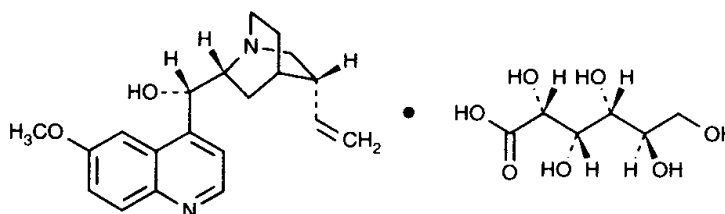


## QUINIDINE GLUCONATE INJECTION, USP

This product is to be used by the physician  
or under his/her direction.

### DESCRIPTION

Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with class 1a activity; it is the d-isomer of quinine and its molecular weight is 324.43. Quinidine gluconate is the gluconate salt of quinidine; its chemical name is cinchonan-9-ol, 6'-methoxy-, (9*S*)-, mono-D-gluconate; its structural formula is



its empirical formula is  $C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$ , and its molecular weight is 520.58, of which 62.3% is quinidine base.

Each vial of Quinidine Gluconate Injection contains 800 mg (1.5 mmol) of quinidine gluconate (500 mg of quinidine) in 10 mL of Sterile Water for Injection, 0.005% of edetate disodium, 0.25% phenol, and (as needed) D-gluconic acid  $\delta$ -lactone to adjust the pH.

### CLINICAL PHARMACOLOGY

*Pharmacokinetics and Metabolism*—After intramuscular injection of quinidine gluconate, peak serum levels of quinidine are achieved in a little less than two hours. This time to peak levels is identical to the time measured when quinidine salts are administered orally.

The volume of distribution of quinidine is typically 2-3 L/kg in healthy young adults, but this may be reduced to as little as 0.5 L/kg in patients with congestive heart failure, or increased to 3-5 L/kg in patients with cirrhosis of the liver. At concentrations of 2-5 mg/L (6.5-16.2  $\mu$ mol/L), the fraction of quinidine bound to plasma proteins (mainly to  $\alpha_1$ -acid glycoprotein and to albumin) is 80-88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50-70%. Because  $\alpha_1$ -acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure, but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.

Quinidine clearance typically proceeds at 3-5 mL/min/kg in adults, but clearance in pediatric patients may be twice or three times as rapid. The elimination half-life is about 6-8 hours in adults and 3-4 hours in pediatric patients. Quinidine clearance is unaffected

by hepatic cirrhosis, so the increased volume of distribution seen in cirrhosis leads to a proportionate increase in the elimination half-life.

Most quinidine is eliminated hepatically via the action of cytochrome P450III<sub>A4</sub>; there are several different hydroxylated metabolites, and some of these have antiarrhythmic activity.

The most important of quinidine's metabolites is 3-hydroxy-quinidine (3HQ), serum levels of which can approach those of quinidine in patients receiving conventional doses of quinidine gluconate. The volume of distribution of 3HQ appears to be larger than that of quinidine, and the elimination half-life of 3HQ is about 12 hours.

As measured by antiarrhythmic effects in animals, by QT<sub>c</sub> prolongation in human volunteers, or by various *in vitro* techniques, 3HQ has at least half the antiarrhythmic activity of the parent compound, so it may be responsible for a substantial fraction of the effect of quinidine gluconate in chronic use.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption. The net renal clearance is about 1 mL/min/kg in healthy adults.

When renal function is taken into account, quinidine clearance is apparently independent of patient age.

Assays of serum quinidine levels are widely available, but the results of modern assays may not be consistent with results cited in the older medical literature. The serum levels of quinidine cited in this package insert are those derived from specific assays, using either benzene extraction or (preferably) reverse-phase high-pressure liquid chromatography. In matched samples, older assays might unpredictably have given results that were as much as two or three times higher. A typical "therapeutic" concentration range is 2-6 mg/L (6.2 - 18.5 μmol/L).

