Drug-induced arrhythmias

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The objective of this review is to characterize the mechanisms, risk factors, and offending pharmacotherapeutic agents that may cause drug-induced arrhythmias in critically ill patients. PubMed, other databases, and citation review were used to identify relevant published literature. The authors independently selected studies based on relevance to the topic. Numerous drugs have the potential to cause drug-induced arrhythmias. Drugs commonly administered to critically ill patients are capable of precipitating arrhythmias and include antiarrhythmics, antianginals, antiemetics, gastrointestinal stimulants, antibacterials, narcotics, antipsychotics, inotropes, digoxin, anesthetic agents, bronchodilators, and drugs that cause electrolyte imbalances and bradyarrhythmias. Drug-induced arrhythmias are insidious but prevalent. Critically ill patients frequently experience drug-induced arrhythmias; however, enhanced appreciation for this adverse event has the potential to improve prevention, treatment, patient safety, and outcomes in this patient population. (Crit Care Med 2010; 38[Suppl.]:S188–S197)

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The mechanical process of atrial and ventricular contraction is a result of electrical depolarization in myocardial tissue. Normally, the sinoatrial (SA) node in the right atrium is the origin and determines the frequency of depolarization; thus, SA node is considered the heart's intrinsic pacemaker. Other tissues in the heart also possess automaticity, or the ability to spontaneously generate electrical impulses, but at a slower rate than the SA node. In resting adults, the SA node's normal intrinsic depolarization rate in 1 min varies between 60 and 100, whereas the atrioventricular (AV) node or ventricular tissue possesses intrinsic depolarization rates ranging between 40 and 60 and 30 and 40 per minute, respectively (1). If the SA node fails to generate depolarization, often the AV node will take over the role as pacemaker. In healthy adults, depolarization occurs in the SA node, and the electrical activity cascades through the atria via Bachmann's bundle and other internodal pathways ultimately reaching the AV node. These impulses are conducted through the AV node into the bundle of His and ultimately into the right-bundle branch and the anterior and posterior divisions of the left-bundle branch. Each bundle branch is further split into Purkinje fibers, which reach the remaining ventricular tissue and result in ventricular depolarization and subsequent mechanical contraction.

Depolarization is a result of ionic shifting within myocardial cells called *myocytes*. Typically, myocytes possess a resting membrane potential of −70 mV to −90 mV as a result of the sodium-potassium adenosine triphosphatase (ATPase) pump, which maintains high extracellular concentrations of sodium and low extracellular concentrations of potassium (1). After atrial depolarization, the ventricular action potential begins with the membrane potential reaching a threshold potential (usually −60 mV to −80 mV). At this point, fast sodium channels open (phase 0 of the action potential), allowing positively charged sodium ions to rush intracellularly, thereby depolarizing the cell to a point at which it overshoots the membrane potential to +20 mV to +30 mV (1). During this phase, the QRS complex is present on the surface electrocardiogram (ECG), and ventricular contraction occurs. At this point of membrane potential overshoot, fast sodium channels become inactivated, and repolarization of the cell begins in phases 1 to 4 of the action potential.

Phase 1 repolarization results from potassium ions being driven out of the cell and the membrane potential returning to near 0 mV. During phase 2 repolarization, potassium ions continue to be excreted, but the membrane potential remains at a plateau, near 0 mV, by a concomitant intracellular influx of calcium and sodium via slow channels. During phase 3 of repolarization, and T-wave presence on the ECG, potassium efflux occurs at a higher rate than calcium and sodium influx, further lowering the membrane potential. Of note, the duration of time between the ECG Q wave and the end of the T wave, or the QT interval, is used as a measurement of ventricular repolarization time, whereas atrial repolarization cannot be measured because it occurs during, and is masked by, ventricular depolarization and the QRS complex on the ECG. Phase 4 completes the action potential with the ATPase pump, promoting the efflux of sodium, and returning to the resting membrane potential between −70 mV to −90 mV. Atrial depolarization and contraction follow the ventricular action potential (as evident by the ECG P wave), and the process repeats.

Common mechanisms of arrhythmias

Arrhythmias can be caused by formation of abnormal impulses, abnormal conduction of impulses, or a combination of both (1, 2). Essential in the development of arrhythmias is the generation of an abnormal impulse immediately after the absolute refractory period of cardiac tissue. During the absolute refractory period, impulses cannot trigger depolariza-

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tion of myocytes. This occurs during phases 1, 2, and the first half of phase 3 of the ventricular action potential and is represented on the ECG by the time between the Q wave through the first half of the T wave. In the second half of phase 3, and the second half of the T wave, cardiac tissue regains its ability to be depolarized and enters into a relative refractory period. Development of abnormal impulses during this period can lead to abnormal conduction and may precipitate arrhythmias (3, 4).

Abnormal impulse formation occurs when cardiac tissues develop abnormal automaticity (2). This becomes problematic when the rate of tissue automaticity exceeds that of the rate of the SA node, or alternatively in the presence of SA node dysfunction and slowed tissue automaticity. Factors, which may increase automaticity, include enhanced sympathetic nervous system activity, hypokalemia, hypomagnesemia, medications (e.g., catecholamines and digoxin), dilation of the atrium or ventricles, and tissue hypoxia. Conversely, enhanced parasympathetic nervous system activity can suppress automaticity. If the abnormal automaticity originates from the SA node, sinus tachycardia can develop, whereas derangements in the AV nodal automaticity can lead to junctional tachycardia. If the atrium develops increased automaticity, premature atrial contractions, atrial tachycardia, or atrial fibrillation may occur. Abnormal ventricular automaticity can lead to ventricular premature depolarizations, ventricular tachycardia (VT), or ventricular fibrillation.

