CASES

Falling between the cracks: a case of amiodarone toxicity

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A 64-year-old woman presented to the emergency department with a 12-day history of nausea, vomiting and diarrhea, along with a six-month history of progressive shortness of breath. Atrial fibrillation had been diagnosed seven months earlier, at which time she had started taking amiodarone (400 mg twice daily) and warfarin (1 mg daily). Her medical history included hypertension, peripheral vascular disease, degenerative disc disease and a 30-year history of smoking. Aside from amiodarone and warfarin, her medications included meloxicam (15 mg daily), oxycodone (as needed) and alendronate (70 mg weekly). In the preceding four days, she had started tetracycline (250 mg four times daily) for suspected respiratory tract infection and paroxetine (20 mg daily) for depression.

Our patient was admitted to a community hospital for investigation of gastrointestinal complaints and dyspnea, described above. Shortly after admission, sinus bradycardia developed with ectopic beats and a prolonged corrected QT interval greater than 690 ms. Subsequent cardiac arrest caused by torsades de pointes required cardiopulmonary resuscitation and cardioversion. Abnormalities in her laboratory profile included the following: leukocyte count 12.7 (normal 4–10) $\times 10^9$/L, potassium level 3.1 (normal 3.5–5.0) mmol/L, alanine transaminase level 166 (normal ≤ 33) U/L, aspartate transaminase level 295 (normal < 32) U/L, alkaline phosphatase level 120 (normal 33–104) U/L and γ-glutamyltransferase level 84 (normal < 31) U/L. Her thyroid-stimulating hormone level was reduced at 0.182 (normal 0.27–4.20) mIU/L, with an elevated free thyroxine level of 38 (normal 10–24) pmol/L. Her chest radiograph showed prominent interstitial markings with a nodular opacity in the right upper lobe. Amiodarone toxicity was suspected in the differential diagnosis of pulmonary interstitial disease because of the constellation of hepatic, thyroid and electrophysiologic findings in the context of overexposure to amiodarone. She was transferred to the coronary care unit in our tertiary care hospital, where amiodarone was discontinued and an isoproterenol infusion started.

Our patient's stay in hospital was complicated by worsening shortness of breath and hypoxemia with high oxygen requirements. A computed tomographic scan of her thorax showed emphysema as well as dense consolidations in the right and left upper lobes, dense atelectasis in the lower lobes and dense attenuation of the liver, suggestive of amiodarone exposure and possible toxicity. Her thyroid studies and radioactive iodine uptake scan were consistent with amiodarone-induced hyperthyroidism, and she was given methimazole. Her liver enzymes returned to normal several weeks following the discontinuation of amiodarone.

Discussion

Our patient presented with multisystem amiodarone toxicity including cardiac, pulmonary, thyroid and hepatic toxicity following inadvertent continuation of her loading dose of amiodarone, 400 mg twice daily, for seven months; the usual loading period is seven days. Her total cumulative dose of amiodarone was greater than 170 g. Although serum amiodarone concentrations were not measured at the time of the initial

KEY POINTS

- Amiodarone is a frequently prescribed antiarrhythmic agent with a number of well-documented adverse drug effects.
- Adherence to guidelines for baseline and follow-up monitoring for patients taking amiodarone is generally poor.
- Regular monitoring based on guidelines for efficacy and toxicity by a physician familiar with use of amiodarone is essential, with referral to a specialist as necessary.
- Although lower maintenance doses of amiodarone are considered safer, toxicity must still be considered when there is any change in the patient's condition.

Competing interests: P. Timothy Pollak has served on the Canadian Cardiovascular Society's consensus panel on atrial fibrillation and has given expert testimony (unpaid) to Health Canada on bioequivalence criteria. His institution has received funding from the Canadian Institutes for Health Research for research on amiodarone and atrial fibrillation. None declared by Constanze Mackenzie, Jaffer Syed or Gideon Koren.

This article has been peer reviewed.

