ISMP Medication Error Report Analysis

Fatal Patient-Controlled Anesthesia Adverse Events

Name Confusion with New Cancer Drugs

Medication Safety Officer Group to Become a Part of ISMP

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These medication errors have occurred in health care facilities at least once. They will happen again—perhaps where you work. Through education and alertness of personnel and procedural safeguards, they can be avoided. You should consider publishing accounts of errors in your newsletters and/or presenting them at your inservice training programs.

Your assistance is required to continue this feature. The reports described here were received through the Institute for Safe Medication Practices (ISMP) Medication Errors Reporting Program. Any reports published by ISMP will be anonymous. Comments are also invited; the writers' names will be published if desired. ISMP may be contacted at the address shown below.

Errors, close calls, or hazardous conditions may be reported directly to ISMP through the ISMP Web site (www.ismp.org), by calling 800-FAIL-SAFE, or via e-mail at ismpinfo@ismp.org. ISMP guarantees the confidentiality and security of the information received and respects reporters' wishes as to the level of detail included in publications.

FATAL PATIENT-CONTROLLED ANESTHESIA ADVERSE EVENTS

A patient underwent surgical repair of a heel injury. Within 15 minutes of arrival in the postanesthesia care unit (PACU), he received intravenous (IV) doses of meperidine 75 mg, morphine 4 mg, and fentanyl 25 mcg for pain. The patient's surgeon also ordered "PCA per anesthesia." A nurse anesthetist wrote an order for morphine patient-controlled analgesia (PCA) 1 mg/mL, 3 mg per demand dose, lock out of 10 minutes, and a basal rate of 1 mg/h. The patient was obese and anxious about inadequate pain control, but the prescribed demand dose – potentially adding up to 18 mg/h – along with a basal infusion were too much given the patient's opioid-naïve status. In fact, based on morphine prescribing information, the dose might have been high even for an opioid-tolerant patient.

A pharmacist reviewed the PCA order, but he did not investigate the patient's current opioid usage. He did not question the 3 mg demand dose or the basal

infusion, neither of which is recommended for an opioid-naïve patient. The morphine PCA was started around 8:00 p.m., while the patient was in the PACU. The patient had not received preoperative PCA instructions, so the PACU nurse taught the patient to self-administer the doses. No further education was provided, and the patient's family was not warned about the hazards of anyone other than the patient administering a dose.

Within 30 minutes of starting the PCA, the patient had given himself 3 doses of morphine, 3 mg each. He reported that his pain was "receding," but a pain score was not documented. Over the next 5 hours, the patient administered 17 more doses for a total of 20 doses (60 mg), and the basal infusion delivered an additional 5.5 mg of morphine. Most of the doses were administered between 8:00 p.m. and midnight. It is unknown whether the patient's wife, who remained at the patient's bedside until midnight, periodically awakened the patient and encouraged him to administer a dose or if she administered doses for him while he slept.

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Indications and Usage

NEXTERONE (amiodarone HCl) Premixed Injection is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. NEXTERONE also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with NEXTERONE, patients may be transferred to oral amiodarone therapy.

Use NEXTERONE for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but NEXTERONE may be safely administered for longer periods if necessary.

Important Risk Information

NEXTERONE (amiodarone HCl) Premixed Injection is contraindicated in patients with:

