

**CASE 1**

This presumed ulceration was actually the site of a former open comedo. The patient had a workup, including a rapid plasma reagin test (because the lesion resembled a syphilitic gumma) and culture. These were negative. Biopsy revealed granulation tissue without evidence of inflammation, dysplasia, or metaplasia. The patient's poor hygiene, combined with years of neglect, apparently had led to extension of the comedo. The keratin plug eventually sloughed or was expressed at some point, leaving the surrounding tissue distorted and cavernous in appearance. The reason for the patient's weight loss was never discovered.

**CASE 2**

The patient has an infected sebaceous cyst of the preauricular area. Containing sebum, a cheese-like material, these cysts are found most often around the ear. They are usually soft and mobile, and are asymptomatic unless they become infected or enlarge rapidly. Acute infection is treated with antibiotics, application of hot compresses, incision, and drainage if indicated. Spontaneous resolution can occur, but the treatment of choice is complete removal of the cyst by meticulous dissection of the entire capsule to preclude recurrence. Lesions like this patient's should be differentiated from the infected preauricular cyst and fistula that occur as a result of disunion of the hillocks of the first and second branchial arches, which usually present as a small opening in the preauricular skin. The clinician should also keep in mind that sebaceous adenoma, sebaceous lymphadenoma, or sebaceous carcinoma can arise from the sebaceous gland that rests within the parotid glands.

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## CURRENT TRENDS IN THE MANAGEMENT OF INSOMNIA

The authors focus on finding the underlying cause of chronic insomnia, which can range from medical disorders to psychiatric conditions to, most commonly, psychophysiologic causes. Establishing the cause is the key to developing an effective treatment plan.

**By Andrew L. Chesson, Jr., MD, and Shawn A. Milligan, MD**

Insomnia is best considered a symptom or complaint rather than a disease, requiring a diligent search for the underlying cause. Aspects of insomnia reported by patients may include difficulty in falling asleep, repeated or lengthy awakenings, waking up early, inadequate total sleep time, or poor quality of sleep. Individual differences in sleep requirements and in the consequences of not sleeping well (such as tiredness, lack of energy, difficulty concentrating, irritability, or daytime sleepiness), as well as conflicts between subjective and objective measures of nighttime sleep, all contribute to the challenge of assessing insomnia.

The prevalence of insomnia can be readily appreciated. Approximately one-third of adult Americans have reported being affected by insomnia during the course of a year. About 9% to 15% of patients with insomnia regard the problem as severe. Insomnia is more common in females (1.3 times more frequent than in males) and older patients (frequency at age 65 and older is 1.5 times the frequency before age 65). However, studies indicate significant problems with insomnia in 12% of adolescents. Insomnia is also more common in people of rela-

tively low socioeconomic status and education levels.

In primary care practice, the prevalence of insomnia ranges from 10% to 69% in various studies. Gallup polls have revealed that 9% to 12% of respondents had "regular" or "frequent" difficulty sleeping. About 31% of patients report discussing the problem of insomnia with their physicians. In one study of hospitalized patients, there was no mention of insomnia in the patients' charts despite the fact that nearly half of them had complained of the problem when they were interviewed.

The direct cost of insomnia was estimated at \$10.9 billion in 1990, \$15.4 billion in 1994, and \$11.8 billion in 1995. The cost of substances used for insomnia in 1995 was \$1.6 billion.

In 1994, an estimated 7.11 million office visits to physicians for insomnia occurred; in 2.17 million of these visits, no insomnia complaints were recorded in charting but a hypnotic medication was prescribed.

### ACUTE INSOMNIA: EXTREMELY COMMON

One classification system for insomnia is based on how long the patient has had a problem sleeping. These categories include transient (lasting one to three nights), acute (lasting from three nights to three weeks), and chronic (lasting more than three weeks, even months or years). The duration of the insomnia will often influence the treatment plan, which is why the question "When

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**CORDARONE I.V.**—Brief summary of prescribing information  
**SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**CONTRAINDICATIONS:** In patients with: 1) known hypersensitivity to any of its components; 2) cardiogenic shock; 3) marked sinus bradycardia; 4) 2nd- or 3rd-degree AV block unless a functioning pacemaker is available.