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***CMAJ* 2011. DOI:10.1503/cmaj.100351**

presentation to hospital, blood drawn 10 months after the discontinuation of amiodarone still showed measurable concentrations of amiodarone at 0.4 mg/L (the therapeutic range for atrial fibrillation is 0.75–1.5 mg/L) and the metabolite, desethylamiodarone (DEA), at 0.9 mg/L (the therapeutic range for atrial fibrillation is 0.75–1.5 mg/L). Assuming a typical half-life of 56 days, the initial drug concentrations were calculated to exceed 10 mg/L, many times the therapeutic target.

Amiodarone is an antiarrhythmic agent with complex pharmacology and toxicology. Available in Canada since 1986, it remains the most widely used antiarrhythmic agent in the country.[1] An evaluation of antiarrhythmic use for patients with atrial fibrillation in Canada documented an increase in amiodarone use from 1.6% to 17.9% over the 16-year period from 1991 to 2007.[2] Atrial fibrillation affects about 250 000 Canadians.[3]

Amiodarone is frequently initiated in a hospital environment but requires long-term monitoring

Table 1: Amiodarone-related adverse effects and recommended monitoring[4–6]

System	Adverse effect	Frequency, %	Clinical findings	Recommended monitoring*
Pulmonary	Pulmonary fibrosis, infiltrates, acute respiratory distress syndrome	0.5–17	Acute or subacute dyspnea, nonproductive cough, pleuritic chest pain, weight loss, fever	• Chest radiography - Baseline - Annually • Computed tomography - If there is clinical suspicion of pulmonary toxicity • Pulmonary function tests - Baseline - As needed for symptoms or new findings on radiography
Thyroid	Hyperthyroidism	1–23	Weight loss, weakness, goiter, tremor, recurrence of tachyarrhythmia, unexpected change in warfarin dosing	• Thyroid function tests (thyroid-stimulating hormone, free thyroxine, triiodothyronine) - Baseline - Every six months - Not helpful during first three months of treatment
	Hypothyroidism	1–32	Weight gain, fatigue, dry skin	• Antithyroid peroxidase antibodies - Baseline only
Cardiac	Bradycardia, atrioventricular block	5	Fatigue, syncope	• Electrocardiography - Baseline - Annually - As needed
	Arrhythmia	1	Palpitations	
Gastrointestinal	AST, ALT elevation	15–30	Usually asymptomatic	• Liver transaminases (AST, ALT) - Baseline - Every six months
	Hepatitis, cirrhosis	< 3	Fatigue, malaise, anorexia, nausea, vomiting, hepatomegaly	
	Nausea, anorexia constipation	30		
Ocular	Corneal deposits	> 90		• Ophthalmologic evaluation - Baseline only if there are substantial pre-existing visual abnormalities - As needed
	Halo vision	< 5	Worse at night	
	Optic neuropathy	< 1	Visual acuity or peripheral vision changes	
Dermatologic	Blue-grey skin discoloration	< 10	Sun-exposed skin only	• Physical examination
	Photosensitivity	25–75		
Central nervous system	Peripheral neuropathy	0.3/annually		• Physical examination
	Ataxia, tremor, impaired sleep	3–30	Tremor, especially during loading doses	

Note: ALT = alanine aminotransferase, AST = aspartate aminotransferase.
*Based on clinical practice guidelines published by the Heart Rhythm Society.[5]

of efficacy and adverse effects. This mandates some form of outpatient monitoring. Well-known potential adverse effects are listed in Table 1[4–6] and can lead to discontinuation of therapy in up to 18% of patients.[7] With long-term use, the prevalence of adverse effects can reach 50%, largely related to cumulative dose[5] and serum drug levels.[6] The severity of adverse effects related to amiodarone ranges from laboratory abnormalities without symptoms, mild to moderate symptoms (most commonly thyroid and pulmonary) to temporary or permanent disability.[8]

Risk factors for toxicity

Amiodarone has a number of unique pharmacokinetic and pharmacodynamic properties that contribute to its adverse effect profile and toxicity (Box 1).[4,6,9] Because of its large volume of distribution and long elimination half-life, amiodarone requires loading doses to achieve an initial effect in a reasonable time frame. Typically, after a 10-g loading dose divided over one week (intravenous or oral), the dose is decreased to a lower maintenance dose of 100–400 mg per day to produce safe steady-state conditions.[3]