*Mechanisms of Action*—In patients with malaria, quinidine acts primarily as an intraerythrocytic schizonticide, with little effect upon sporozoites or upon pre-erythrocytic parasites. Quinidine is gametocidal to *Plasmodium vivax* and *P. malariae*, but not to *P. falciparum*.

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4 depolarization, shifting the threshold voltage upward toward zero. The result is slowed conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular defibrillation threshold as well. Quinidine's actions fall into class Ia in the Vaughan-Williams classification.

By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia.

In patients with the sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in sinus rate.

Quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes* (see Warnings).

In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an  $\alpha$ -adrenergic antagonist (that is, as a vasodilator).

#### *Clinical Effects*

**Malaria:** Intravenous quinidine has been associated with clearing of parasitemia and high rates of survival in patients with severe *P. falciparum* malaria and hyperparasitemia. Placebo-controlled trials have not been performed, but clearing of these levels of parasitemia is unprecedented in the absence of effective therapy. Use of quinidine in patients infected with chloroquine-sensitive malaria or in chloroquine-resistant non-falciparum malaria has not been reported.

**Maintenance of sinus rhythm after conversion from atrial fibrillation:** In six clinical trials (published between 1970 and 1984) with a total of 808 patients, quinidine (418 patients) was compared to nontreatment (258 patients) or placebo (132 patients) for the maintenance of sinus rhythm after cardioversion from chronic atrial fibrillation. Quinidine was consistently more efficacious in maintaining sinus rhythm, but a meta-analysis found that mortality in the quinidine-exposed patients (2.9%) was significantly greater than mortality in the patients who had not been treated with active drug (0.8%). Suppression of atrial fibrillation with quinidine has theoretical patient benefits (eg, improved exercise tolerance; reduction in hospitalization for cardioversion; lack of arrhythmia-related palpitations, dyspnea, and chest pain; reduced incidence of systemic embolism and/or stroke), but these benefits have never been demonstrated in clinical trials. Some of these benefits (eg, reduction in stroke incidence) may be achievable by other means (anticoagulation).

By slowing the rate of atrial flutter/fibrillation, quinidine can decrease the degree of atrioventricular block and cause an increase, sometimes marked, in the rate at which supraventricular impulses are successfully conducted by the atrioventricular node, with a resultant paradoxical increase in ventricular rate (see Warnings).

**Non-life-threatening ventricular arrhythmias:** In studies of patients with a variety of ventricular arrhythmias (mainly frequent ventricular premature beats and non-sustained ventricular tachycardia), quinidine (total N=502) has been compared to flecainide (N=141), mexiletine (N=246), propafenone (N=53), and tocainide (N=67). In each of these studies, the mortality in the quinidine group was numerically greater than the mortality in the comparator group. When the studies were combined in a meta-analysis, quinidine was associated with a statistically significant threefold relative risk of death.

At therapeutic doses, quinidine's only consistent effect upon the surface electrocardiogram is an increase in the QT interval. This prolongation can be monitored as a guide to safety, and it may provide better guidance than serum drug levels (see Warnings).

## INDICATIONS AND USAGE

*Treatment of malaria*—Quinidine gluconate injection is indicated for the treatment of life-threatening *Plasmodium falciparum* malaria.

*Conversion of atrial fibrillation/flutter*—Quinidine gluconate injection is also indicated (when rapid therapeutic effect is required, or when oral therapy is not feasible) as a means of restoring normal sinus rhythm in patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response. If this use of quinidine gluconate does not restore sinus rhythm within a reasonable time, then its use should be discontinued.

*Treatment of ventricular arrhythmias*—Quinidine gluconate injection is also indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician are life-threatening. Because of the proarrhythmic effects of quinidine, its use with ventricular arrhythmias of lesser severity is generally not recommended, and treatment of patients with asymptomatic ventricular premature contractions should be avoided. Where possible, therapy should be guided by the results of programmed electrical stimulation and/or Holter monitoring with exercise.

Antiarrhythmic drugs (including quinidine) have not been shown to enhance survival in patients with ventricular arrhythmias.