**WARNINGS:** Hypotension was the most common adverse effect seen with Cordarone I.V. in clinical trials (288 of 1836 patients; 16%). Clinically significant hypotension was most often seen in the first several hours of treatment and was not dose related, but appeared to be related to rate of infusion. Hypotension necessitating alterations in therapy was reported in 3% of patients, with permanent discontinuation required in <2%. Treat hypotension initially by slowing the infusion; additional standard therapy may be needed including vasopressor drugs, positive inotropic agents, and volume expansion. **The initial rate of infusion should be monitored closely and should not exceed that prescribed in DOSAGE AND ADMINISTRATION** (see full prescribing information).

**Bradycardia and AV Block:** Drug-related bradycardia occurred in 90 (4.9%) of 1836 patients receiving Cordarone I.V. in clinical trials; it was not dose related. Treat bradycardia by slowing the infusion rate or discontinuing Cordarone I.V. In some patients, a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during controlled trials. Treat patients with a known predisposition to bradycardia or AV block with Cordarone I.V. in a setting where a temporary pacemaker is available.

**Long-term Use:** See labeling for oral Cordarone. Experience is limited in patients receiving Cordarone I.V. for >3 weeks.

**Neonatal Hypo- or Hyperthyroidism:** Although oral Cordarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If Cordarone I.V. is given during pregnancy, apprise the patient of the potential hazard to the fetus (see full prescribing information).

**PRECAUTIONS:** Cordarone I.V. should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, are thoroughly familiar with the risks and benefits of Cordarone, and have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

**Liver Enzyme Elevations:** Elevations of blood hepatic enzyme values—ALT, AST, and GGT—are seen commonly in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because values may be elevated in patients who have had recent myocardial infarction, CHF, or multiple electrical defibrillations. In clinical studies, approximately 54% of patients had baseline liver enzyme elevations; 13% had clinically significant elevations. Liver enzyme elevations may improve during therapy or remain at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

Rare cases of fatal hepatocellular necrosis have been reported after Cordarone I.V. Two patients were treated for atrial arrhythmias with an initial infusion rate of 1500 mg over 5 hours, a rate much higher than recommended. Both patients developed hepatic and renal failure within 24 hours after the start of Cordarone I.V. and died on day 14 and 4. Because these episodes of hepatic necrosis may have been due to rapid infusion rate with possible rate-related hypotension, **the initial rate of infusion should be monitored closely and should not exceed that prescribed in DOSAGE AND ADMINISTRATION** (see full prescribing information).

In patients with life-threatening arrhythmias, weigh the potential risk of hepatic injury against the potential benefit of Cordarone I.V., but carefully monitor patients for evidence of progressive hepatic injury. Give consideration to reducing administration rate or withdrawing Cordarone I.V. in such cases.

**Proarrhythmia:** Like all antiarrhythmics, Cordarone I.V. may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsades de pointes, has been associated with prolongation by Cordarone I.V. of the QTc interval to  $\geq 500$  ms. Although QTc prolongation occurred frequently in Cordarone I.V. patients, torsades de pointes or new-onset VF occurred infrequently (<2%). Monitor patients for QTc prolongation during Cordarone I.V. infusion. Combination of amiodarone with other antiarrhythmic therapy that prolongs QTc should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.

The need to coadminister amiodarone with any other drug known to prolong the QTc interval must be based on a careful assessment of the potential risks and benefits.

A careful assessment of the potential risks and benefits of administering Cordarone I.V. must be made in patients with thyroid dysfunction due to the possible arrhythmia breakthrough or exacerbation of arrhythmia, which may result in death, in these patients.

**Pulmonary Disorders: ARDS:** Two percent of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies. ARDS can arise after a variety of lung injuries, such as those resulting from trauma, shock, prolonged cardiopulmonary resuscitation, and aspiration pneumonia, conditions present in many of the patients enrolled in the clinical studies. It is not possible to determine what role, if any, Cordarone I.V. played in causing or exacerbating the pulmonary disorder in those patients. Postoperatively, ARDS has been reported in patients receiving oral Cordarone who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies are performed,  $\text{FIO}_2$  and the determinants of oxygen delivery to the tissues (e.g.,  $\text{SaO}_2$ ,  $\text{PaO}_2$ ) should be closely monitored in Cordarone patients.