Membrane depolarization occurring as a result of abnormal calcium and sodium influx during or immediately after repolarization of cardiac tissue has also been associated with abnormal impulse generation and arrhythmias (2). This triggered automaticity can occur in two distinct forms: 1) early after-depolarization (EAD); and 2) late after-depolarization (LAD). EAD involves transient membrane depolarization during repolarization, whereas LAD involves transient membrane depolarization after repolarization but before phase 4 of the action potential (1). Factors leading to EAD include use of type Ia antiarrhythmics, hypokalemia, and other factors that may slow stimulation rates by blocking ion channels. It is noteworthy that drugs that block potassium ion transfer in cardiac tissue and thus delay repolarization, e.g., type III antiarrhythmics, may lead to EAD and have been associated with torsades de pointes (TdP). Specifically, LAD has been associated with the use of digoxin and catecholamines, and has been suppressed by calcium-channel blockers.

In addition to generation of abnormal impulses, abnormal impulse conduction may occur. This is commonly referred to as reentry and often follows formation of abnormal impulses and can be a precipitating cause of arrhythmias. Three conditions must be present for reentry to occur: 1) two conduction pathways must be present in the tissue for the abnormal impulse to travel; 2) a unidirectional block in one of the two pathways of conduction must prohibit progression of the impulse but allow retrograde conduction. This enables the impulse to travel down the nonblocked pathway and return to the previous impulse path via the retrograde pathway (effectively creating a loop); 3) reduced impulse velocity within one of the two pathways is necessary to allow time for the tissue in the other pathway to regain its ability to depolarize (1). Without slowed conduction in one pathway, the other pathway would still be in its absolute refractory period; thus, a conduction loop could not exist. This triad of two pathways, unidirectional block, and slowed conduction in one pathway may lead to a closed loop of conduction in a specific area of tissue, yielding cyclic depolarization and potentially a tachyarrhythmia.

Risk factors for drug-induced arrhythmias

Risk factors for the development of drug-induced arrhythmias can be classified as modifiable and nonmodifiable. One of the more important nonmodifiable risk factors is underlying heart disease. Cardiac dilation from long-standing heart failure can result in abnormal automaticity, whereas anaerobic metabolism in ischemic myocardial tissues can raise the resting membrane potential and ultimately lead to abnormal impulse conduction (i.e., reentry) (1). Patients with anatomical changes to the normal conduction system, ion channel polymorphisms, or congenital long QT syndrome are also at higher risk for developing arrhythmias. Finally, patients who have a history of arrhythmias are at increased risk of recurrence when certain medications are administered. Risk factors for arrhythmias associated with specific medications, such as skeletal muscle myopathies with succinylcholine administration and congenital long QT syndrome with medications known to prolong the QTc interval, will be addressed in the subsequent sections.

It is important to identify patients who might be at risk for developing drug-induced arrhythmias, so measures can be taken to minimize the modifiable factors. As electrolytes are integral in the generation and propagation of electrical depolarizations within the heart, it is important to ensure patients' electrolytes are within physiologic parameters. Guidelines and protocols are available for the management of electrolyte abnormalities (5–7).

Derangements in potassium are well known to cause arrhythmias. Because the sodium-potassium ATPase pump requires potassium to keep the resting membrane potential between −70 mV and −90 mV, hypokalemia can cause an increase in the resting membrane potential (8). This rise in resting membrane potential can increase automaticity and abnormal impulse formation in cardiac myocytes. Additionally, the action potential and the refractory period can be prolonged in hypokalemia. Because the refractory period becomes prolonged, hypokalemia can also lead to reentry arrhythmias (9, 10). In contrast, hyperkalemia typically results in a decrease in electrical conduction within the heart. After peaked T waves, this can be seen as a widening of the QRS complex followed by loss of the P wave. When hyperkalemia is severe enough, "sine wave configuration," ventricular fibrillation, and asystole can result (5, 9). However, the rate at which hyperkalemia develops seems to be important, because the rapid administration of potassium leads to enhanced automaticity, which can transition into ventricular fibrillation (9).

Magnesium plays a crucial role in numerous physiologic functions and is a cofactor for >300 enzymatic reactions *in vivo* (11). It activates ATPase, which is the energy source for the sodium-potassium ATPase pump, and promotes intracellular transport of cations, including potassium and calcium (12). Hypomagnesemia can often occur concomitantly with hypokalemia and hypocalcemia; thus, it can be difficult to adequately replete the potassium or calcium without also repleting magnesium (13). Therefore, it is always imperative to ensure magnesium levels are within physiologic range when replacing other electrolytes. Although the

adverse cardiovascular effects of magnesium abnormalities may be more associated with the refractory hypokalemia and hypocalcemia, severe magnesium abnormalities can also be problematic. Severe hypomagnesemia can enhance automaticity and can predispose a patient to developing TdP, whereas hypermagnesemia can cause bradycardia, first-degree heart block, and prolongation of the QT interval (14).