- Known hypersensitivity to any of the components of NEXTERONE, including iodine
- Cardiogenic shock
- Marked sinus bradycardia
- Second- or third-degree atrio-ventricular (AV) block unless a functioning pacemaker is available
- NEXTERONE should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone therapy, and who have access to facilities adequate for monitoring the effectiveness and side effects of treatment.
- Hypotension is the most common adverse reaction seen with intravenous amiodarone. In clinical trials, treatment-emergent, drug-related hypotension was reported in 16% (288/1836) of patients treated with intravenous amiodarone. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and appeared to be related to the rate of infusion. Monitor the initial rate of infusion closely and do not exceed the recommended rate. In some cases, hypotension may be refractory and result in a fatal outcome. Treat hypotension initially by slowing the infusion; additional standard therapy may be needed, including: vasopressors, positive inotropic agents and volume expansion.
- In 4.9% (90/1836) of patients in clinical trials, drug-related bradycardia that was not dose-related occurred while patients were receiving intravenous amiodarone for life-threatening VT/VF. Treat bradycardia by slowing the infusion rate or discontinuing NEXTERONE. Treat patients with a known predisposition to bradycardia or AV block with NEXTERONE in a setting where a temporary pacemaker is available.
- Elevations of blood hepatic enzyme values ALT, AST, GGT are commonly seen in patients with immediately life-threatening VT/VF. In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of NEXTERONE therapy. Carefully monitor patients receiving NEXTERONE for evidence of progressive hepatic injury. In such cases, consider reducing the rate of administration or withdrawing NEXTERONE.
- Like all antiarrhythmics, NEXTERONE may cause worsening of existing arrhythmias or precipitate a new arrhythmia. Monitor patients for QTc prolongation during infusion with NEXTERONE. Reserve the combination of amiodarone with other antiarrhythmic therapies that prolong the QTc to patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.
- There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with intravenous amiodarone. Findings included pulmonary infiltrates and masses on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure or death. Two percent (2%) of patients were reported to have acute respiratory distress syndrome (ARDS) during clinical studies involving 48 hours of therapy. Pulmonary toxicity including pulmonary fibrosis is a well-recognized complication of long-term amiodarone use.
- Amiodarone inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and may cause increased T4 levels, decreased T3 levels, and increased levels of inactive reverse T3 (rT3) in clinically euthyroid patients. Amiodarone can cause either hypothyroidism or hyperthyroidism. Evaluate thyroid function prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid function tests may persist for several weeks or even months following NEXTERONE withdrawal.
- The most important adverse reactions were hypotension, asystole/cardiac arrest/pulseless electrical activity (PEA), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. The most common adverse reactions leading to discontinuation of intravenous amiodarone therapy were hypotension (1.6%), asystole/cardiac arrest/PEA (1.2%), VT (1.1%), and cardiogenic shock (1%).
- Drug Interactions
 - **Since amiodarone is a substrate for CYP3A and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone.**
 - **Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates for p-glycoprotein.** HMG-CoA reductase inhibitors that are CYP3A4 substrates in combination with amiodarone have been associated with reports of myopathy/rhabdomyolysis. Limit the dose of simvastatin in patients on amiodarone to 20 mg daily. Limit the daily dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required.
 - **Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy.** Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.

Please see brief summary of Full Prescribing Information on the following pages.

Nexterone (amiodarone HCl)

Premixed Injection

Drug Delivery.
For the way you pharmacy.

It's About Time.

Two-year shelf life

Extended stability for greater convenience.

No admixing

Helps minimize errors due to compounding.

Ready to use

Because every second counts.

Nexterone

(amiodarone HCl) Premixed Injection

It's the only cGMP manufacturer-prepared, premixed amiodarone on the market. Find out how Nexterone (amiodarone HCl) can help you. Contact your Baxter representative to place an order at **888.229.0001**. For more information on how Nexterone (amiodarone HCl) can enhance patient care, visit nexterone.com.

DESCRIPTION	PRODUCT CODE	STRENGTH/ VOLUME	CONCENTRATION	NDC #	PACK FACTOR (cartons/case)
NEXTERONE (amiodarone HCl) Premixed Injection	2G3451	150 mg/100 mL	1.5 mg/mL	43066-150-10	12
	2G3450	360 mg/200 mL	1.8 mg/mL	43066-360-20	10

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NEXTERONE (amiodarone HCl) Premixed Injection for intravenous use

Brief Summary of Prescribing Information. See PI for Full Prescribing Information.

