Torsade de Pointes, Prolonged QT Intervals, and Patients With Cancer

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Many kinase inhibitors, chemotherapeutic agents, antiemetics, antibiotics, and antifungal agents can prolong QT intervals, placing the patient at risk for the life-threatening ventricular arrhythmia Torsade de pointes (Tdp). In addition, common electrolyte imbalances experienced by many patients with cancer compound the risk. Because numerous medications used in oncology and common electrolyte imbalances in patients with cancer increase the risk for Tdp, oncology nurses must be informed about this life-threatening arrhythmia.

Torsade de pointes (Tdp) is a French term meaning “twisting of the points” and was first described by Dessertenne in 1966 (Luderitz, 2009). This ventricular tachycardia can rapidly change to ventricular fibrillation and result in cardiac arrest. The Tdp electrocardiogram (ECG) tracing shows a QRS that changes in height and shape, and twists around the isoelectric line, sometimes pointing downward and sometimes pointing upward (see Figure 1). Tdp usually occurs when ventricular depolarization is delayed, as evidenced by a prolonged QT interval.

QT Intervals

The QT interval represents ventricular depolarization and repolarization. Ventricular depolarization is the stimulation of ventricular cardiac cells to contract, and ventricular repolarization is the recovery or relaxation of the ventricular cardiac cell. The QT interval starts at the beginning of the Q wave, finishes at the end of the T wave (see Figure 2), and varies depending on gender, age, and heart rate. To determine whether the QT interval is within normal limits for the patient’s heart rate, count the number of small boxes between two consecutive R waves and divide by two. Then count the number of small boxes in the QT interval. Compare the difference. A normal QT interval should be less than half of the distance between the R waves. To determine the QT interval, multiply the number of small boxes in the QT interval by 0.04 seconds (Huff, 2006).

A normal QT interval is usually half the distance between two consecutive R waves (Huff, 2006); a QT interval higher than 440–500 msec is considered prolonged (Huff, 2006). The QT interval is affected by the heart rate. A faster heart rate results in a shorter QT interval, whereas a slower heart rate results in a longer QT interval. To improve the detection of patients at risk for Tdp and to measure the QT interval more accurately, the QT interval should be corrected for the heart rate.

Prolonged QT intervals

Prolonged QT intervals indicate that ventricular repolarization is delayed, which allows time for an ectopic focus to take control and, therefore, places the ventricles at risk for a ventricular arrhythmia, such as Tdp. Causes of prolonged QT intervals include hereditary long QT interval syndrome, predisposing DNA polymorphisms, bradyarrhythmias, myocardial ischemia, electrolyte imbalances (hypocalcemia, hypokalemia, and hypomagnesemia), and medications (Drew et al., 2010). The risk also is increased with older age and in women (Drew et al., 2010). Significant medication classifications that can prolong QT intervals include antipsychotics, tricyclic antidepressants, antibiotics, antifungals, and antidysrhythmics (Drew et al., 2010; Zareba, 2007).

Prolonged QT Intervals and Patients With Cancer

Hypokalemia, hypomagnesemia, and hypocalcemia are electrolyte imbalances commonly found in patients with cancer. Low levels of those electrolytes can prolong QT intervals (Drew et al., 2010; Huff, 2006). Diarrhea, a common issue in patients with cancer, can cause hypokalemia. Cancer, surgery to the bowel, radiation involving the gastrointestinal tract, antibiotics, epithelial growth factor inhibitors, and certain chemotherapeutic agents (e.g., 5-fluorouracil, capcitabine, cytarabine) all can cause diarrhea and, therefore, hypokalemia (Muehlbauer et al., 2009; Polovich, Whitford, & Olsen, 2011). Examples of chemotherapeutic agents that can cause hypomagnesemia include cisplatin and carboplatin (Polovich et al., 2011). Renal damage and amphotericin B also can cause hypomagnesemia (Novello & Blumstein, 2010). Chemotherapeutic agents (e.g., cisplatin), tumor lysis syndrome, diuretics, bisphosphonates,

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(e.g., pamidronate), and renal failure all can cause hypocalcemia (Manish & Muster, 2010; Polovich et al., 2011).