The risks of lung, thyroid and hepatic toxicity increase with higher maintenance and cumulative amiodarone doses. One study has reported that a 100-g increase in cumulative amiodarone dose is associated with a 44% increased risk of adverse drug events.[8] Pulmonary toxicity has been reported with maintenance doses greater than 200 mg per day[10] and increases with cumulative amiodarone doses greater than 100 g (odds ratio 10.29 [95% confidence interval 3.42–30.92]) compared with patients who received less than 100 g amiodarone.[11] Similarly, a cumulative amiodarone dose of more than 144 g has been related to a more than 10-fold increase in the risk of hyperthyroidism (odds ratio 12.9 [95% confidence interval 6.1–27.3]) compared with patients taking other antiarrhythmics.[12] Although hepatotoxicity has not been associated with cumulative dose, there is a relation with higher serum amiodarone concentrations (> 2.5 mg/L), with 7% of patients having alanine transaminase levels more than three times the upper normal limit.[6]

Box 1: Pharmacologic properties contributing to amiodarone toxicity[4,6,9]

- Long half-life (average 56 days)
- Large range in bioavailability across the population (30%–80%), with bioavailability increasing with coingestion of food
- Active metabolite with half-life longer than parent drug
- Large volume of distribution (around 66 L/kg)
- Highly lipophilic parent drug and metabolite accumulate in plasma, fat, muscle (including myocardial tissue), lungs, liver and skin with chronic use
- High iodine content with potential for unmasking thyroid abnormalities
- Potential for multiple drug interactions because of inhibition of cytochrome P450 enzymes and P-glycoprotein drug efflux transporter

Table 2: Selected drug interactions with amiodarone[4,5,9]

Drug	Mechanism of interaction	Effect
ß-blockers	Additive ß-blockade; cytochrome P450 2D6 inhibition (metoprolol, timolol, propranolol)	Bradycardia, atrioventricular block; increased ß-blocker plasma concentration
Nondihydropyridine calcium channel blockers (diltiazem, verapamil)	Additive calcium channel blockade	Bradycardia, atrioventricular block
Digoxin	P-glycoprotein inhibition	Increased digoxin plasma concentration and effect
Cyclosporine	Cytochrome P450 3A4 and P-glycoprotein inhibition	Increased cyclosporine plasma concentration and effect
Antidepressants (selective serotonin reuptake inhibitors, tricyclics)	Additive prolongation of QT interval; cytochrome P450 inhibition	Risk of arrhythmia including torsades de pointes; increased drug concentrations
Antimicrobial (macrolides, azole antifungals, fluoroquinolones)	Cytochrome P450 3A4 inhibition (macrolides and azoles); additive QT prolongation	Increased drug concentrations; risk of arrhythmia
Warfarin	Cytochrome P450 2C9 inhibition	Increased warfarin concentration, increased international normalized ratio
Antiarrhythmic drugs (quinidine, disopyramide, procainamide, flecainide, sotalol)	Additive antiarrhythmic effects (Vaughan Williams class I–IV); prolongation of QT interval	Increased risk of ventricular arrhythmia and torsades de pointes
HMG-CoA reductase inhibitor (simvastatin)	Cytochrome P450 3A4 inhibition	Increased statin levels and half-life

Note: HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

Interactions

Treatment with amiodarone is also complicated by substantial drug interactions (Table 2).[4,5,9] Amiodarone is primarily metabolized in the liver by cytochrome P450 isozymes 3A4 to its active metabolite, DEA.[6] It is a potent inhibitor of cytochrome P450 1A2, 2C9, 2D6 and 3A4, and may interact with other drugs, such as digoxin, via inhibition of the P-glycoprotein membrane transport system, a drug efflux pump.[9] In general, interactions relate to changes in the concentration of the drug interacting with amiodarone and not changes in amiodarone concentration. This is a result of amiodarone's enormous volume of distribution.[6] Amiodarone concentrations and the potential for drug interactions persist for many weeks after discontinuation of the drug because of its long half-life of 56 days.