1 INDICATIONS AND USAGE

NEXTERONE is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. NEXTERONE also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with NEXTERONE, patients may be transferred to oral amiodarone therapy [see *Dosage and Administration (2) in full prescribing information*].

Use NEXTERONE for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but NEXTERONE may be safely administered for longer periods if necessary.

4 CONTRAINDICATIONS

NEXTERONE is contraindicated in patients with:

- Known hypersensitivity to any of the components of NEXTERONE Premixed Injection, including iodine. Hypersensitivity reactions may involve rash, angioedema, cutaneous/mucosal hemorrhage (bleeding), fever, arthralgias (joint pains), eosinophilia (abnormal blood counts), urticaria (hives), thrombotic thrombocytopenic purpura, or severe periarthritis (inflammation around blood vessels).
- Cardiogenic shock.
- Marked sinus bradycardia.
- Second- or third-degree atrio-ventricular (AV) block unless a functioning pacemaker is available.

5 WARNINGS AND PRECAUTIONS

NEXTERONE should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone therapy, and who have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

5.1 Hypotension

Hypotension is the most common adverse reaction seen with intravenous amiodarone. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with intravenous amiodarone. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion. Hypotension necessitating alterations in intravenous amiodarone therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients.

Treat hypotension initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. *Monitor the initial rate of infusion closely and do not exceed the recommended rate [see Dosage and Administration (2) in full prescribing information].*

In some cases, hypotension may be refractory and result in a fatal outcome [see *Adverse Reactions (6.2) in full prescribing information*].

5.2 Bradycardia and Atrio-ventricular Block

In 90 (4.9%) of 1836 patients in clinical trials, drug-related bradycardia that was not dose-related occurred while they were receiving intravenous amiodarone for life-threatening VT/VF. Treat bradycardia by slowing the infusion rate or discontinuing NEXTERONE. In some patients, inserting a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during the controlled trials. Treat patients with a known predisposition to bradycardia or AV block with NEXTERONE in a setting where a temporary pacemaker is available.

5.3 Liver Enzyme Elevations

Elevations of blood hepatic enzyme values [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)] are commonly seen in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because the values may be elevated in patients who have had recent myocardial infarction, congestive heart failure, or multiple electrical defibrillations. Approximately 54% of patients receiving intravenous amiodarone in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 81% of patients with both baseline and on-therapy data available, the liver enzyme elevations either improved during therapy or remained at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

Acute, centrilobular confluent hepatocellular necrosis leading to hepatic coma, acute renal failure, and death has been associated with the administration of intravenous amiodarone at a much higher loading dose concentration and much faster rate of infusion than recommended [see *Dosage and Administration (2) in full prescribing information*].

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of NEXTERONE therapy. Carefully monitor patients receiving NEXTERONE for evidence of progressive hepatic injury. In such cases, consider reducing the rate of administration or withdrawing NEXTERONE.

5.4 Proarrhythmia

Like all antiarrhythmic agents, NEXTERONE may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsade de pointes (TdP), has been associated with prolongation, by intravenous amiodarone, of the QTc interval to 500 ms or greater. Although QTc prolongation occurred frequently in patients receiving intravenous amiodarone, TdP or new-onset VF occurred infrequently (less than 2%). Monitor patients for QTc prolongation during infusion with NEXTERONE. Reserve the combination of amiodarone with other antiarrhythmic therapies that prolong the QTc to patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly [see *Drug Interactions (7) in full prescribing information*].

Amiodarone causes thyroid dysfunction in some patients, which may lead to potentially fatal breakthrough or exacerbated arrhythmias.

5.5 Pulmonary Disorders

Early-onset Pulmonary Toxicity

There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with intravenous amiodarone. Findings have included pulmonary infiltrates and masses on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure or death.

ARDS

Two percent (2%) of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies involving 48 hours of therapy.