Examples of medications used in oncology that are associated with prolonged QT intervals are listed in Table 1 and include medications in the major drug classifications of antineoplastic agents, antiemetics, opioids, antifungals, and antibiotics (Woosely, 2011). Additional medications that can prolong QT intervals or have been associated with a risk for Tdp can be found at www.QTdrugs.org. Dolasetron mesylate, arsenic trioxide, and methadone are three medications used in oncology that have received much attention because of their potential to cause Tdp. Many of the newer kinase inhibitors—such as crizotinib and vemurafenib—also can prolong QT intervals, placing the patient at increased risk for Tdp.

Dolasetron mesylate: Dolasetron mesylate is a serotonin 5-HT3 receptor antagonist used for chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting. On December 17, 2010, the U.S. Food and Drug Administration (FDA) issued an alert that the injection form of dolasetron mesylate should not be used to prevent nausea and vomiting associated with chemotherapy in adults or children. New data had shown that dolasetron mesylate injection given at doses used to prevent chemotherapy-induced nausea and vomiting (for adults, 100 mg via IV) increased the risk of developing Tdp because it could cause a dose-dependent prolongation of the QT, PR, and QRS interval (FDA, 2010). The FDA also noted that patients at higher risk for Tdp included those with underlying heart conditions or existing heart rate or rhythm problems. Dolasetron mesylate injection can still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used (for adults, 12.5 mg via IV or less) are less likely to result in abnormal heart rhythms (FDA, 2010; sanofi-aventis, 2011). The oral form can be used to prevent chemotherapy-induced nausea and vomiting because the risk of developing an abnormal heart rhythm is less than that seen with the IV form of the drug; however, caution should be used in patients with risk factors for Tdp when using lower IV doses of dolasetron mesylate for postoperative nausea and vomiting (FDA, 2010; sanofi-aventis, 2011). Caution also should be used in patients with risk factors for developing Tdp when using lower IV doses of dolasetron mesylate for postoperative nausea and vomiting (FDA, 2010; sanofi-aventis, 2011).

Arsenic trioxide: Arsenic trioxide is an antineoplastic agent that is well known for its risk for QT prolongation and Tdp. This agent is indicated for remission induction and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to or have relapsed from retinoid and anthracycline chemotherapy, and whose APL has t(15;17) translocation or PML/RARA gene expression (Cephalon, Inc., 2010). Recommendations to prevent this life-threatening arrhythmia include a baseline 12 lead ECG, serum potassium, calcium, magnesium, and creatinine levels, as well as discontinuation of other medications that can prolong QT intervals (Cephalon, Inc., 2010; Mayorga, Richardson-Hardin, & Dicke, 2002). Any electrolyte abnormalities should be corrected, as should corrective interventions for QT intervals greater than 500 msec (Cephalon, Inc., 2010; Mayorga et al., 2002). Electrolytes should be monitored throughout therapy, along with serial ECGs. Arsenic trioxide should be held for serum potassium levels less than 4 mEq/L, magnesium levels less than 1.8 mg/dl, and QT intervals greater than 500 msec (Cephalon, Inc., 2010; Mayorga et al., 2002).

Methadone: Methadone, an opioid frequently used in the management of cancer pain, can prolong QT intervals and increase the patient’s risk for Tdp (Stringer, Welsh, & Tommasello, 2009; Woosely, 2011). Although the occurrence...
of arrhythmias in patients receiving methadone has been known for some time, prolonged QT intervals and Tdp associated with methadone did not appear in the literature until the mid 2000s (Stringer et al., 2009). As with other medications with this risk, the patient should be assessed for risk factors prior to starting methadone. In addition to standard risk factors, the methadone dose also is a risk factor in that higher doses present an increased risk. Krantz, Martin, Stimmel, Mehta, and Haigney (2009) published clinical guidelines for methadone which recommend a pretreatment ECG, interval screening ECGs, and annual follow-up ECGs. Those recommendations, however, may not be appropriate for the palliative care setting, where methadone frequently is used.