## CONTRAINDICATIONS

Quinidine is contraindicated in patients who are known to be allergic to it, or who have developed thrombocytopenic purpura during prior therapy with quinidine or quinine.

In the absence of a functioning artificial pacemaker, quinidine is also contraindicated in any patient whose cardiac rhythm is dependent upon a junctional or idioventricular pacemaker, including patients in complete atrioventricular block.

Quinidine is also contraindicated in patients who, like those with myasthenia gravis, might be adversely affected by an anticholinergic agent.

## WARNINGS

*Inappropriate infusion rate*—Overly rapid infusion of quinidine (*see* Dosage and Administration) may cause peripheral vascular collapse and severe hypotension.

*Proarrhythmic effects*—Like many other drugs (including all other class 1a antiarrhythmics), quinidine prolongs the QT<sub>c</sub> interval, and this can lead to *torsades de pointes*, a life-threatening ventricular arrhythmia (*see* Overdosage). The risk of *torsades* is increased by any of bradycardia, hypokalemia, hypomagnesemia, and high serum levels of quinidine, but it may appear in the absence of any of these risk factors. The best predictor of this arrhythmia appears to be the length of the QT<sub>c</sub> interval, and quinidine should be used with extreme care in patients who have preexisting long-QT syndromes, who have histories of *torsades de pointes* of any cause, or who have previously responded to quinidine (or other drugs that prolong ventricular repolarization) with marked lengthening of the QT<sub>c</sub> interval. Estimation of the incidence of *torsades* in patients with therapeutic levels of quinidine is not possible from the available data.

Other ventricular arrhythmias that have been reported with quinidine include frequent extrasystoles, ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

*Paradoxical increase in ventricular rate in atrial flutter/fibrillation*—When quinidine is administered to patients with atrial flutter/fibrillation, the desired pharmacologic

reversion to sinus rhythm may (rarely) be preceded by a slowing of the atrial rate with a consequent increase in the rate of beats conducted to the ventricles. The resulting ventricular rate may be very high (greater than 200 beats per minute) and poorly tolerated. This hazard may be decreased if partial atrioventricular block is achieved prior to initiation of quinidine therapy, using conduction-reducing drugs such as **digitalis**, **verapamil**, **diltiazem**, or a  $\beta$ -receptor blocking agent.

*Exacerbated bradycardia in sick sinus syndrome*—In patients with the sick sinus syndrome, quinidine has been associated with marked sinus node depression and bradycardia.

*Pharmacokinetic considerations*—Renal or hepatic dysfunction causes the elimination of quinidine to be slowed, while congestive heart failure causes a reduction in quinidine's apparent volume of distribution. Any of these conditions can lead to quinidine toxicity if dosage is not appropriately reduced. In addition, interactions with coadministered drugs can alter the serum concentration and activity of quinidine, leading either to toxicity or to lack of efficacy if the dose of quinidine is not appropriately modified (*see* Precautions/Drug Interactions).

*Vagolysis*—Because quinidine opposes the atrial and A-V nodal effects of vagal stimulation, physical or pharmacological vagal maneuvers undertaken to terminate paroxysmal supraventricular tachycardia may be ineffective in patients receiving quinidine.

## PRECAUTIONS

*Heart block*—In patients without implanted pacemakers who are at high risk of complete atrioventricular block (*eg*, those with digitalis intoxication, second-degree atrioventricular block, or severe intraventricular conduction defects), quinidine should be used only with caution.

*Drug interactions*—Altered pharmacokinetics of quinidine: Drugs that alkalinize the urine (**carbonic-anhydrase inhibitors**, **sodium bicarbonate**, **thiazide diuretics**) reduce renal elimination of quinidine.

By pharmacokinetic mechanisms that are not well understood, quinidine levels are increased by coadministration of **amiodarone** or **cimetidine**. Very rarely, and again by mechanisms not understood, quinidine levels are decreased by coadministration of **nifedipine**.