Pulmonary Fibrosis

Only 1 of more than 1000 patients treated with intravenous amiodarone in clinical studies developed pulmonary fibrosis. In that patient, the condition was diagnosed 3 months after treatment with intravenous amiodarone, during which time the patient received oral amiodarone. Pulmonary toxicity is a well-recognized complication of long-term amiodarone use (see *package insert for oral amiodarone*).

5.6 Loss of Vision

Cases of optic neuropathy and optic neuritis, usually resulting in visual impairment, have been reported in patients treated with oral amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. Perform an ophthalmic examination if symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision. Re-evaluate the necessity of amiodarone therapy if optic neuropathy or neuritis is suspected. Perform regular ophthalmic examination, including fundoscopy and slit-lamp examination, during administration of NEXTERONE.

5.7 Long-Term Use

There has been limited experience in patients receiving intravenous amiodarone for longer than 3 weeks. See *package insert for oral amiodarone*.

5.8 Thyroid Abnormalities

Amiodarone inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and may cause increased T4 levels, decreased T3 levels, and increased levels of inactive reverse T3 (rT3) in clinically euthyroid patients. Amiodarone is also a potential source of large amounts of inorganic iodine and can cause either hypothyroidism or hyperthyroidism. Evaluate thyroid function prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid function tests may persist for several weeks or even months following NEXTERONE withdrawal.

There have been postmarketing reports of thyroid nodules/thyroid cancer in patients treated with amiodarone. In some instances hyperthyroidism was also present [see *Adverse Reactions (6.2) in full prescribing information*].

Hyperthyroidism and Thyrotoxicosis

Hyperthyroidism occurs in about 2% of patients receiving amiodarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of thyrotoxicosis and arrhythmia breakthrough or aggravation, all of which may result in death. There have been reports of death associated with amiodarone-induced thyrotoxicosis. Consider the possibility of hyperthyroidism if any new signs of arrhythmia appear.

Identify hyperthyroidism by relevant clinical signs and symptoms, subnormal serum levels of thyroid stimulating hormone (TSH), abnormally elevated serum free T4, and elevated or normal serum T3. Since arrhythmia breakthroughs may accompany amiodarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of amiodarone. Amiodarone hyperthyroidism may be followed by a transient period of hypothyroidism.

The institution of antithyroid drugs, β -adrenergic blockers or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism.

When aggressive treatment of amiodarone-induced thyrotoxicosis has failed or amiodarone cannot be discontinued because it is the only drug effective against the resistant arrhythmia, surgical management may be an option. Experience with thyroidectomy as a treatment for amiodarone-induced thyrotoxicosis is limited, and this form of therapy could induce thyroid storm. Therefore, surgical and anesthetic management require careful planning.

Neonatal Hypo- or Hyperthyroidism

Amiodarone can cause fetal harm when administered to a pregnant woman. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with oral administration. Inform the patient of the potential hazard to the fetus if NEXTERONE is administered during pregnancy or if the patient becomes pregnant while taking NEXTERONE.

Hypothyroidism

Hypothyroidism has been reported in 2% to 4% of patients in most series, but in 8% to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Manage hypothyroidism by reducing the NEXTERONE dose and considering the need for thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue oral amiodarone in some patients.

5.9 Surgery

Perform close perioperative monitoring in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction defects of halogenated inhalational anesthetics.

5.10 Corneal Refractive Laser Surgery

Advise patients that most manufacturers of corneal refractive laser surgery devices contraindicate corneal refractive laser surgery in patients taking amiodarone.

5.11 Electrolyte Disturbances

Correct hypokalemia or hypomagnesemia whenever possible before initiating treatment with NEXTERONE, as these disorders can exaggerate the degree of QTc prolongation and increase the potential for TdP. Give special attention to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received intravenous amiodarone for at least one week, 5% received it for at least 2 weeks, 2% received it for at least 3 weeks, and 1% received it for more than 3 weeks, without an increased incidence of severe adverse reactions. The mean duration of therapy in these studies was 5.6 days; median exposure was 3.7 days.