Kinase inhibitors: The number of kinase inhibitors that have been approved by the FDA for the treatment of cancer has increased rapidly. Many of the agents have been found to prolong QT intervals. Kinase inhibitors that prolong QT intervals are listed in Table 1; however, new agents are continually being approved and, therefore, nurses should review product information prior to administering any agent. For many of the agents, the manufacturers’ recommendations include general warnings to avoid use in patients with congenital prolonged QT syndrome and to use with caution in patients with conditions that may increase the risk for prolonged QT intervals (e.g., bradycardia, electrolyte disturbances, and concurrent use of other medications that prolong QT intervals). In addition, they recommend periodic monitoring of electrolyte levels, correction of imbalances, and monitoring of QT levels. However, some agents have specific monitoring guidelines and restrictions (e.g., vemurafenib, vandetanib). For example, during clinical trials for vandetanib, cases of Tdp and sudden death were reported, prompting the manufacturer to make this agent available only through a cancer risk evaluation and mitigation strategy program (AstraZeneca Pharmaceuticals, 2010). Because the half life of vandetanib is 19 days, the manufacturer recommends that ECGs should be obtained 2–4 weeks and 8–12 weeks after starting treatment with vandetanib and then every three months. The manufacturer also warns that, because of the prolonged half life, adverse reactions including a prolonged QT interval may not resolve quickly and that the patient should be monitored appropriately.

Nursing Implications

The American Heart Association and the American Cardiology Foundation, with the endorsement of the American Association of Critical Care Nurses, released a scientific statement emphasizing the healthcare professional’s role in the prevention, detection, and management of Tdp (Drew et al., 2010). Key recommendations include assessment for risk factors, accurate measuring of QT intervals when cardiac monitoring is indicated, and prompt response to Tdp. In addition to those recommendations, oncology nurses should be knowledgeable about resources to determine whether a medication can prolong QT intervals, as well as any specific monitoring recommendations (e.g., arsenic trioxide, methadone).

A comprehensive patient history and physical examination are the first steps in the prevention and detection of prolonged QT intervals and Tdp. The health history should include family history and a review of symptoms focusing on cardiac-related symptoms. Any reported symptoms of prolonged QT intervals, such as fainting, palpitations, and bradycardia, should be noted in the nursing history (Drew et al., 2010). A history of current cancer treatments and symptoms, which could lead to electrolyte imbalances, should be assessed and documented. The nurse should obtain an accurate and current medication history assessing for any medications the patient is taking that could prolong QT intervals.

The physical assessment should include vital signs and a cardiac assessment. If indicated or ordered, an ECG should be obtained and the QT interval measured. The provider should be notified regarding QT prolongation. Blood chemistry results should be reviewed for low levels of calcium, magnesium, and potassium. If those are low, the nurse should administer electrolyte replacements and monitor follow-up electrolyte levels as ordered. In the event that a prolonged QT interval progresses to Tdp, the nurse should notify the provider immediately and prepare for a potential emergency as Tdp can rapidly progress to ventricular fibrillation. Emergency equipment (e.g., a code cart) should be readily available. The nurse should ensure that the patient has a functioning large bore IV and that oxygen is immediately accessible.

Conclusion

Tdp is a life-threatening emergency that can occur in patients with cancer. Numerous medications used in oncology can cause prolonged QT intervals and, therefore, increase a patient’s risk for Tdp. The oncology nurse plays a key role in the prevention and detection of Tdp by assessing for risk factors, signs

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Antibiotics and antifungals</td>
<td>Azithromycin, ciprofloxin, clarithromycin, erythromycin, fluconazole, levofloxacin, and voriconazole</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Chlorpromazine, dolasetron mesylate, droperidol, granisetron, haloperidol, and ondansetron</td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>Arsenic trioxide, crizotinib, dasatinib, erbulin, laptatinib, nilotinib, romidepsin, sorafenib, sunitinib, tamoxifen citrate, vandetanib, and vemurafenib</td>
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<tr>
<td>Opioids</td>
<td>Methadone</td>
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<tr>
<td>Miscellaneous agents</td>
<td>Diphenhydramine, octreotide, and tacrolimus</td>
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Note: Based on information from AstraZeneca Pharmaceuticals, 2010; Bayer Healthcare Pharmaceuticals, 2011; Bristol-Myers Squibb, 2011; Celgene Corporation, 2011; Cephalon, Inc., 2010; Drew et al., 2010; Eisai, Inc., 2011; Genentech USA, 2011; Pfizer, Inc., 2012; U.S. Food and Drug Administration, 2010; Woosley, 2011.
and symptoms, and by monitoring for prolonged QT intervals.

References


Do You Have an Interesting Topic to Share?

Safety provides readers with information on safety issues affecting patients with cancer and those caring for them. Length should be no more than 1,000–1,500 words, exclusive of tables, figures, insets, and references. If interested, contact Associate Editor Camille A. Servodidio, RN, MPH, CRNQ, OCN®, CCRP, at cservod@harthosp.org.