In addition to electrolyte abnormalities, critically ill patients frequently have conditions that can alter the pharmacokinetics of medications, increasing the risk of medication-induced arrhythmias. A decrease in renal or hepatic drug clearance can increase plasma concentration levels of certain medications or their metabolites. This is particularly important in medications with a narrow therapeutic index. The types of renal replacement therapies available are expanding, but pharmacokinetic studies can lag behind the advancements, making it difficult to know how medications should be dosed in patients requiring these therapies. Also, critically ill patients often have complex medical regimens. It is important to review medication profiles daily, paying attention to any pharmacokinetic or pharmacodynamic interactions that might be present. It is frequently necessary to make either dosing changes or changes in specific agents to help mitigate adverse drug events from occurring.

Medications prolonging the QT interval

Numerous drugs have been associated with prolongation of the QT interval and subsequent development of polymorphic VT (TdP). The main mechanism of drug-induced long QT syndrome (LQTS) involves blockade of a specific potassium channel, the rapid component of the delayed rectifier, I_{Kr}, which ultimately prolongs repolarization (15, 16). Other less common mechanisms, such as enhancing inward sodium current (17) or reducing cell surface expression of functional channels (18, 19), have also been associated with acquired LQTS. Drugs that precipitate TdP usually delay ventricular repolarization in a heterogeneous fashion, permitting formation of several loci of reentry (20).

Risk factors for drug-induced TdP include: hypokalemia, severe hypomagnesemia, bradycardia, recent conversion from atrial fibrillation (especially with a QT-prolonging drug), heart failure, digoxin use, high drug concentrations, rapid infusion rates of QT-prolonging drugs, baseline QT prolongation, female sex, LQTS, and ion channel polymorphisms (21). At present, >60 drugs may be associated with QT prolongation and TdP (Tables 1 and 2). An advisory board of the Arizona Center for Education and Research on Therapeutics maintains three updated lists (http://www.qtdrugs.org) (22) that include: drugs that are generally accepted to carry a risk of TdP (Table 1); drugs that prolong the QT interval and/or, in some reports, have been associated with TdP but lack substantial evidence (Table 2); and drugs that have a risk for TdP and/or QT prolongation but only under certain conditions (e.g., congenital LQTS, overdose, and drug interactions). It is noteworthy that type Ia antiarrhythmics (particularly quinidine) and type III antiarrhythmics are well known to cause TdP, whereas type Ib and Ic antiarrhythmics rarely cause TdP. However, amiodarone, despite its ability to prolong the QT interval, causes TdP in <1% of those exposed, compared with other type III antiarrhythmics, which cause TdP in 2% to 4% of patients (1).

The prevalence of drug-induced LQTS was recently evaluated by Molokhia and colleagues (23). They determined that, on an annual basis, 7.8 to 14.8 per population million survive to reach the hospital after development of drug-induced LQTS (defined by the combination of TdP, QT prolongation, and drug exposure). However, the true prevalence of drug-induced LQTS is difficult to determine, given that many patients will not survive out-of-hospital arrest, and most adverse drug events remain unreported. Freeman and colleagues (24) evaluated the pharmacoepidemiology of QT interval-prolonging drugs in critically ill patients. Using the database Project Impact, they found that 2.9% (6125 of 212,016) of patients were exposed to QT interval-prolonging drugs for an average of 53.1% of their intensive care unit (ICU) length of stay. They also determined that the 1,139 (18.6%) pa-

Table 1. Drugs generally accepted to carry a risk of torsades de pointes[a] (22)

Cardiovascular
Antianginals
Bepridil (Vascor, Ortho McNeil Pharmaceutical, Raritan, NJ)
Antiarrhythmics
Disopyramide (Norpace, Searle, Skokie, IL)
Dofetilide (Tikosyn, Pfizer, New York, NY)
Ibutilide (Corvert, Pfizer, New York, NY)
Procainamide (Pronestyl/Procan, Bristol-Myers Squibb, Princeton, NJ)
Quinidine (Cardioquin/Quinaglute, Purdue Pharmaceutical Products, Samford, CT)
Sotalol (Betapace, Bayer Healthcare Pharmaceuticals, Montville, NJ)
Amiodarone (Cordarone, Wyeth Pharmaceuticals, Madison, NJ)
Gastrointestinal
Antiemetic
Chlorpromazine (Thorazine, GlaxoSmithKline, Research Triangle Park, NC)
Droperidol (Inapsine, Taylor Pharmaceuticals, San Clemente, CA)
Gastrointestinal stimulant
Cisapride (Propulsid, Janssen Pharmaceutical Products, Titusville, NJ)
Immunologic
Anticancer agents
Arsenic trioxide (Trisenox, Cephalon, West Chester, PA)
Antimicrobials
Antibacterials
Clarithromycin (Biaxin, Abbott Laboratories, Abbott Park, IL)
Sparfloxacin (Zagam, Mylan Bertek Pharmaceuticals, Sugarland, TX)
Erythromycin (Erythrocin, Abbott Laboratories, Abbott Park, IL)
Pentamidine (Pentam/NebuPent, American Pharmaceutical Partners Inc., Los Angeles, CA)
Chloroquine (Aralen, Sanofi Winthrop Pharmaceuticals, New York, NY)
Halofantrine (Halfan, GlaxoSmithKline, Research Triangle Park, NC)
Neurologic
Narcotics
Levomethadyl (Orlaam, Roxane Laboratories, Columbus, OH)
Methadone (Dolophine/Methadose, Eli Lilly, Indianapolis, IN)
Psychiatric
Antipsychotics
Haloperidol (Haldol, Ortho McNeil Pharmaceutical Inc., Raritan, NJ)
Mesoridazine (Serentil, Boehringer Ingelheim, Ridgefield, CT)
Thioridazine (Mellaril, Novartis Pharmaceuticals Corp, East Hanover, NJ)
Pimozide (Orap, OraPharma Inc., Warminster, PA)

[a]Last updated by QTdrugs.org advisory board on 3/25/2008.

