Loperamide is a nonprescription opioid widely used for the treatment of diarrhea. Although it is relatively safe at therapeutic doses, increasing reports describe its misuse and abuse at very high doses either for euphoric effects or to attenuate symptoms of opioid withdrawal. Life-threatening loperamide toxicity can result from the relatively new clinical syndrome of loperamide-induced cardiac toxicity. These patients are often young and may present in cardiac arrest or with unheralded, recurrent syncope in conjunction with ECG abnormalities, including marked QT-interval prolongation, QRS-interval widening, and ventricular dysrhythmias. Features of conventional opioid toxicity may also be present. The mainstays of treatment include advanced cardiac life support and supportive care, although selected patients may be candidates for overdrive pacing, intravenous lipid emulsion, or extracorporeal membrane oxygenation. In patients who survive loperamide toxicity, consideration should be given to the treatment of an underlying opioid use disorder, if present. [Ann Emerg Med. 2017;70:245-252.]
study, subjects given quinidine with loperamide developed impaired respiratory response to carbon dioxide rebreathing, whereas another noted decreased pupil size. However, studies in which loperamide was administered with P-gp inhibitors demonstrate that central nervous system effects do not consistently accompany increases in plasma loperamide concentrations, perhaps because the dose required to inhibit brain P-gp is higher than that required to inhibit intestinal P-gp.

At very high plasma concentrations, loperamide interferes with cardiac conduction. Loperamide blocks human ether-a-go-go–related gene potassium channels with high affinity at concentrations of 15.7 μg/L (Kang et al.) to 20.5 μg/L (Klein et al.) and blocks sodium channels at concentrations of 114 to 141 μg/L. To contextualize this, the average peak concentration after an 8-mg dose is 1.18 μg/L. These effects contribute to QT-interval prolongation and QRS-interval widening and create a substrate for life-threatening dysrhythmias.

**LOPERAMIDE MISUSE AND ABUSE**

Misuse and abuse of loperamide, often at exceptionally high doses, has been increasingly reported since the first documented instance in 2005. Although undoubtedly an underestimate of the true incidence, loperamide exposures reported to the National Poison Data System nearly doubled between 2010 and 2015, with 1,736 intentional exposures during the study period. Individual experiences with loperamide are recounted on Web sites including Bluelight, Drugs Forum, and Erowid. In a sample of 258 posts from one such Web site, 69% discussed the use of high-dose loperamide to alleviate opioid withdrawal symptoms, whereas 23% described its use for euphoric effects. Unlike other opioids, loperamide is easily procured and inexpensive (one national retailer offers 400 2-mg tablets for $7.59). It has been likened to “poor man’s methadone,” with users reporting average daily amounts of 70 mg, and some receiving several hundred milligrams per day, far more than the maximum approved dose of 16 mg/day. Moreover, some users purposefully inhibit CYP3A4 (for example, with cimetidine or grapefruit juice), P-gp (for example, with quinidine or black pepper, which contains piperine, an inhibitor of both P-gp and CYP3A4), or both to enhance the systemic absorption and central nervous system penetration of loperamide. Several accounts posted on Internet forums clearly describe a resulting opioid toxidrome, some with near-fatal respiratory depression. One user who ingested 72 mg of loperamide with black pepper likened the euphoric effect to that of 90 mg of OxyContin (oxycodone).

**CARDIAC TOXICITY**

Loperamide toxicity is not characterized solely by opioid effects. Recently, numerous reports of serious cardiac dysrhythmias have emerged, some of them fatal. We conducted a literature review of the PubMed database from inception to April 5, 2017, using the terms “loperamide and toxicity,” “loperamide and cardiac,” “loperamide and abuse,” and “loperamide and overdose,” as well as a manual review of relevant references to identify all reported cases of loperamide exposures and toxicity. We also reviewed conference abstracts from 2011 to 2016 for the North American Congress of Clinical Toxicology, the European Association of Poisons Centres and Clinical Toxicologists, the Society of Critical Care Medicine, and the Society for Academic Emergency Medicine, and from 2013 to 2017 for the American College of Medical Toxicology (ACMT), identifying two additional cases that were not subsequently published. To date, more than 20 individual case reports of loperamide cardiac toxicity have been published, and a recent investigation of the Food and Drug Administration Adverse Event Reporting System database identified 48 cases of serious cardiac events associated with loperamide. These reports typically describe young patients with decreased level of consciousness or with unheralded syncope, which may be recurrent, in association with markedly abnormal ECG results. Reported ECG findings are outlined in the Table. An additional 22 cases have been reported of patients found dead with elevated postmortem loperamide plasma concentrations; 19 of the cases were from one series in North Carolina. Whether these patients died of loperamide-induced respiratory depression or cardiac toxicity is unknown.

