of multi-drug resistant pathogens, agents such as colistin and polymyxin B are being used more often to treat resistant bacteria. These agents are associated with central nervous system toxicity of dizziness and ataxia, with reported drug-related seizure in association with intrathecal and intraventricular use of colistin in central nervous system infection. Isoniazid has been associated with seizure activity by inhibiting the synthesis of gamma-aminobutyric acid in the central nervous system.

Other antibiotic agents associated with central nervous system toxicity include tetracyclines, sulfonamides, aminoglycosides, and rifampin. Pain medications are commonly used in the orthopedic patient populations and there is a risk of drug-related seizure with use of these agents. In particular, seizure has been associated with agents such as tramadol, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Tramadol is a widely used analgesic, especially known for having a decreased potential for addiction. In addition to its analgesic properties, tramadol also inhibits serotonin and norepinephrine reuptake. In a case series by Spiller et al., 87 cases of tramadol overdose reported to poison centers, 7% reported seizure activity. The lowest dose associated with seizure in this series was 500 mg. In an evaluation of patients with current history of tramadol and other drug abuse, seizures were reported in 54% of patients. It should be noted this patient group was taking tramadol in combination with alcohol, illicit agents, and drugs of abuse, with a trend to seizure activity with a lower tramadol dose when taken in combination with alcohol.

In a retrospective evaluation of claims and diagnost data by Gardner et al., the incidence of seizure was <1% in the study group, with increased seizure risk associated with alcohol abuse, history of stroke, or prior brain injury. Overall, seizure activity has been reported with both therapeutic doses and overdose with a higher incidence of seizures reported in patients taking higher than prescribed doses and in patients using tramadol in combination with other agents of abuse and alcohol.

Opioid agents have the potential of precipitating seizure activity, but this is generally related to the dose and route of administration of individual agents. Meperidine, however, has a well-defined mechanism of neurotoxicity. Meperidine is metabolized to the liver to an active metabolite, normeperidine, which has been linked to neuroexcitation and seizure activity. Given the long half life of normeperidine, 15 to 40 hours, as compared to the half life of the parent drug meperidine, 3 to 6 hours, the neuroexcitatory effect of the metabolite can persist longer than the analgesic effects of meperidine.

Epidural and intrathecal administration of morphine has been linked to seizure activity, although not seen with intravenous administration. Morphine-related seizure activity has the potential to be reversible with use of naloxone and is likely caused by effects on both opioid receptors and gamma-aminobutyric acid receptors. Fentanyl and its analogues,
Antidepressants, although less commonly used for depression with the advent of newer antidepressants, are used both for treatment of depression and as sleep aids due to sedative effects, among other indications. Seizure activity with tricyclic antidepressant use is more typically seen with high dose and overdose.

Numerous other agents have case reports or rare, idiopathic incidence of seizures listed in their prescribing information, but it is important to consider that there typically are common factors that can be used to identify patients at high risk of drug-related seizure. The most common risk factor for developing drug-related seizure is the mechanism by which the suspected agent would cause seizure activity. For most antibiotic agents that interfere with gamma-aminobutyric acid receptors, acute administration of the gamma-aminobutyric acid agonists benzodiazepine agents has been suggested as first-line therapy.

Management of patients with suspected drug associated seizure activity should focus on removal of the offending agent, either by discontinuation or by dosing the agent appropriately for the patient’s condition and organ function in the case of unintentional overdose. Acute treatment of seizure activity should take into account the mechanism by which the suspected agent would cause seizure activity. For most antibiotics that interfere with gamma-aminobutyric acid receptors, acute administration of the gamma-aminobutyric acid agonists benzodiazepine agents has been suggested as first-line therapy.

Additionally, phenytoin has been shown to be ineffective in animal models of seizure induced by β-lactam agents. However, if the offending antibiotic agent is isoniazid, pyridoxine given intravenously is the recommended treatment. In some cases, hemodialysis could be used to remove readily dialyzable agents, however data from controlled studies are lacking. Additionally, it is largely unknown what the cross reactivity for seizure is when switching to a different antibiotic class in these patients, but considerations such as renal function and appropriateness of selected dose should be considered.

The general consensus for treatment of seizure activity related to other drug classes recommends benzodiazepine agents for acute management of seizure activity. Data regarding treatment beyond initial removal of the potential offending agent and acute management of seizure with benzodiazepine or barbiturate agents are lacking. The decision to initiate long-term anticonvulsant therapy in these patients should take patient progress after removal of the offending agent and underlying patient medical problems into account.

Several groups of patients may be at risk for drug-induced seizures, most commonly patients with compromised renal function given that many of these agents are cleared renal-
In general, patients with an underlying seizure condition are more susceptible to development of drug-related seizures. Medications such as NSAIDs, haloperidol, and tramadol, which lower the seizure threshold, have the potential to exacerbate seizure activity in patients with underlying seizure histories. The elderly may also be more susceptible to drug-induced seizures as well. In many cases, elderly patients have insidious renal dysfunction that is not immediately identified by aberrant laboratory values like an elevated serum creatinine. In addition, many elderly individuals have a lower volume of distribution for some medications, which may increase the serum drug concentrations, even after a ‘normal’ dose.

Drug-associated seizure activity is a potential, although uncommon, adverse effect of commonly used medications. Antibiotic agents, including β-lactams, fluoroquinolones, and metronidazole, pain medications, particularly tramadol and meperidine, and antidepresant agents have all been linked to drug-associated seizure activity. Identification of patients with renal impairment, identification of patients with prior seizure activity, and those with advanced age, along with appropriate dosage adjustment, can assist in prevention of drug-associated seizure activity.

REFERENCES