Hepatic elimination of quinidine may be accelerated by coadministration of drugs (**phenobarbital**, **phenytoin**, **rifampin**) that induce production of cytochrome P450III<sub>A</sub>4.

Perhaps because of competition of the P450III<sub>A</sub>4 metabolic pathway, quinidine levels rise when **ketaconazole** is coadministered.

Coadministration of **propranolol** usually does not affect quinidine pharmacokinetics, but in some studies, the  $\beta$ -blocker appeared to cause increases in the peak serum levels of quinidine, decreases in quinidine's volume of distribution and decreases in total quinidine clearance. The effects (if any) of coadministration of **other  $\beta$ -blockers** on quinidine pharmacokinetics have not been adequately studied.

Hepatic clearance of quinidine is significantly reduced during coadministration of **verapamil**, with corresponding increases in serum levels and half-life.

Altered pharmacokinetics of other drugs: Quinidine slows the elimination of **digoxin** and simultaneously reduces digoxin's apparent volume of distribution. As a result, serum

digoxin levels may be as much as doubled. When quinidine and digoxin are coadministered, digoxin doses usually need to be reduced. Serum levels of **digitoxin** are also raised when quinidine is coadministered, although the effect appears to be smaller.

By a mechanism that is not understood, quinidine potentiates the anticoagulatory action of warfarin, and the anticoagulant dosage may need to be reduced.

Cytochrome P450IID6 is an enzyme critical to the metabolism of many drugs, notably including **mexiletine**, some **phenothiazines**, and most **polycyclic antidepressants**. Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers."

When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the cases of prodrugs whose actions are actually mediated by P450IID6-produced metabolites (for example, **codeine** and **hydrocodone**, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers.

Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6.

Perhaps by competing for pathways of renal clearance, coadministration of quinidine causes an increase in serum levels of **procainamide**.

Serum levels of **haloperidol** are increased when quinidine is coadministered.

Presumably because both drugs are metabolized by cytochrome P450III A4, coadministration of quinidine causes variable slowing of the metabolism of **nifedipine**. Interactions with other dihydropyridine calcium-channel blockers have not been reported, but these agents (including **felodipine**, **nicardipine**, and **nimodipine**) are all dependent upon P450III A4 for metabolism, so similar interactions with quinidine should be anticipated.

Altered pharmacodynamics of other drugs: Quinidine's anticholinergic, vasodilating, and negative inotropic actions may be additive to those of other drugs with these effects, and antagonistic to those of drugs with cholinergic, vasoconstricting, and positive inotropic effects. For example, when quinidine and **verapamil** are coadministered in doses that are each well tolerated as monotherapy, hypotension attributable to additive peripheral  $\alpha$ -blockade is sometimes reported.

Quinidine potentiates the actions of depolarizing (succinylcholine, decamethonium) and nondepolarizing (*d*-tubocurarine, pancuronium) neuromuscular blocking agents. These phenomena are not well understood, but they are observed in animal models as well as in humans. In addition, *in vitro* addition of quinidine to the serum of pregnant women reduces the activity of pseudocholinesterase, an enzyme that is essential to the metabolism of succinylcholine.

Diltiazem significantly decreases the clearance and increases the  $t_{1/2}$  of quinidine, but quinidine does not alter the kinetics of diltiazem. Non-interactions of quinidine with other drugs: Quinidine has no clinically significant effect on the pharmacokinetics of **diltiazem**,

**flecainide, mephenytoin, metoprolol, propafenone, propranolol, quinine, timolol, or tocainide.**

Conversely, the pharmacokinetics of quinidine are not significantly affected by **caffeine, ciprofloxacin, digoxin, felodipine, omeprazole, or quinine**. Quinidine's pharmacokinetics are also unaffected by cigarette smoking.

*Carcinogenesis, mutagenesis, impairment of fertility*—Animal studies to evaluate quinidine's carcinogenic or mutagenic potential have not been performed. Similarly, there are no animal data as to quinidine's potential to impair fertility.