When amiodarone is combined with other medications such as β-blockers, calcium channel blockers and other antiarrhythmic drugs, the additive effects can result in adverse cardiovascular events including prolongation of the QT interval and subsequent proarrhythmia. Although both amiodarone and its metabolite, DEA, prolong the QT interval, the reported incidence of torsades de pointes is relatively low (1%), reported mostly in the context of bradycardia, hypokalemia, increases in drug dosage or drug interactions with other medications that prolong the QT interval (a list of drugs associated with prolongation of the QT interval is available at www.azcert.org/).[13] Therefore, starting new medications in a patient receiving amiodarone often requires reductions in drug dosage, monitoring of drug concentrations (e.g., digoxin, cyclosporine) or international normalized ratio (e.g., warfarin), or an electrocardiogram.[4]

Therapeutic drug monitoring

Although risk factors for amiodarone toxicity in various organ systems have been identified,[5] regular monitoring for adverse effects is still the cornerstone of follow-up care for patients taking this medication. Clinical practice guidelines for amiodarone monitoring have been published by the Heart Rhythm Society (formerly North American Society of Pacing and Electrophysiology)[5] and are summarized in Table 1.

Despite amiodarone's well-known toxicities and evidence that appropriate monitoring improves patient safety, adherence to monitoring guidelines for patients taking amiodarone is poor.[8] Two studies looked at adherence to recommended practice monitoring guidelines in US tertiary care hospitals. Adherence to complete baseline monitoring was as low as 11%, with adherence to follow-up monitoring at 13%[14] and only 9% of patients receiving all the recommended monitoring.[8] Errors in medication monitoring and lack of monitoring have been identified as common sources of preventable adverse drug events. One study found that one-third of adverse drug events related to amiodarone were preventable.[8]

Serum amiodarone and DEA levels can be measured in many hospitals, with serious toxicity more commonly reported at concentrations greater than 2.5 mg/L. Although not routinely done, therapeutic drug monitoring of amiodarone levels has been shown to be useful, in particular for the prevention of hepatotoxicity, because elevations in liver transaminases are uncommon if serum concentrations are maintained at less than 1.5 mg/L.[6] There may also be a role for measuring amiodarone concentrations in the context of suspected toxicity or with recurrence of arrhythmia to determine if the drug should be titrated to reach a safe and effective range or simply discontinued.[5]

The role of the medical team

Preventing adverse events is the responsibility of all participants in patient care, including the initial prescribing physician, primary care and specialist physicians, and the pharmacist dispensing medications. Box 2[15] outlines principles to minimize adverse events when medications are prescribed.

Effective follow-up for prescription of new medications, especially those initiated in hospital, requires communication of explicit management goals to the primary care physician. A prospective multicentre study in Ontario showed that there is poor communication and exchange of information between physicians involved with the care of the same patient, leading to failure in continuity of care.[16] In another study, two-thirds of interactions between drugs or between drugs and diseases identified in primary care involved a drug initiated by a hospital physician.[17]

Box 2: Principles to minimize adverse drug events[15]

- Informed consent, an appropriate indication, knowledge about alternatives for the recommended therapy, and follow-up monitoring for efficacy and potential side effects
- Referral to a specialist familiar with the drug, if required
- Consideration and documentation of potential drug interactions with the addition of any new medication
- Use of resources with information on drug interactions including *Compendium of Pharmaceuticals and Specialties*, electronic databases and websites, such as www.azcert.org (reference lists of QT-prolonging medications)
- Appropriate communication and exchange of information among all health care professionals involved in the patient's care, as well as with the patient
- Accountability of all participants in patient care for appropriate follow-up for the medication

Amiodarone remains a useful drug for treatment of atrial fibrillation, but like all drugs, it requires appropriate follow-up, monitoring for efficacy and safety, and patient education. Appropriate communication and information exchange among all health care professionals involved in the patient's care and with the patient are essential.

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Contributors: Constanze Mackenzie was responsible for the conception of the manuscript and case review. All authors made important contributions to the interpretation of the case and writing the manuscript, and approved the final version submitted for publication.