Table 2. Drugs that prolong the QT interval and/or in some reports have been associated with torsades de pointes but at this time lack substantial evidence[a] (22)

- Cardiovascular
  - α_1 blockers
    - Alfuzosin (Uroxatral, Sanofi-Aventis, Bridgewater, NJ)
  - Antianginals
    - Ranolazine (Ranexa, Gilead Sciences Inc., Foster City, CA)
  - Antiarrhythmics
    - Flecainide (Tambocor, Graceway Pharmaceuticals LLC, Bristol, TN)
  - Antihypertensives
    - Isradipine (Dynacirc, Novartis Pharmaceuticals Corp, East Hanover, NJ)
    - Moexipril/HCTZ (Uniretic, Schwarz Pharma Inc, Mequon, WI)
    - Nicardipine (Cardene, EKR Therapeutics, Cedar Knolls, NJ)
  - Diuretics
    - Indapamide (Lozol, Sanofi-Aventis, Bridgewater, NJ)
  - Erectile dysfunction
    - Vardenafil (Levitra, Schering-Plough Corp, Kenilworth, NJ)
- Diagnostic
  - Imaging contrast agents
    - Perflutren lipid microspheres (Definity, Lantheus Medical Imaging Inc., North Billerica, MA)
- Endocrinologic
  - Oxytocic
    - Oxytocin (Pitocin, JHP Pharmaceuticals LLC, Parsippany, NJ)
- Gastrointestinal
  - Antiemetic
    - Ondansetron (Zofran, GlaxoSmithKline, Research Triangle Park, NC)
    - Granisetron (Kytril, Roche Pharmaceuticals, Nutley, NJ)
    - Dolasetron (Anzemet, Sanofi-Aventis, Bridgewater, NJ)
  - Antidiarrheal (carcinoid)
    - Octreotide (Sandostatin, Novartis Pharmaceuticals Corp, East Hanover, NJ)
- Immunologic
  - Anticancer agents
    - Tamoxifen (Nolvadex, AstraZeneca Pharmaceuticals LP, Wilmington, DE)
    - Lapatinib (Tykerb/Tyverb, GlaxoSmithKline, Research Triangle Park, NC)
    - Nilotinib (Tasigna, Novartis Pharmaceuticals Corp, East Hanover, NJ)
    - Sunitinib (Sutent, Pfizer Inc., New York, NY)
  - Immunosuppressant
    - Tacrolimus (Prograf, Astellas Pharma Inc., Deerfield, IL)
- Antimicrobials
  - Antibacterials
    - Azithromycin (Zithromax, Pfizer Inc., New York, NY)
    - Gatifloxacin (Tequin, Bristol-Myers Squibb, Princeton, NJ)
    - Gemifloxacin (Factive, Oscient Pharmaceuticals, Waltham, MA)
    - Levofloxacin (Levaquin, Ortho McNeil Pharmaceutical Inc., Raritan, NJ)
    - Moxifloxacin (Avelox, Schering-Plough Corp, Kenilworth, NJ)
    - Ofloxacin (Floxin, Daiichi Pharmaceutical Corp, Montvale, NJ)
    - Telithromycin (Ketek, Sanofi-Aventis, Bridgewater, NJ)
  - Antifungal
    - Voriconazole (VFend, Pfizer Inc., New York, NY)
  - Antiviral
    - Foscarnet (Foscavir, AstraZeneca Pharmaceuticals LP, Wilmington, DE)
    - Amantadine (Symmetrel, Endo Pharmaceuticals Inc., Chadds Ford, PA)
    - Atazanavir (Reyataz, Bristol-Myers Squibb, Princeton, NJ)
- Neurologic
  - Anticonvulsants
    - Felbamate (Felbatol, Meda Pharmaceuticals Inc., Somerset, NJ)
    - Fosphenytoin (Cerebyx, Parke-Davis, New York, NY)
  - Muscle relaxants
    - Tizanidine (Zanaflex, Elan Pharma, Cambridge, MA)
  - Sedatives
  - Chloral hydrate (Noctec, Bristol-Myers Squibb, Princeton, NJ)
- Psychiatric
  - Antidepressants
    - Venlafaxine (Effexor, Wyeth Pharmaceuticals, Madison, NJ)
  - Antipsychotics
    - Ziprasidone (Geodon, Pfizer Inc., New York, NY)
    - Clozapine (Clozaril, Novartis Pharmaceuticals Corp, East Hanover, NJ)
    - Quetiapine (Seroquel, AstraZeneca, Wilmington, DE)
    - Risperidone (Risperdal, Janssen Pharmaceutical Products, Titusville, NJ)
    - Sertindole (Serlect/Serdolect, Lundbeck, Paramus, NJ)
    - Paliperidone (Invega, Janssen Pharmaceutical Products, Titusville, NJ)
  - Mood stabilizers
    - Lithium (Lithobid/Eskalith, Noven Pharmaceuticals, Miami, FL)

[a]Last updated by QTdrugs.org advisory board on 4/15/2009.

tients, who were concomitantly administered more than one QT-prolonging drug, had an absolute increase in mortality (+5.1%, $p < .001$) and ICU length of stay (+6.1 days, $p < .001$) when compared with those only receiving one QT-prolonging drug (n = 4986).