Published cases of loperamide cardiotoxicity involve chronic ingestion of doses ranging from 100 to 800 mg per day. With the exception of 3 reports of patients who died after developing pulseless electrical activity arrest or asystole, all cases exhibited striking ECG abnormalities (Figures 1 to 3) of a widened QRS interval (up to 200 ms) and a prolonged QT interval (up to 704 ms), and all developed ventricular dysrhythmias, including monomorphic or polymorphic ventricular tachycardia (torsades de pointes).

The ability of high-dose loperamide to block cardiac potassium and sodium channels provides the basis for ECG abnormalities and dysrhythmias. As noted, the concentrations required to block these channels are unattainable at standard doses, but sufficiently high concentrations are readily achieved in patients with
<table>
<thead>
<tr>
<th>Case Report</th>
<th>Age, Sex</th>
<th>Dose</th>
<th>Clinical Presentation</th>
<th>ECG Changes</th>
<th>Treatment</th>
<th>Loperamide Plasma Concentration, µg/L</th>
<th>Outcome</th>
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<tr>
<td>Rasla et al, 2017</td>
<td>28, M</td>
<td>400 mg/day x 5 mo</td>
<td>Presyncope, palpitations</td>
<td>QTc 601 ms, ventricular tachycardia</td>
<td>Magnesium, isoproterenol</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>Bhatti et al, 2017</td>
<td>37, F</td>
<td>400 mg</td>
<td>Loss of consciousness</td>
<td>QTc &gt; 600 ms</td>
<td>Naloxone 0.4 mg, isoproterenol</td>
<td>Undetectable</td>
<td>Survived</td>
</tr>
<tr>
<td>Kozak et al, 2017</td>
<td>41, M</td>
<td>&gt;100 mg/day</td>
<td>Recurrent syncope</td>
<td>QTc 702 ms, torsade de pointes</td>
<td>Magnesium, amiodarone, cardioversion, electrical pacing</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>Katz et al, 2017</td>
<td>28, M</td>
<td>N/A</td>
<td>Dyspnea, Presyncope</td>
<td>QTc 168 ms, QTc 693 ms, torsade de pointes</td>
<td>Magnesium, sodium bicarbonate, lidocaine, isoproterenol, electrical pacing</td>
<td>120</td>
<td>Survived</td>
</tr>
<tr>
<td>O’Connell et al, 2016</td>
<td>28, F</td>
<td>400–600 mg/day</td>
<td>Recurrent syncope, palpitations</td>
<td>QTc 192 ms, QTc 642 ms, ventricular tachycardia, torsade de pointes</td>
<td>Magnesium, sodium bicarbonate, lidocaine, isoproterenol</td>
<td>83.2</td>
<td>Survived</td>
</tr>
<tr>
<td>Lasoff et al, 2016</td>
<td>24, M</td>
<td>400 mg/day + cimetidine</td>
<td>Generalized weakness</td>
<td>QTc 146 ms, QTc 544 ms, ventricular tachycardia, torsade de pointes</td>
<td>Amiodarone, sodium bicarbonate, isoproterenol</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>Upadhaya et al, 2016</td>
<td>46, M</td>
<td>100 mg/day x 5 y, 200 mg/day x 2 days</td>
<td>Syncope, cardiac arrest</td>
<td>QTc &gt; 600 ms, ventricular fibrillations, torsade de pointes</td>
<td>Defibrillation, magnesium, amiodarone, lidocaine, metoprolol</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>Vaughan et al, 2016</td>
<td>20, M</td>
<td>288 mg/day</td>
<td>Recurrent syncope, palpitations, dyspnea</td>
<td>QTc 200 ms, QTc 600 ms, torsade de pointes</td>
<td>Defibrillation, electrical pacing, isoproterenol</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>Mukarram et al, 2016</td>
<td>26, M</td>
<td>192 mg/day</td>
<td>Syncope, myosis</td>
<td>QTc 146 ms, QTc 544 ms, ventricular tachycardia, torsade de pointes</td>
<td>Amiodarone, sodium bicarbonate, isoproterenol</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>Wightman et al, 2016</td>
<td>48, F</td>
<td>40–80 mg/day</td>
<td>Decreased level of consciousness</td>
<td>QTc 164 ms, QT 582–614 ms, ventricular tachycardia</td>
<td>Magnesium, self-limited</td>
<td>210</td>
<td>Survived</td>
</tr>
<tr>
<td>Eggleston et al, 2016</td>
<td>24, M</td>
<td>N/A</td>
<td>Loss of consciousness and then cardiac arrest</td>
<td>Asystole</td>
<td>Naloxone, CPR</td>
<td>77*</td>
<td>Died</td>
</tr>
<tr>
<td>Spinner et al, 2017</td>
<td>39, M</td>
<td>N/A</td>
<td>Loss of consciousness and then cardiac arrest</td>
<td>Arrhythmic escape, ventricular tachycardia, torsade de pointes</td>
<td>CPR, Lidocaine, amiodarone cardioversion, electrical pacing</td>
<td>140*</td>
<td>Died</td>
</tr>
<tr>
<td>Eggleston et al, 2015</td>
<td>30, M</td>
<td>400 mg/day x 7 days</td>
<td>Syncope and then cardiac arrest</td>
<td>QTc 192 ms, QT 704 ms, torsade de pointes</td>
<td>Defibrillation, isoproterenol</td>
<td>120</td>
<td>Survived</td>
</tr>
<tr>
<td>Marce et al, 2015</td>
<td>26, M</td>
<td>100–250 mg/day</td>
<td>Recurrent syncope</td>
<td>QTc &gt; 700 ms, torsade de pointes</td>
<td>Cardioversion, isoproterenol</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>MacDonald et al, 2015</td>
<td>26, M</td>
<td>800 mg/day x 18 mo</td>
<td>Cardiac arrest</td>
<td>PEA</td>
<td>N/A</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Enakpene et al, 2015</td>
<td>25, F</td>
<td>N/A</td>
<td>Syncope, nausea, vomiting, and then cardiac arrest</td>
<td>QTc 140-170 ms, QTc 490-527 ms, torsade de pointes</td>
<td>Sodium bicarbonate, magnesium, atropine, lipid emulsion, electrical pacing, ECMO</td>
<td>32</td>
<td>Died</td>
</tr>
</tbody>
</table>
purposeful loperamide overdose (Table), especially in the setting of concomitant P-gp or CYP3A4 inhibition.\textsuperscript{22-25} Indeed, the median postmortem loperamide peripheral blood concentration among the 19 deaths implicating loperamide reported in North Carolina was 230 \(\mu\)g/L.\textsuperscript{52}