The most important adverse reactions were hypotension, asystole/cardiac arrest/pulseless electrical activity (PEA), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. Overall, treatment was discontinued for about 9% of the patients because of adverse reactions. The most common adverse reactions leading to discontinuation of intravenous amiodarone therapy were hypotension (1.6%), asystole/cardiac arrest/PEA (1.2%), VT (1.1%), and cardiogenic shock (1%).

Table 4 lists the most common (incidence $\geq 2\%$) adverse reactions during intravenous amiodarone therapy considered at least possibly drug-related. These data were collected in clinical trials involving 1836 patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse reactions appeared to be dose-related.

Table 4: ADVERSE REACTIONS IN PATIENTS RECEIVING INTRAVENOUS AMIODARONE IN CONTROLLED AND OPEN-LABEL STUDIES ($\geq 2\%$ INCIDENCE)

Study Event	Controlled Studies (n=814)	Open-Label Studies (n=1022)	Total (n=1836)
Body as a whole			
Fever	24 (2.9%)	13 (1.2%)	37 (2.0%)
Cardiovascular System			
Bradycardia	49 (6.0%)	41 (4.0%)	90 (4.9%)
Congestive heart failure	18 (2.2%)	21 (2.0%)	39 (2.1%)
Heart arrest	29 (3.5%)	26 (2.5%)	55 (2.9%)
Hypotension	165 (20.2%)	123 (12.0%)	288 (15.6%)
Ventricular tachycardia	15 (1.8%)	30 (2.9%)	45 (2.4%)
Digestive System			
Liver function tests normal	35 (4.2%)	29 (2.8%)	64 (3.4%)
Nausea	29 (3.5%)	43 (4.2%)	72 (3.9%)

Other adverse reactions reported in less than 2% of patients receiving intravenous amiodarone in controlled and uncontrolled studies included the following: abnormal kidney function, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, prolonged QT interval, respiratory disorder, shock, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of amiodarone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: anaphylactic/anaphylactoid reaction (including shock), fever

Cardiovascular: hypotension (sometimes fatal), sinus arrest

Dermatologic: toxic epidermal necrolysis (sometimes fatal), exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, skin cancer, pruritus, angioedema

Endocrine: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hematologic: pancytopenia, neutropenia, hemolytic anemia, aplastic anemia, thrombocytopenia, agranulocytosis, granuloma

Hepatic: hepatitis, cholestatic hepatitis, cirrhosis

Injection Site Reactions: pain, erythema, edema, pigment changes, venous thrombosis, phlebitis, thrombophlebitis, cellulitis, necrosis, and skin sloughing

Musculoskeletal: myopathy, muscle weakness, rhabdomyolysis

Nervous System: hallucination, confusional state, disorientation, and delirium, pseudotumor cerebri

Pancreatic: pancreatitis

Renal: renal impairment, renal insufficiency, acute renal failure

Respiratory: bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest and ARDS), bronchiolitis obliterans organizing pneumonia (possibly fatal), dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates and/or mass, pleuritis

Thyroid: thyroid nodules/thyroid cancer

Vascular: vasculitis

7 DRUG INTERACTIONS

Since amiodarone is a substrate for CYP3A and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone.

Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates for p-glycoprotein.

HMG-CoA reductase inhibitors that are CYP3A4 substrates in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis.

Limit the dose of simvastatin in patients on amiodarone to 20 mg daily. Limit the daily dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required.

Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D

Reproductive and teratology studies performed in rabbits and rats at doses of up to 100 mg/kg per day (about 1.4 times the maximum recommended human dose on a body surface area basis) revealed no evidence of embryotoxicity at 5 mg/kg and no teratogenicity was observed at any dosage in rabbits. Maternal toxicity and embryotoxicity were observed in rats in the 100 mg/kg group.

Use NEXTERONE during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

8.2 Labor and Delivery

It is not known whether the use of amiodarone during labor or delivery has any immediate or delayed adverse effects.