Acute management of TdP should incorporate direct current cardioversion shock to terminate episodes lasting >5 secs. At present, intravenous magnesium is the medical treatment of choice for this arrhythmia. In a small case series, intravenous magnesium sulfate (2 g as a slow intravenous push) was shown to suppresses EADs and terminate TdP (25). Given that TdP is frequently recurrent, efforts to increase heart rate between 105 and 120 beats/min *via* pacing or an isoproterenol continuous infusion are incorporated in its management. In a study by Tzivoni et al (25), magnesium sulfate was given as a continuous infusion of 3–20 mg/min until the QT interval dropped <500 msecs in nine of 12 patients. Use of drugs that further prolong the time required for repolarization, such as procainamide, are contraindicated during TdP. After acute management of TdP, discontinuation of drugs known to prolong the QT interval and correction of underlying electrolyte derangements (hypokalemia, hypomagnesemia, hypocalcemia) are often necessary. In refractory or high-risk patients, consider placement of a permanent pacemaker and/or implantable defibrillator.

In an effort to prevent development of TdP, patients receiving medications that may prolong the QT interval should be monitored by members of the patient care team, with decision support technology, or a combination of both. The upper limit of the normal QT interval is commonly reported as approximately 450 msecs; however, its length is influenced by heart rate and gender (26). In clinical practice, the use of either Bazett's ($QTcB = QT/\sqrt{RR}$) or Fridericia's formulas ($QTcF = QT/3\sqrt{RR}$) is necessary to correct the QT interval (QTc) for the influence of varying heart rate (i.e., QT shortens with tachycardia and is prolonged in bradycardia) (27, 28). Although Bazett's correction is most commonly used, given its mathematical simplicity, it has been shown to overcorrect at short RR intervals and to undercorrect at long RR intervals. Fridericia's (28) correction seems to approximate more accurately subject-specific QTc intervals that were determined, using linear mixed modeling

techniques. Prolongation of the QTc interval beyond 500 msecs is a frequently reported threshold to evaluate risks/benefits of the offending therapy, reduce drug doses, or withdraw therapy altogether (26, 30). The decision to modify therapy based on a lengthening QTc interval is one that must be made for each patient individually. Others (26, 30) have proposed not utilizing an absolute QTc threshold but rather determining the difference between pre- and post-drug exposure QTc and modifying therapy at the point this difference exceeds 60 msecs. An extensive scientific statement regarding prevention of TdP in hospital settings has recently been published by the American Heart Association and the American College of Cardiology Foundation (31).

Antiarrhythmic agents

A group of medications frequently implicated with causing arrhythmias is paradoxically the antiarrhythmic agents. *Proarrhythmia* is the term used to describe drug-induced arrhythmias with antiarrhythmic medications. The true prevalence of proarrhythmia is not easy to determine because it can be difficult to ascertain if an arrhythmia that occurs while receiving treatment with an antiarrhythmic agent is due to proarrhythmia vs. just a medication failure and breakthrough of the underlying arrhythmia. However, proarrhythmia has been clearly identified in several clinical trials.

The Cardiac Arrhythmia Suppression Trial (32, 33) was a landmark trial, which randomized 1498 patients to encainide, flecainide, moricizine (all class Ic antiarrhythmics) or placebo to prevent sudden death after myocardial infarction. The trial was stopped early due to an increase in the rate of death due to arrhythmias (5.7% in the treatment groups vs. 2.2% in placebo, $p = .0004$) and nonarrhythmic cardiac causes (2.2% in the treatment groups vs. 0.7% in placebo, $p = .01$). After the publication of the Cardiac Arrhythmia Suppression Trial, the routine use of antiarrhythmic agents was questioned. The Cardiac Arrest Study Hamburg trial (34) was designed to determine the frequency of sudden death, cardiac mortality, and total mortality in patients randomized to metoprolol, amiodarone, propafenone, or implantable cardioverter defibrillator after surviving sudden cardiac death. However, the propafenone arm, another class Ic agent, was stopped early when it was found that 1-yr mortality was actually increased. Additionally, two meta-analyses (35, 36) were published showing an increased rate of mortality in patients taking class Ia agents, specifically quinidine.

The same properties that suppress arrhythmias are probably responsible for the proarrhythmic effects as well. Class Ic agents block sodium channels and substantially slow intraventricular conduction. Ischemia can predispose a patient to reentry tachycardias. Slowing conduction with class Ic agents in postmyocardial infarction patients in the Cardiac Arrhythmia Suppression Trial probably led to a prolongation in the reentrant circuit, allowing for a reentry VT to develop (37). This is the most likely explanation for the increase in mortality seen in this trial; therefore, class Ic agents should never be used in patients with underlying coronary artery disease. Class Ia agents also slow conduction but to a lesser extent than the class Ic agents, and they also prolong repolarization. This latter effect makes the class Ia agents more prone to cause arrhythmias resulting from triggered activity or EAD, such as TdP. Class Ib agents, such as lidocaine and mexilitine, are more selective in exerting their antiarrhythmic actions in abnormal or damaged myocytes and have not been associated with proarrhythmia (38).

