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ISMP Medication Error Report Analysis

Nalbuphine-Naloxone Mix-ups

Compounding Pharmacy Registration with the FDA

FDA Draft Guidance

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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.

NALBUPHINE-NALOXONE MIX-UPS

A patient safety officer reported that her hospital had 2 incidents in which patients received nalbuphine instead of naloxone. The hospital uses a barcoding system for drug administration; in both instances, the nurses involved felt that the patients' conditions warranted bypassing this technology.

In the first instance, a patient receiving an epidural infusion had PRN orders for both naloxone and nalbuphine injections. The patient developed increased somnolence while receiving the epidural infusion. A nurse called the rapid response team and naloxone was ordered. Nalbuphine and naloxone appeared one after the other on the automated dispensing cabinet (ADC) screen. The nurse inadvertently selected nalbuphine on the patient's profile instead of naloxone.

The second event at this hospital involved a pharmacy technician who accidentally stocked an ADC with nalbuphine instead of naloxone.

We are aware of similar events in the ISMP National Medication Errors Reporting Program database. To cite one example, intravenous (IV) nalbuphine instead of naloxone was administered to a patient during the reversal phase of anesthesia. The patient also received IV diphenhydramine. She was extubated and sent to a postanesthesia care unit, where she quickly experienced increased respiratory effort and was re-intubated and transferred to the intensive care unit. Prior to transferring the patient, the anesthesiologist discovered the medication error when he reviewed the ampules used during the case. The patient was extubated later that day and experienced no further respiratory distress.

It is not unusual for patients to have both nalbuphine and naloxone prescribed during a hospitalization. Thus, a patient-specific medication drawer may contain both of these drugs. Although barcode scanning in the pharmacy and during ADC replacement will help avoid errors, nursing staff may bypass scanning if the patient's condition warrants such action. To prevent

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Nexterone
(amiodarone HCl) Premixed Injection

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.

Baxter Healthcare Corporation
Deerfield, IL 60015

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 periarteritis (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, centrolobular 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 ≥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 (≥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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this occurrence in the operating room (OR), the hospital involved in this report removed nalbuphine from stock after determining there was no need for it in the OR. Tall-man lettering on ADC screens and pharmacy shelf labels may help avoid mix-ups. If space permits, the words "rescue agent" could be added next to naloxone entries. Locked lidded drawers for nalbuphine could also prevent inadvertent selection of the wrong drug.

COMPOUNDING PHARMACY REGISTRATION WITH THE FDA

There is no requirement for compounding pharmacies to register with the US Food and Drug Administration (FDA), and there are no FDA-specified procedures that must be followed by compounding pharmacies to ensure safety. Some compounding pharmacies do register with FDA; but just because the pharmacy is "FDA-registered," it does not mean that it is routinely inspected by FDA. Nor does "FDA-registered" mean that the FDA has reviewed or approved any compounded preparations produced by the pharmacy.

Registering with the FDA is a simple, electronic process. It puts the compounding pharmacy on the FDA's radar screen. If the FDA chooses to inspect the pharmacy, identified problems will be addressed. Some pharmacies report multiple FDA inspections. If a compounding pharmacy claims to be "FDA approved," this is misleading and inaccurate. FDA approves drugs and biologics and inspects facilities that manufacture approved drugs according to 21 CFR 210-211 (Human Drug c-GMPs [current good manufacturing practices]).

Another misconception is that FDA registration and assignment of a National Drug Code (NDC) mean that the pharmaceutical preparation is FDA approved. The NDC is a numerical identifier, not an assignment of FDA approval. Upon registering with the FDA, a compounding pharmacy is provided with a labeler code, which includes 4 or 5 digits of the first NDC segment. The remaining digits are determined by the company to identify its product (strength, dosage form, formulation, form, packaging). In some ways, this is similar to what has happened with "grandfathered" (pre-1938) drugs, which also are not regulated by FDA; companies can market them and assign them an NDC number. So, "registered with FDA" just means that the company, whether a manufacturer, compounding pharmacy, or re-packager/distributor, has done this. The FDA will have the company's name and know of its existence.