8.3 Nursing Mothers

Amiodarone and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug.

8.4 Pediatric Use

The safety and effectiveness of amiodarone in pediatric patients have not been established; therefore, the use of amiodarone in pediatric patients is not recommended.

8.5 Geriatric Use

Clinical studies of amiodarone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Carefully consider dose selection in an elderly patient.

10 OVERDOSAGE

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of intravenous amiodarone include hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity. Treat hypotension and cardiogenic shock by slowing the infusion rate or with standard therapy: vasopressor drugs, positive inotropic agents, and volume expansion. Bradycardia and AV block may require temporary pacing. Monitor hepatic enzyme concentrations closely. Amiodarone is not dialyzable.

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Around 2:00 a.m., the patient was found in respiratory arrest. Resuscitation efforts were unsuccessful.

Since PCA initiation, nurses monitored the patient every 30 minutes for the first hour, every hour for the next 3 hours, and then every 2 hours. However, monitoring was less frequent than required by hospital policy and was less often than typically recommended for patients receiving PCA.¹ In addition, the assessment of pain was infrequent, and the assessment of respiratory status did not include the depth, pattern, effort of respirations, and breath sounds. Pulse oximetry was not used to measure oxygen saturation, although policy required its use and the oximetry equipment was available in the patient's room.

Further, a standard sedation assessment scale was not utilized. Progressive signs of impending respiratory arrest were not recognized, particularly those related to the patient's level of sedation. After the first hour of PCA use, the patient was assessed as "awake and alert" with a pain assessment score of 4 (scale, 1-10). As the evening went on, the patient became "sleepy and drowsy but easily aroused," although no pain assessment was documented. By midnight, 4 hours after starting the PCA, the patient was "sleeping and snoring loudly," and no attempts were made to arouse the patient to assess his level of sedation and pain. Two hours later, the patient was described as "sleeping and snoring loudly, but arousable" with no further details. Shortly thereafter, the patient was found in respiratory arrest.

One factor that probably contributed to the patient's respiratory arrest is the delayed transfer of morphine across the blood-brain barrier.^{2,3} The repeated administration of relatively high doses of morphine at short intervals and the delayed transfer of the drug to the brain made it possible for the fatal event to occur almost 2 hours after the bulk of self-administered doses were taken. A patient with severe pain may tolerate larger doses of morphine, because the pain helps counteract the respiratory-depressant effects of opioids.^{2,4,5} However, once the pain subsides, previously adequate breathing can quickly become inadequate with the onset of sedation or sleep.^{4,5}

Given the widespread use of PCA, most hospitals likely have a PCA story to tell.¹ Fortunately, not all of these stories have resulted in death. However, studies have documented the association of PCA with harmful and fatal errors,^{2,6} and analyses of voluntary reports of events have shown a 4-fold higher risk of harm with PCA errors than with other reported medication errors.¹ In most cases, characteristics that place patients at higher risk for opioid-induced respiratory depression have not been considered, and patient monitoring has been inadequate.^{7,8}

ISMP has written about PCA errors numerous times^{9,10} and has described many of the causative factors, including prescribing errors, failure to determine the patient's opioid tolerance and identify risk factors associated with respiratory depression, lack of information to patients and families about PCA, and inadequate monitoring. Whereas many things went wrong in the event described previously, the remainder of this article will focus on appropriate monitoring of patients receiving PCA – a critical, lifesaving activity that can provide an early warning of impending complications, thus preventing patient harm even in the presence of an error. Along with a basic physical assessment and collection of vital signs, the following parameters are important when monitoring patients who are receiving PCA.

Pain Assessment

The patient's level of pain must be continually assessed during use of PCA to evaluate the treatment's effectiveness. Use of a standard pain scale and/or tool (eg, Wong-Baker Faces Scale) is highly recommended for accuracy and ease of eliciting a patient's description of discomfort.¹ The goal of PCA is pain relief, but pain relief can also signal the loss of a compensatory mechanism that combats the respiratory-depressant effects of opioids. Thus, monitoring should be stepped up and PCA doses may need to be reduced if pain relief is accompanied by oversedation.