**MANAGEMENT**

The management of loperamide toxicity is largely supportive, although some recommendations can be cautiously extrapolated from first principles and anecdotal experience.

In the setting of acute overdose, loperamide should adsorb to activated charcoal, the use of which is advisable within 2 to 4 hours after a large overdose, provided the patient’s mental status is normal. An extended administration window is justified in part because of loperamide’s effect on peristalsis, and in part because of the limited therapies otherwise available, particularly in patients who regularly ingest large amounts of loperamide and may already have dangerously elevated plasma concentrations.\textsuperscript{55} Gastrointestinal decontamination has no role in the absence of acute overdose.

In the presence of respiratory depression or degrees of somnolence that might impair airway protection, naloxone should be administered in addition to supportive care. Given the possibility of opioid withdrawal, the lowest effective dose of naloxone should be used. Successful use of naloxone at doses of 0.01 to 0.4 mg has been described in 1 adult case\textsuperscript{39} and 5 pediatric patients (4-month-old,\textsuperscript{56} 15-month-old,\textsuperscript{57} 8-day-old, and 2 others of uncertain age\textsuperscript{3}) presenting with central nervous system depression or respiratory depression. The need for repeated doses of naloxone should be anticipated in light of loperamide’s slow elimination.

For patients with loperamide cardiotoxicity, standard advanced cardiac life support therapy should be followed in patients with cardiac arrest, including cardioversion or defibrillation for shockable rhythms and intravenous magnesium for polymorphic ventricular tachycardia. Repeated shocks may be required, as reported in one case requiring cardioversion more than 15 times.\textsuperscript{51} Thirteen patients with torsades de pointes appeared to benefit from overdrive pacing using transvenous electrical pacing or isoproterenol to suppress ventricular ectopy and prevent recurrent dysrhythmias.