*Pregnancy*—Pregnancy Category C—Animal reproductive studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidine should be given to a pregnant woman only if clearly needed.

In one neonate whose mother had received quinidine throughout her pregnancy, the serum level of quinidine was equal to that of the mother, with no apparent ill effect. The level of quinidine in amniotic fluid was about three times higher than that found in serum.

*Labor and Delivery*—Quinine is said to be oxytocic in humans, but there are no adequate data as to quinidine's effect (if any) on human labor and delivery.

*Nursing mothers*—Quinidine is present in human milk at levels slightly lower than those in maternal serum; a human infant ingesting such milk should (scaling directly by weight) be expected to develop serum quinidine levels at least an order of magnitude lower than those of the mother. On the other hand, the pharmacokinetics and pharmacodynamics of quinidine in human infants have not been adequately studied, and neonates' reduced protein binding of quinidine may increase their risk of toxicity at low total serum levels. Administration of quinidine should (if possible) be avoided in lactating women who continue to nurse.

*Pediatric use*—In antimalarial trials, quinidine was as safe and effective in pediatric patients as in adults. Notwithstanding the known pharmacokinetic differences between pediatric patients and adults (*see* Pharmacokinetics and Metabolism), pediatric patients in these trials received the same doses (on a mg/kg basis) as adults.

Safety and effectiveness of antiarrhythmic use in pediatric patients have not been established.

*Geriatric use*—Safety and efficacy of quinidine in elderly patients has not been systematically studied. Clinical studies of quinidine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. The reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

Quinidine preparations have been used for many years, but there are only sparse data from which to estimate the incidence of various adverse reactions. The adverse reactions most frequently reported have consistently been gastrointestinal, including diarrhea, nausea, vomiting, and heart-burn/esophagitis. In one study of 245 adult outpatients who received quinidine to suppress premature ventricular contractions, the incidences of reported adverse experiences were as shown in the table below. The most serious quinidine-associated adverse reactions are described above under Warnings.

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Adverse Experiences in a 245-Patient PVC Trial	
	<u>Incidence (%)</u>
diarrhea	85 (35)
"upper gastrointestinal distress"	55 (22)
lightheadedness	37 (15)
headache	18 (7)
fatigue	17 (7)
palpitations	16 (7)
angina-like pain	14 (6)
weakness	13 (5)
rash	11 (5)
visual problems	8 (3)
change in sleep habits	7 (3)
tremor	6 (2)
nervousness	5 (2)
discoordination	3 (1)

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Intramuscular injections of quinidine gluconate are typically followed by moderate to severe local pain. Some patients will develop tender nodules at the site of injection that persist for several weeks.

Vomiting and diarrhea can occur as isolated reactions to therapeutic levels of quinidine, but they may also be the first signs of **cinchonism**, a syndrome that may also include tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium. Cinchonism is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose.

A few cases of **hepatotoxicity**, including granulomatous hepatitis, have been reported in patients receiving quinidine. All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once quinidine was withdrawn.

**Autoimmune and inflammatory syndromes** associated with quinidine therapy have included fever, urticaria, flushing, exfoliative rash, bronchospasm, pneumonitis, psoriasiform rash, pruritus and lymphadenopathy, hemolytic anemia, vasculitis, thrombocytopenic purpura, uveitis, angioedema, agranulocytosis, the sicca syndrome, arthralgia, myalgia, elevation in serum levels of skeletal-muscle enzymes, and a disorder resembling systemic lupus erythematosus.

Convulsions, apprehension, and ataxia have been reported, but it was not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion. There are many reports of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare.

Other adverse reactions occasionally reported include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, and abnormalities of pigmentation.

## OVERDOSAGE

There are only scattered reports of overdosage with intravenous quinidine, but overdoses with oral quinidine have been well described. Death has been described after a 5-gram ingestion by a toddler, while an adolescent was reported to survive after ingesting 8 grams of quinidine.