Sedation Assessment

Sedation is an extremely useful assessment parameter for observing the clinical effects of opioids. In fact, sedation is the most important predictor of respiratory depression in patients receiving IV opioids – a fact that only 22% of physicians, pharmacists, and nurses knew when taking a recent opioid knowledge assessment.⁵ Sedation generally precedes significant respiratory depression. Pain can counteract opioid-induced respiratory depression, and sleep can intensify the depressant effects. In addition, as carbon dioxide levels increase with respiratory depression, patients experience a reduced level of consciousness that is additive to the opioid sedative effects.¹ Thus, for patients receiving PCA, *early* recognition of excessive sedation and intervention is essential.

A standard sedation scale should be used when patients receiving PCA are assessed. The San Diego Patient Safety Council, which created a useful set of PCA guidelines for opioid-naïve patients,¹ prefers the Richmond Agitation Sedation Scale (RASS)¹¹; it is simple to use, and it combines sedation and agitation into one scale. However, some hospitals use the Passero, Ramsey, or Glasgow Coma scales.

To assess sedation, health professionals must evaluate how much stimulation is necessary to evoke the desired response from the patient; thus, the patient must be observed. If the patient is awake, the practitioner should ask the patient a question and evaluate his or her response to determine whether the patient is alert and oriented. If the patient is not alert (eyes closed), the patient's response to verbal stimuli should be assessed first. For example, the RASS¹¹ recommends stating the patient's name and asking the patient to open his or her eyes and look at the speaker. The degree of movement and length of eye contact is evaluated to assess the sedation level. If the patient does not respond to verbal requests, physical stimulation is used, such as lightly shaking the patient's shoulder to evaluate the response. Practitioners should have clear guidance regarding which levels of the sedation scale would indicate the need to increase the frequency of monitoring, to adjust PCA doses, to stop the PCA, to call the prescriber, to provide airway support and/or oxygen, and/or to administer naloxone.

Respiratory Assessment

Respiratory assessments should include the evaluation of the rate and quality of respirations. A respiratory rate of 10 breaths per minute or less

should signal possible discontinuation of PCA.¹ The depth of respirations (ie, normal, shallow, deep), pattern of respirations (ie, regular, irregular), quality of respiratory effort (ie, effortless, comfortable, labored), and breath sounds (ie, clear, noisy, snoring, gurgling, stridor) are all important parameters when respiration quality is assessed.

The Anesthesia Patient Safety Foundation (APSF) recommends routine use of technology to continuously monitor ventilation in patients known to be at high risk for respiratory depression (eg, preexisting respiratory impairment, sleep apnea, elderly, or obese); its use should be considered when possible for all patients receiving PCA.⁷ Continuous pulse oximetry should be routine, although practitioners should be aware that oximetry readings may remain near normal for minutes after a patient stops breathing.⁸ Thus, the APSF suggests using capnography (even if intermittent) to detect unrecognized hypoventilation and carbon dioxide retention.⁷ APSF also recommends limiting the use of supplemental oxygen for patients receiving PCA, especially if pulse oximetry is the only technology used to detect hypoventilation. For patients receiving supplemental oxygen, there is no evidence that monitoring of oxygen saturation provides an additional measure of safety.¹²

Table 1. Guidelines for patient-controlled analgesia (PCA) monitoring

Assessment of opioid tolerance	Vital signs	Pain	Sedation	Respiratory		
				Rate	Quality	SPO ₂ and/or ETCO ₂
Baseline assessment before PCA	X	X	X	X	X	X
PCA initiation or change in drug/syringe	X	X	X	X	X	X
Q 15 min x 1 hour						
Q 1 hour x 4 hours						
Then Q 2 hours						
PCA dose change or bolus	X	X	X	X	X	X
Q 1 hour x 4 hours						
Then Q 2 hours						
Adverse event or patient deterioration (eg, adverse change in sedation score)	X	X	X	X	X	X
Q 15 min x 1 hour						
Q 1 hour x 4 hours						
Then Q 2 hours						
Hand-offs/Shift change	X	X	X	X	X	X