Prolongation of the QT interval is more likely than QRS-interval widening, given the lower loperamide concentration needed to block cardiac potassium channels. Although no specific treatment exists for loperamide-induced QT-interval prolongation, it is sensible...
to ensure that other reversible factors for QT-interval prolongation (such as hypokalemia, hypomagnesemia, and other medications) have been rectified.

To address QRS-interval widening caused by loperamide sodium channel blockade, a trial of intravenous sodium bicarbonate (1 to 2 mEq/kg) is a reasonable intervention while ensuring adequate ventilation, but whether this will improve conduction is unclear. In published cases, patients received various concomitant treatments, including magnesium, potassium chloride,

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**Figure 1.** ECG with QRS-interval duration of 200 ms and QTc interval of 600 ms in a 20-year-old patient presenting with recurrent syncope caused by loperamide-induced cardiac toxicity. Reproduced with permission: Vaughn et al.44

**Figure 2.** ECG demonstrating onset of torsades de pointes in a 20-year-old patient with loperamide-induced cardiac toxicity. Reproduced with permission: Vaughn et al.44
sodium bicarbonate, and antiarrhythmic drugs (eg, amiodarone, lidocaine), with reportedly little clinical or ECG improvement. As a lipophilic, highly protein-bound (97%) drug, loperamide would not be appreciably cleared by hemodialysis. However, intravenous lipid emulsion is a consideration for patients with severe cardiotoxicity. Published experience to date is limited to 3 cases. The doses of lipid used were not specified, and too few clinical details were presented to evaluate any potential effects. Despite the absence of good data, we believe loperamide’s high lipophilicity (log P 4.77) justifies a trial of intravenous lipid emulsion in patients who remain severely unstable despite otherwise optimal care. Recommended dosing guidelines are offered by the American College of Medical Toxicology and at http://www.lipidrescue.org; however, these recommendations are not specific to loperamide toxicity. Dosing should be individualized and should proceed with the recognition that intravenous lipid emulsion may be ineffective and is not devoid of risk. Loperamide is slowly eliminated in the setting of toxicity, and prolonged infusions of intravenous lipid emulsion are generally best avoided.

Venoarterial extracorporeal membrane oxygenation (ECMO) is another potential treatment for patients with severe loperamide cardiotoxicity. One published case describes the use of venoarterial ECMO in a patient who presented in cardiac arrest. The patient ultimately died, although whether care was withdrawn or ECMO was ineffective is unknown. We suggest considering ECMO, if available, in patients with severe loperamide cardiotoxicity refractory to other measures.

In patients who survive loperamide toxicity, attention may be required to other issues. Although to our knowledge no published reports describe the use of methylaltrexone or naloxegol for the treatment of severe loperamide-induced constipation, it is intuitive that they would work in a fashion similar to that observed when constipation caused by conventional opioid analgesics is treated. Consideration should also be given to management of any underlying opioid use disorder. This may include initiation of opioid agonist therapy with buprenorphine and referral to an addiction treatment program. Evidence from patients with opioid addiction shows that inpatient initiation of buprenorphine coupled with outpatient referral to an addiction specialist led to significantly better retention in long-term treatment and reduced illicit opioid use 6 months after hospitalization.

CONCLUSION
Loperamide misuse and abuse are increasingly recognized and potentially fatal, owing in part to ease of access to the drug and its extremely low cost. Death can result from either central opioid effects or cardiac dysrhythmias. This relatively new presentation of cardiac toxicity is underappreciated and requires prompt recognition and discontinuation of loperamide. Unexplained syncope or ventricular dysrhythmias, especially in patients with a history of an opioid use disorder, should lead clinicians to entertain the possibility of loperamide toxicity, particularly when QT prolongation or QRS widening is apparent. Clinical encounters in the hospital can serve as an opportunity to identify an underlying opioid use disorder, initiate opioid agonist therapy when appropriate, and arrange referral to specialized addiction care for long-term management.
in any way related to the subject of this article as per ICMJE conflict
of interest guidelines (see www.icmje.org). The authors have stated
that no such relationships exist.

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