The most important ill effects of acute quinidine overdoses are ventricular arrhythmias and hypotension. Other signs and symptoms of overdose may include vomiting, diarrhea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium.

*Arrhythmias*—Serum quinidine levels can be conveniently assayed and monitored, but the electrocardiographic QT<sub>c</sub> interval is a better predictor of quinidine-induced ventricular arrhythmias.

The necessary treatment of hemodynamically unstable polymorphic ventricular tachycardia (including *torsades de pointes*) is withdrawal of treatment with quinidine and either immediate cardioversion or, if a cardiac pacemaker is in place or immediately available, immediate overdrive pacing. After pacing or cardioversion, further management must be guided by the length of the QT<sub>c</sub> interval.

Quinidine-associated ventricular tachyarrhythmias with normal underlying QT<sub>c</sub> intervals have not been adequately studied. Because of the theoretical possibility of QT-prolonging effects that might be additive to those of quinidine, other antiarrhythmics with Class I (disopyramide, procainamide) or Class III activities should (if possible) be avoided. Similarly, although the use of bretylium in quinidine overdose has not been reported, it is reasonable to expect that the  $\alpha$ -blocking properties of bretylium might be additive to those of quinidine, resulting in problematic hypotension.

If the post-cardioversion QT<sub>c</sub> interval is prolonged, then the pre-cardioversion polymorphic ventricular tachyarrhythmia was (by definition) *torsades de pointes*. In this case, lidocaine and bretylium are unlikely to be of value, and other Class I antiarrhythmics (disopyramide, procainamide) are likely to exacerbate the situation. Factors contributing to QT<sub>c</sub> prolongation (especially hypokalemia and hypomagnesemia) should be sought out and (if possible) aggressively corrected. Prevention of recurrent *torsades* may require sustained overdrive pacing or the cautious administration of isoproterenol (30-150 ng/kg/min).

*Hypotension*—Quinidine-induced hypotension that is not due to an arrhythmia is likely to be a consequence of quinidine-related  $\alpha$ -blockade and vasorelaxation. Simple repletion of central volume (Trendelenburg positioning, saline infusion) may be sufficient therapy; other interventions reported to have been beneficial in this setting are those that increase peripheral vascular resistance, including  $\alpha$ -agonist catecholamines (norepinephrine, metaraminol) and the Military Anti-Shock Trousers.

*Treatment*—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In

managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

*Accelerated removal*—Adequate studies of orally-administered activated charcoal in human overdoses of quinidine have not been reported, but there are animal data showing significant enhancement of systemic elimination following this intervention, and there is at least one human case report in which the elimination half-life of quinidine in the serum was apparently shortened by repeated gastric lavage. Activated charcoal should be avoided if an ileus is present; the conventional dose is 1 gram/kg, administered every 2-6 hours as a slurry with 8 mL/kg of tap water.

Although renal elimination of quinidine might theoretically be accelerated by maneuvers to acidify the urine, such maneuvers are potentially hazardous and of no demonstrated benefit.

Quinidine is not usefully removed from the circulation by dialysis.

Following quinidine overdose, **drugs that delay elimination of quinidine (cimetidine, carbonic-anhydrase inhibitors, diltiazem, thiazide diuretics) should be withdrawn** unless absolutely required.

## DOSAGE AND ADMINISTRATION

Because the kinetics of absorption may vary with the patient's peripheral perfusion, intramuscular injection of quinidine gluconate is not recommended.

*Treatment of *P. falciparum* malaria*—Two regimens have each been shown to be effective, with or without concomitant exchange transfusion. There are no data indicating that either should be preferred to the other.

In **Regimen A**, each patient received a **loading dose** of 15 mg/kg of quinidine base (that is, 24 mg/kg of quinidine gluconate) in 250 mL of normal saline infused over 4 hours. Thereafter, each patient received a **maintenance regimen** of 7.5 mg/kg of base (12 mg/kg of quinidine gluconate) infused over 4 hours every 8 hours, starting 8 hours after the beginning of the loading dose. This regimen was continued for 7 days, except that in patients able to swallow, the maintenance infusions were discontinued, and approximately the same daily doses of quinidine were supplied orally, using 300-mg tablets of quinidine sulfate.