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

**Surgery:** Close perioperative monitoring is recommended in amiodarone-treated patients undergoing general anesthesia as they may be more sensitive to the myocardial depressant and conduction effects of halogenated inhalational anesthetics.

**Drug Interactions:** Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4). This isoenzyme is present in the liver and intestines. Amiodarone is also known to be an inhibitor of CYP3A4. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4. While only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, chiefly with the oral formulation, the potential for other interactions should be anticipated. This is especially important for drugs associated with serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation.

Since amiodarone is a substrate for CYP3A4, drugs/substances that inhibit CYP3A4 may decrease the metabolism and increase serum concentrations of amiodarone, with the potential for toxic effects. Examples of this include the following:

**Protease inhibitors** inhibit CYP3A4 to varying degrees. Inhibition of CYP3A4 by indinavir has been reported to result in increased serum concentrations of amiodarone. Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during therapy should be considered.

**Histamine H2 antagonists:** Cimetidine inhibits CYP3A4 and can increase serum amiodarone levels.

**Other substances:** Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone.

**Amiodarone may suppress certain CYP450 enzymes (enzyme inhibition). This can result in unexpectedly high plasma levels of other drugs, which are metabolized by those CYP450 enzymes and may lead to toxic effects. Examples include the following:**

**Immunosuppressives:** Cyclosporine (CYP3A4 substrate) administered with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

**Cardiovasculars: Cardiac Glycosides** - In patients receiving digoxin therapy, administration of oral amiodarone regularly results in an increase in serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken with digoxin increases the serum concentration by 70% after one day. **On administration of oral amiodarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If treatment is continued, serum levels should be closely monitored and patients observed for evidence of toxicity.

**Antiarrhythmics** - Other antiarrhythmic drugs, such as quinidine, procainamide, disopyramide, and phenytoin, have been used with amiodarone. There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. Phenytoin decreases serum amiodarone levels. Amiodarone taken with quinidine increases quinidine serum concentration by 33% after 2 days. Amiodarone taken with procainamide for less than 7 days increases plasma concentrations of procainamide and *n*-acetyl procainamide by 55% and 33%, respectively. Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone. Plasma levels of flecainide have been reported to increase with oral amiodarone; because of this, the dosage of flecainide should be adjusted when these drugs are administered concomitantly. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring. Combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to oral amiodarone, the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of oral amiodarone. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

**Antihypertensives:** Amiodarone should be used with caution in patients receiving **B-receptor blocking agents** (e.g., propranolol, a CYP3A4 inhibitor) or **calcium channel antagonists** (e.g., verapamil, a CYP3A4 substrate, and diltiazem, a CYP3A4 inhibitor) because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, amiodarone can continue to be used after insertion of a pacemaker.

**Anticoagulants:** Potentiation of warfarin-type (CYP2C9 and CYP3A4 substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the administration of warfarin with amiodarone increases the prothrombin time by 100% after 3 to 4 days, **the dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

**Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A4 (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this include the following:**

**Antibiotics: Rifampin** is a potent inducer of CYP3A4. Administration of rifampin with oral amiodarone has been shown to result in decreases in serum concentration of amiodarone and desethylamiodarone.

**Other substances, including herbal preparations: St. John's Wort** (hypericum perforatum) induces CYP3A4. There is the potential that the use of St. John's Wort with amiodarone could result in reduced amiodarone levels.

**Other reported drug interactions with amiodarone:**

**Fentanyl** (CYP3A4 substrate) may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with lidocaine (CYP3A4 substrate) given for local anesthesia. Seizure associated with increased lidocaine concentrations has been reported with administration of intravenous amiodarone.

**Dextromethorphan** is a substrate for both CYP2D6 and CYP3A4. Amiodarone inhibits CYP2D6.

**Cholestyramine** increases elimination of amiodarone and may reduce serum levels and half-life.

**Disopyramide** increases QT prolongation, which could cause arrhythmia.

Hemodynamic and electrophysiologic interactions have been observed after administration with **propranolol, diltiazem, and verapamil.**

**Electrolyte Disturbances:** Correct cases of hypokalemia or hypomagnesemia whenever possible before treating with Cordarone I.V., as these disorders can exaggerate the degree of QTc prolongation and increase the potential for torsades de pointes. Give special attention to electrolyte and acid-base balance in patients with severe or prolonged diarrhea or receiving concomitant diuretics.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenicity studies were conducted with Cordarone I.V. However, oral Cordarone caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors in rats was greater than the incidence in controls even at the lowest dose tested, i.e., 5 mg/kg/day (approx. 0.08 times the maximum recommended human maintenance dose). Mutagenicity studies conducted with amiodarone HCl were negative. No fertility studies were conducted with Cordarone I.V. (see full prescribing information).