Note: ETCO₂ = capnography; SPO₂ = saturation of peripheral oxygen.
Source: Adapted from San Diego Patient Safety Council.¹

Frequency of Assessments

To be effective, patient monitoring must be conducted at the proper intervals. Guidelines for assessing the adequacy of monitoring frequencies have been developed by the San Diego Patient Safety Council (see **Table 1**).¹ Hospitals may want to monitor patients more frequently at night, as opioid-induced respiratory depression is more common between midnight and 6:00 a.m.⁴ The purpose and frequency of monitoring should be explained to patients and their families so they understand the need to be awakened and monitored frequently.

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NAME CONFUSION WITH NEW CANCER DRUGS

Unless you are a full-time cancer specialist, it is difficult to keep up with all the new oncology drugs entering the market. Many of them have similar names that are difficult to distinguish. As one of our oncology colleagues noted recently, health care practitioners who use anti-infective drugs are familiar with their names and generally find drug name similarity useful for ensuring they are dealing with the correct antibiotic class. In comparison, the nomenclature of new oncology drugs is somewhat confusing, even to oncology specialists who exclusively use these drugs to treat cancer.

The cancer drug nomenclature situation is challenging for practitioners when oncology is a small part of their practice. It can be overwhelming to keep track of the names of compounds and the families of drugs, such as tyrosine kinase inhibitors, of which there are hundreds of potential targets. A recent concern involves 2 new oral therapies in the tyrosine kinase inhibitor family. A reporter noted the ease of confusion between pazopanib (*Votrient*) that is used to treat renal cell cancer, thyroid cancer, and soft-tissue sarcoma and ponatinib (*Iclusig*) that is used to treat chronic myelogenous leukemia and Philadelphia chromosome-positive [Ph+] acute lymphoblastic leukemia. Fortunately, tablet strengths and dosages of these drugs are quite different, which will help prevent and detect errors when the drugs are prescribed and dispensed.

Computer systems that list oral chemotherapy linked to available dosage strengths will help to minimize the potential for error, as will a list of appropriate dosing information for labeled indications. We also believe that tall-man lettering with the unique letter characters differentiated (PONATinib and PAZOPanib) can be helpful. Naming authorities will have to deal with hundreds of new compounds, gene therapies, and biosimilars. The challenge is to retain enough name similarity to represent a particular class of drugs while preventing drug name confusion.

MEDICATION SAFETY OFFICER GROUP TO BECOME A PART OF ISMP

ISMP recently announced that the American Society of Medication Safety Officers (ASMSO) is being incorporated within ISMP. Medication safety officers (MSOs), including pharmacists, nurses, and physicians,

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will now have a direct link to information on improving medication use and will play a greater role in identifying emerging safety issues. ASMSO will be renamed the Medication Safety Officer Society (MSOS) to provide a framework for meeting the needs of the MSO community on an international scale. Official changes will take place later this year.

ASMSO is a multidisciplinary organization founded in 2005 for medication safety officers and medication management leaders. Its goal is to provide an open forum for information sharing and collaboration that encourages excellence in safe medication use. Christian Hartman,

PharmD, MBA, FSMSO, is founder and director-at-large of ASMSO.

ISMP will continue to operate MSOS's listserv and Web site, and members will have increased opportunities to contribute to ISMP's medication safety advocacy efforts and the development of best practices, educational programs, and other guidance for error prevention. The merger provides members with the opportunity to have an even greater impact on safety through the collaborative efforts of a larger group dedicated to medication safety. For more information on ASMSO, please visit www.asmsso.org/. ■