In **Regimen B**, each patient received a **loading dose** of 6.25 mg/kg of quinidine base (that is, 10 mg/kg of quinidine gluconate) in approximately 5 mL/kg of normal saline over 1-2 hours. Thereafter, each patient received a **maintenance infusion** of 12.5 µg/kg/min of base (that is, 20 µg/kg/min of quinidine gluconate). In patients able to swallow, the maintenance infusion was discontinued, and eight-hourly oral quinine sulfate was administered to provide approximately as much daily quinine base as the patient had been receiving quinidine base (for example, each adult patient received 650 mg of quinine sulfate every eight hours).

Quinidine/quinine therapy was continued for 72 hours or until parasitemia had decreased to 1% or less, whichever came first. After completion of quinidine/quinine therapy, adults able to swallow received a single 1500-mg/75-mg dose of sulfadoxine/pyrimethamine (FANSIDAR<sup>®</sup>, Roche Laboratories) or a seven-day course of tetracycline (250 mg four times daily), while those unable to swallow received seven-day courses of intravenous doxycycline hyclate (VIBRAMYCIN<sup>®</sup>, Roerig), 100 mg twice daily. Most of the patients described as having been treated with this regimen also underwent exchange transfusion. Small

children have received this regimen without dose adjustment and with apparent good results, notwithstanding the known differences in quinidine pharmacokinetics between pediatric patients and adults (*see* Clinical Pharmacology).

Even in patients without preexisting cardiac disease, antimalarial use of quinidine has occasionally been associated with hypotension, QT<sub>c</sub> prolongation, and cinchonism; *see* Warnings.

***Treatment of symptomatic atrial fibrillation/flutter***—A patient receiving an intravenous infusion of quinidine must be carefully monitored, with frequent or continuous electrocardiography and blood-pressure measurement. The infusion should be discontinued as soon as sinus rhythm is restored: the QRS complex widens to 130% of its pre-treatment duration; the QT<sub>c</sub> interval widens to 130% of its pre-treatment duration, and is then longer than 500 ms; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension.

To prepare quinidine for infusion, the contents of the supplied vial (80 mg/mL) should be diluted to 50 mL (16 mg/mL) with 5% dextrose. The resulting solution may be stored for up to 24 hours at room temperature or up to 48 hours at 4°C (40°F).

Because quinidine may be absorbed to PVC tubing, tubing length should be minimized. In one study (*Am J Health Syst Pharm.* 1996; 53:655-8), use of 112 inches of tubing resulted in 30% loss of quinidine, but drug loss was less than 3% when only 12 inches of tubing was used.

An infusion of quinidine must be delivered slowly, preferable under control of a volumetric pump, no faster than 0.25 mg/kg/min (that is, no faster than 1 mL/kg/hour). During the first few minutes of the infusion, the patient should be monitored especially closely for possible hypersensitive or idiosyncratic reactions.

Most arrhythmias that will respond to intravenous quinidine will respond to a total dose of less than 5 mg/kg, but some patients may require as much as 10 mg/kg. If conversion to sinus rhythm has not been achieved after infusion of 10 mg/kg, then the infusion should be discontinued, and other means of conversion (*eg*, direct-current cardioversion) should be considered.

***Treatment of life-threatening ventricular arrhythmias***—Dosing regimens for the use of intravenous quinidine gluconate in controlling life-threatening ventricular arrhythmias have not been adequately studied. Described regimens have generally been similar to the regimen described just above for the treatment of symptomatic atrial fibrillation/flutter.

## HOW SUPPLIED

The 80 mg/mL, 10 mL Multiple-Dose Vial is available as:

1 NDC 0002-1407-01 (VL530)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature].

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**Eli Lilly and Company, Indianapolis, IN 46285, USA**

PV 3850 AMP

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