**Pregnancy: Category D.** See **WARNINGS, Neonatal Hypo- or Hyperthyroidism.** In addition to infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals (see full prescribing information). Cordarone I.V. should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

**Nursing Mothers:** Amiodarone is excreted in human milk; breast-feeding could expose the nursing infant to a significant dose of drug. Nursing offspring of lactating rats administered amiodarone demonstrated reduced viability and reduced body weight gains. Weigh the risk of exposing the infant to amiodarone against the potential benefit of arrhythmia suppression in the mother. Advise the mother to discontinue nursing.

**Labor and Delivery:** It is not known whether use of Cordarone during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect on duration of gestation or parturition.

**Pediatric Usage:** Safety and efficacy of Cordarone in the pediatric population have not been established; such use is not recommended. Cordarone I.V. contains the preservative benzyl alcohol. There have been reports of fatal "gasping syndrome" in neonates following the administration of intravenous solutions containing benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

**ADVERSE REACTIONS:** In a total of 1836 patients in clinical trials, 14% received Cordarone I.V. for  $\geq 1$  week, 5% received it for  $\geq 2$  weeks, 2% received it for 3 weeks, and 1% received it for >3 weeks, without an increased incidence of severe adverse reactions. The mean duration of therapy was 5.6 days; median exposure was 3.7 days. The most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/EMD, cardiogenic shock, CHF, bradycardia, LFT abnormalities, VT, and AV block. Treatment was discontinued for about 9% of patients because of adverse effects, most commonly hypotension (1.6%), asystole/cardiac arrest/EMD (1.2%), VT (1.1%), and cardiogenic shock (1%).

The following are the most common (incidence  $\geq 2\%$ ) and possibly drug-related adverse events during Cordarone I.V. clinical trials involving 1836 patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse events appeared to be dose-related: Fever, 2.0%; Bradycardia, 4.9%; CHF, 2.1%; Heart arrest, 2.9%; Hypotension, 15.6%; VT, 2.4%; LFTs abnormal, 3.4%; Nausea, 3.9%. Other possibly drug-related adverse events reported in <2% of patients receiving Cordarone I.V. in clinical studies included 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.

In postmarketing surveillance, sinus arrest, pseudotumor cerebri, toxic epidermal necrolysis, exfoliative dermatitis, pancytopenia, neutropenia, erythema multiforme, angioedema, bronchospasm, and anaphylactic shock also have been reported with amiodarone therapy.

This Brief Summary text is based on Direction Circular CI 5032-5, Revised 10/12/01.

**References:** 1. Dorian P. ALIVE. Presented at the American Heart Association Scientific Sessions 2001, Anaheim, Calif. Nov. 11-14, 2001. 2. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med.* 1999; 341:871-878. 3. American Heart Association. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2000;102(suppl):I-86-I-165.

**Cordarone**  
(amiodarone HCl) **I.V.**  
150 mg/3 mL

## DIAGNOSIS AT A GLANCE

By Youn W. Park, MD, J. Chris Cook, DO, and Brian R. Irwin, DO



Case submitted by Dr. Irwin

### CASE 1

A 71-year-old nonverbal man with poor body habitus presents from a nursing home for workup of recent weight loss. During the physical exam, a 2-cm, well-circumscribed ulceration on his back is noted. There is no tenderness, erythema, or edema. No discharge or blood can be expressed. According to nursing home staff, this lesion has not changed since the patient's admission 8 years ago. Medical records make no mention of an ulcer, but there is a reference to a "crusty, black" lesion in exactly the same area 15 years earlier.

### What is your diagnosis?



Case submitted by Drs. Park and Cook

### CASE 2

A 22 year-old woman presents with a painful, tender swelling of the preauricular area following an upper respiratory infection. The soft mass she has had on the area for several weeks was originally asymptomatic. A computed tomography scan characterizes it as a cystic mass superficial to the parotid gland.

### What is your diagnosis?

Turn page for answers