The class III agents, amiodarone, sotalol, and dofetilide, seem to be somewhat safer in terms of proarrhythmia. Studies (39, 40) with amiodarone have shown either a neutral or beneficial impact on mortality in postmyocardial infarction patients. One study (41) with d-sotalol showed an increase in mortality, but this has not been seen with the racemic product that is currently marketed (42). Class III agents block potassium channels leading to a prolongation of repolarization; this can be seen as a prolongation of the QT interval on ECG. By prolonging repolarization, these agents have the potential to induce TdP. Although this can be seen with sotalol and dofetilide, it is only rarely seen with amiodarone. In addition to the potassium channel-blocking properties, amiodarone has class II/β-adrenergic receptor-blocking properties, as well as class IV/calcium-channel blocking properties. As such, amiodarone administration is associated with bradycardias.

Because of the limitations of antiarrhythmic agents, the focus on treating arrhythmias has shifted from medication-based to device-based therapy. With the dramatic results of device-based therapy, use of antiarrhythmic medications has decreased (43). Careful selection of the appropriate agent is encouraged anytime antiarrhythmic agents are warranted.

Inotropes

Dobutamine and milrinone are commonly used inotropes in the management of hemodynamic compromise in the ICU (44). Both drugs increase myocardial contractility by ultimately increasing intracellular levels of cyclic adenosine monophosphate (cAMP); however, they do so with different mechanisms. Dobutamine increases cAMP via β-adrenergic receptor-mediated stimulation of adenylate cyclase, which in turn increases cAMP production. In contrast, milrinone prevents intracellular enzymatic degradation of cAMP by inhibiting phosphodiesterase. Regardless of the mechanism, cAMP increases calcium release from the sarcoplasmic reticulum, which increases contractile force of the myocardium through calcium's influence on the actin-myosin apparatus. This increase in intracellular calcium is thought to be associated with the potential of these agents to precipitate atrial and ventricular arrhythmias (44).

Several plausible mechanisms may explain the ability of dobutamine to generate arrhythmias. Dobutamine is considered to be directly arrhythmogenic, given its adrenergic effect on the myocardial cell membrane β receptor, which explains why patients exposed to dobutamine commonly experience a dose-dependent sinus tachycardia (45, 46). Of note, doses of dobutamine >5 μg/kg/min are more prone to cause arrhythmias and provide little benefit on oxygen transport values and hemodynamics (47). Dobutamine's ability to increase automaticity of the SA node, shorten ventricular refractory period, and increase conduction velocity, all which may lead to arrhythmias, is well described (48, 49). The prevalence of dobutamine-induced arrhythmias has been extensively studied during stress echocardiography. In this setting, dobutamine has been reported to cause ventricular arrhythmias in 0.9% and supraventricular rhythm disorders in 0.7% of those exposed (50). According to the manufacturer, approximately 5% of patients experience ventricular premature depolarizations (51).

Unlike dobutamine, milrinone is able to increase inotropy without activating the β-adrenergic receptors; therefore, it was originally thought that it would cause less tachyarrhythmias than dobutamine. Unfortunately, subsequent research has not supported this hypothesis. In the OPTIME-CHF trial (52), 951 patients with acute exacerbations of systolic heart failure were randomized to a 48-hr infusion of either milrinone or placebo. New atrial arrhythmias were seen in 4.6% of the milrinone-treated group compared with 1.5% of patients who received placebo. In another study (53) in cardiac surgery, intraoperative use of milrinone was associated with a doubling of the risk of postoperative atrial fibrillation, occurring in 58.2% of patients who received milrinone vs. only 26.1% of patients who did not receive milrinone ($p < .001$). The prevalence of transient ventricular arrhythmias has been reported to occur in 6.4% to 16% of patients with acute heart failure (54). In phase II and III clinical trials of milrinone, supraventricular arrhythmias were reported in 3.8% of the patients, and ventricular arrhythmias were reported to occur in 12% of patients. Of those patients who experienced ventricular arrhythmias, ventricular ectopic activity accounted for 8.5%, nonsustained VT in 2.8%, sustained VT in 1%, and ventricular fibrillation occurred in 0.2% (55).

Digoxin

Digoxin inhibits the sodium-potassium ATPase pump, resulting in an increase in intracellular calcium concentrations in the cardiac myocyte. This, in turn, slows conduction through the AV node and can cause an increase in cardiac automaticity, which at toxic levels can precipitate numerous arrhythmias (56). Although digoxin toxicity can precipitate almost any type of arrhythmia, some are more common than others. Due to its underlying mechanism of action, ectopy in the form of ventricular premature depolarizations is a relatively common, although a nonspecific, finding. Similarly, conduction block of any degree (although rarely Mobitz type II) can also occur. Careful assessment of the ECG should be performed for patients with a history of atrial fibrillation presenting with an apparent regularization of their rhythm, as this may just represent continued atrial fibrillation with conduction block and an AV nodal escape (56, 57). Other arrhythmias that have been considered pathognomonic for digoxin toxicity include paroxysmal atrial tachycardia with block, accelerated junctional rhythm, and bidirectional VT (56–58).