The FDA has rigorous, research-oriented, and quality manufacturing requirements for approval of products manufactured or mass produced by pharmaceutical companies. The drug application is based on a significant amount of work over several years. A New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) for generics must be submitted and approved by the FDA. Prior to submitting an NDA or ANDA, the company must have carried out the necessary research, and its manufacturing plants must have been inspected and approved by FDA. There are requirements for product source; assays for content of the formulation; stability; sterility; care of equipment and facilities; personnel; packaging, labeling, and nomenclature; postmarket surveillance; and so on. The entire process is outlined and submitted along with the NDA or ANDA in order to get marketing approval.

These processes are incorporated into c-GMPs, which, for sterile products, go beyond the requirements contained in USP <797>. The FDA requires that the drug be made in compliance with c-GMPs with strict adherence to everything approved. No changes can be made without FDA consent, other than minor ones such as rearranging text on a container label. Obtaining approval of products requires more than asking for a labeler code.

Contrast these rigorous requirements imposed on commercial manufacturers with those applied to compounding pharmacies. As a general requirement, compounded products must be dispensed pursuant to an individual patient prescription. Yet, some compounding pharmacies have not required prescriptions or have attempted to obtain them retroactively to meet state and federal regulations. Another issue is that some compounding pharmacies have been acting more as commercial manufacturers. The number of prescriptions that can be sent across state lines may be limited or prohibited depending on the state and out-of-state pharmacy laws and regulations. Even pharmacies that compound sterile preparations (CSPs) from nonsterile active pharmaceutical ingredients and/or ship unlimited quantities of a CSP across state lines are exempt from full c-GMPs and stability standards as required of commercial manufacturers of FDA-approved drugs. These products have not been subject to the same FDA oversight and testing as FDA-approved products from commercial manufacturers.

A compounding pharmacy's work has been considered the "professional practice of pharmacy." States license pharmacies and oversee day-to-day operations. The pharmacies are not required to register products with the FDA, the FDA does not have a comprehensive listing of compounding pharmacies in the United States (they have a compounding pharmacy's name only if it registered with the FDA), and the FDA does not

routinely inspect all compounding pharmacies, registered or not (www.ismp.org/sc?id=179). FDA generally will conduct a "for-cause" inspection of a pharmacy after receiving an adverse event report or complaint about the pharmacy or a compounded product. FDA may also conduct follow-up inspections to determine if problems have been corrected. But compounded drugs are not FDA approved, do not undergo premarketing review, and do not have an FDA sanction of safety and efficacy.

FDA would like to step-up its enforcement activities with compounders that act as manufacturers (www.ismp.org/sc?id=180), so it can prevent occurrences such as the recent meningitis outbreak. This will likely require legislation. Whether this desire on FDA's part will result in new legislation is still in question, but it is something that ISMP and some sterile compounding operations support, while preserving the role of professional pharmacy drug compounding services in creating medications in ready-to-use delivery form for individualized patients.

FDA DRAFT GUIDANCE

The FDA has published a draft guidance, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" (www.ismp.org/sc?id=185). As explained in the document, its purpose is to help prescription drug and biologic product manufacturers minimize medication errors associated with their products. This guidance focuses on safety aspects and provides a set of principles and recommendations for ensuring that critical elements of a product's container label and carton labeling are designed to promote safe dispensing, administration, and use of the product.

We believe the FDA and its Division of Medication Error Prevention and Analysis (DMEPA) have done an excellent job in addressing the majority of labeling issues that have led to confusion and medication errors through the years. The guidance represents the FDA's most current recommendations. Although it does not bind the FDA or manufacturers to use the approaches suggested, in most cases, these approaches will be followed. This work would not be possible without the active participation of health care practitioners in reporting product-related concerns to the ISMP National Medication Errors Reporting Program (ISMP MERP) and the FDA MedWatch Program. ■