Risk factors for digoxin toxicity include altered pharmacokinetics, in particular renal dysfunction and drug interactions, as well as electrolyte imbalances, specifically hypokalemia, hypomagnesemia, and hypercalcemia (59). Dosages of digoxin should always be individualized for each patient, taking into account renal function and other medications. In one small series of 17 patients with digoxin toxicity, nearly all of the cases could have been prevented through either proper education of the patient and appropriate individualization of the doses (57).

The development of antidigoxin Fab fragments/digoxin immune Fab has revolutionized the treatment of digoxin toxicity and resulted in improved survival for these patients. When treated with digoxin immune Fab, approximately 80% of patients will have a complete response to therapy with an additional 10% of patients having a partial response to therapy (60). There are two methods of determining the dose of digoxin immune Fab to administer. It is important to note that recommended dosages are expressed in number of vials of digoxin immune Fab, and not in standard units (i.e., milligrams). There are two preparations of digoxin immune Fab currently available: DigiBind (GlaxoSmithKline; Philadelphia, PA) and DigiFab (BTG plc; London, UK). Each vial is equivalent to 38 mg of DigiBind or 40 mg of DigiFab and will bind roughly 0.5 mg of digoxin. Equations to determine the number of vials to administer are available, for both patients with acute ingestion of a known amount of digoxin, or for patients with chronic ingestion and subsequent digoxin toxicity and a known serum digoxin concentration (61). Of note, digoxin concentrations should not be monitored shortly after administration of digoxin immune Fab, as most assays are not able to distinguish between free and Fab-bound digoxin (57).

Medications causing electrolyte imbalances

Several electrolytes are integral in the initiation and propagation of electrical conduction within the cardiac myocytes. Therefore, medications that alter the serum concentrations of these electrolytes have the potential to indirectly cause arrhythmias. Table 3 presents a list of medications that can cause selected electrolyte imbalances (10, 11, 62, 63). The β-adrenergic agonists, including the catecholamines, are an often-overlooked cause of hypokalemia in critically ill patients. Due to the effects on potassium homeostasis and their direct β-agonist effects, they can commonly cause ar-

Table 3. Medications causing electrolyte abnormalities

Hypokalemia	Hyperkalemia
β-adrenergic agonists	Potassium-sparing diuretics
Catecholamines	Angiotensin-converting enzyme inhibitors
Insulin	Angiotensin receptor blockers
Loop diuretics	Nonsteroidal anti-inflammatory drugs
Theophylline	Succinylcholine
Thiazide diuretics	β-adrenergic blockers
Aminoglycosides	Digoxin
Amphotericin B	Hypermagnesemia
Mineralocorticoids	Magnesium-containing laxatives or antacids[a]
Hypomagnesemia	Parenteral hyperalimentation
Thiazide diuretics	Lithium
Loop diuretics	
Aminoglycosides	
Amphotericin B	
Cisplatin	
Cyclosporine	
Digoxin	
Mannitol	
Methotrexate	
Citrate-containing products	
Pentamidine	
Laxatives	

[a]Typically in patients with underlying renal insufficiency.

rhythmias. Citrate-containing products, including blood products, have been associated with hypomagnesemia. Succinylcholine can also cause a clinically significant hyperkalemia, an effect that is more pronounced in patients with underlying skeletal muscle myopathies. Alternative agents, such as rocuronium, should be considered for rapid sequence intubation in patients with skeletal muscle myopathies. Treatment of arrhythmias that occur due to electrolyte imbalances typically revolve around supportive care and restoration of physiologic concentrations of the electrolyte. Calcium can be administered as a membrane stabilizing agent (5). Guidelines and protocols are available for the management of electrolyte abnormalities (5–7).

Anesthetic agents

For over five decades, the ability of volatile anesthetics (e.g., halothane, enfluane, isoflurane, sevoflurane, and chloroform) to sensitize the myocardium to arrhythmogenic catecholamines has been known (64–69). Volatile anesthetics and α- or β-adrenoceptor agonists are known to individually cause inappropriate intracellular calcium handling and inhibition of sodium channel conductance; however, the inhibitory effects of these two drug classes are additive (70, 71). Sevoflurane, halothane, and isoflurane have also been shown to block the I_{Ks} current (but not significantly inhibit I_{Kr}) in animal models and likely reduce the repolarization reserve (72–75). Delayed ventricular repolarization and QTc interval prolongation (between 30 and 70 msecs) has been reported with enflurane, isoflurane, halothane, and sevoflurane use in healthy humans (76, 77). The prevalence of intraoperative arrhythmias varies greatly with its definition. For example, in the early 1990s, the Multicenter Study of General Anesthesia found that 70.2% of 17,201 patients undergoing general anesthesia experienced tachycardia, bradycardia, or dysrhythmias. In that same report (78, 79), intraoperative arrhythmias that were life threatening and required intervention occurred in 1.6% of patients.

Bronchodilators

Due to the β-stimulating properties of the β_2-adrenergic receptor agonists, it has been theorized that inhaled bronchodilators could place patients at an increased risk of developing tachyarrhythmias, but some authors (80) have questioned the true clinical impact. A meta-analysis by Salpeter and colleagues (81), which evaluated a total of 18 trials, concluded that single doses of β_2 agonists increased heart rate on average by about 9 beats/min (95% confidence interval, 5.32–12.92). For trials of longer duration, the analysis concluded that β_2-agonist treatment was associated with an increased risk for a cardiovascular event (RR, 2.54; 95% confidence interval, 1.59–4.05), although none of the individual trials were able to detect this increased risk. However, the TORCH trial (82), which randomized 6,112 patients to either salmeterol, fluticisone, the combination of the two medications, or placebo, also failed to show any difference in cardiovascular mortality, cardiovascular-related adverse events, or overall mortality. However, it is unknown how many patients at risk for arrhythmias were included in the trial, as one of the exclusion criteria was "other conditions likely to interfere with the study or cause death within 3 yrs" (83) Additionally, the TORCH trial studied a long-acting β_2 agonist, whereas shorter-acting bronchodilators, such as albuterol, are more commonly used in the ICU. Given the totality of the data available, it would seem that β_2-agonist bronchodilators can increase baseline heart rate. In patients with underlying tachyarrhythmias, this has the potential to exacerbate the rhythm. Although levalbuterol was developed to circumvent the cardiovascular effects of albuterol, tachyarrhythmias still occur in 2.7% of patients (84).

Drug-induced bradyarrhythmias

The majority of medications covered so far typically promote tachyarrhythmias. However, it is noteworthy that several medications used in critically ill patients can induce bradyarrhythmias. β blockers and calcium-channel blockers frequently are used to slow heart rate, and amiodarone also has β- and calcium-channel blocking properties. A sometimes overlooked agent for causing bradycardia is clonidine. Several reports (85–87) have associated clonidine therapy with bradycardia. Dexmedetomidine is a newer sedative agent that is similar in structure to clonidine. Bradycardia has been seen in up to 5% of patients in clinical trials with this agent (88). In general, these agents should be avoided, if possible, in patients with advanced heart block.

Treating drug-induced bradyarrhythmias starts first with discontinuing the offending agent and use of β-adrenergic agonists, such as dobutamine, dopamine, or isoproterenol, to stimulate chronotropy, if needed. Glucagon, which bypasses the β receptor to activate adenylate cyclase, has been used successfully in some patients with β-blocker overdose (89). Hyperinsulinemia/euglycemia therapy has been shown to improve hemodynamics and survival in animal models of calcium-channel blocker overdose (90), with similar success seen clinically in a small series of patients (91). For patients who do not respond adequately to medical therapy, transvenous pacing should be considered.

Preventive strategies

The most important step to preventing drug-induced arrhythmias is clinician awareness of predisposing risk factors, proper patient and/or medication selection, and sufficient monitoring while the patient is at risk for an arrhythmia. Monitoring may include placing high-risk patients on centralized telemetry monitoring. Baseline and daily ECG monitoring may be warranted in patients at risk for QTc prolongation. Electrolytes should be closely monitored and corrected as needed. Assessment of renal and/or hepatic function are frequently required while patients are on medications that are known to cause arrhythmias, and appropriate dosage adjustments should be made, if needed.

Given the complexity of critically ill patients and their medical regimen, it is important to have additional mechanisms in place to help optimize patient safety. Advancements in technology have greatly reduced the adverse effects that can occur with some high-risk medications. Models have been developed to help determine the appropriate empirical dose of medications with a narrow therapeutic index, specifically, digoxin (92). Utilizing such a model can result in more clinically appropriate digoxin concentrations and potentially less toxicity.

An area that lends itself well to automated clinical decision support tools is QTc prolongation. This is because so many medications have been implicated in causing QTc prolongation, and there are numerous pharmacokinetic and pharmacodynamic interactions that need to

be evaluated and taken into account when making dosage adjustments. Alerts can be generated at the time of order entry either with computerized provider order entry or when pharmacy enters the order into the computer; however, the effectiveness of this strategy is limited by the low specificity of many software programs for generating clinically useful alerts. Alternatively, implementing a second-level automated alert with pharmacist monitoring and intervention has shown to decrease contraindicated drug combinations and QTc interval prolongation (93, 94). These second-level automated alerts can take into account not only drug-drug interactions but other risk factors as well, such as electrolyte abnormalities, renal function, and improve alert specificity, ultimately leading to alerts that are more clinically useful (95). For a more detailed discussion of the use of technology to prevent adverse drug reactions, see the papers by Weber et al and Stockwell and Kane-Gill in this supplement.

Summary

This review has characterized the mechanisms and risk factors and highlighted commonly administered pharmacotherapeutic agents that have been reported to cause drug-induced arrhythmias. Extensive literature exists which describes individual drugs and their mechanisms for causing this adverse event. Patients in the ICU are at risk for developing drug-induced arrhythmias, some of which can be lethal. Clinicians should be aware of the risks factors for developing drug-induced arrhythmias and take necessary steps to help mitigate them. At minimum, this should include the daily review of every patient's medication profile, making adjustments for renal and hepatic impairment, as well as any pharmacokinetic or pharmacodynamic drug interactions. Ideally, second-level automated alerts with clinical pharmacist monitoring could be implemented. Although drug-induced arrhythmias are insidious, enhanced appreciation and screening for this adverse event have the potential to improve prevention, treatment, patient safety, and outcomes in this patient population.

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