Management of acute paroxysmal supraventricular tachycardia in pregnancy

BRIAN PAHLOW, DO
ALAN K. GEISLER, DO
GEORGE H. DAVIS, DO

The treatment of paroxysmal supraventricular tachycardia (PSVT) in pregnancy is not unlike treatment for the general population. The physician should feel confident that the pharmacologic agents ordinarily used to treat this common problem in the general population are safe for both mother and fetus when administered under monitored conditions. In treating paroxysmal supraventricular tachycardia in pregnancy, when both vagal maneuvers and exhaustive medical therapy fail, synchronized, direct-current cardioversion is a safe and effective form of treatment.

(Keywords: Pregnancy, paroxysmal supraventricular tachycardia, arrhythmia, tachyarrhythmia, cardiac emergency)

Paroxysmal supraventricular tachycardia (PSVT), or paroxysmal atrial tachycardia as it is sometimes called, is a commonly encountered cardiac emergency in the general popu-

lation. The type of treatment instituted and the urgency of its administration are dictated by the presence or absence of hemodynamic instability, which in turn is often directly dependent on the presence or absence of underlying cardiac dysfunction.

The incidence of PSVT in pregnancy is unknown, but it is by no means an uncommon event. This arrhythmia has been reported to increase in the third trimester.¹ Although the comparatively young age and relative absence of significant heart disease in the pregnant population lends itself to a lower incidence of hemodynamic compromise, the fact remains that syncope, hypotension, angina pectoris, and heart failure do occur. The fetus is also at significant risk of incurring anoxic injury secondary to hypoperfusion. This makes constant fetal heart monitoring essential.²

Physicians are generally comfortable treating PSVT in the general population, but they may approach this problem with a great deal more hesitancy in pregnant patients. Two particularly anxiety-provoking questions physicians may ask themselves are: Is the treatment for this problem different in the pregnant population? What effect will the treatment have on the fetus?

It is the intent of this review to briefly examine the common causes of PSVT in pregnant women and to discuss the various modes of treatment and their effects on the mother and fetus. This discussion will help to answer the questions raised and to provide a greater

From the University of Medicine and Dentistry of New Jersey—School of Osteopathic Medicine, Stratford, where, at the time this article was written, Dr Pahlow was a fellow in cardiology; Dr Geisler is assistant professor of clinical medicine, Department of Cardiology; and Dr Davis was a member of the full-time faculty, Department of Obstetrics, Gynecology, and Perinatology. Currently, Dr Pahlow is in private practice in Salem, NJ, and Dr Davis, in Barrington, NJ.

Reprint requests to Alan K. Geisler, DO, 301 South Central Plaza—Laurel Rd, Suite 3100, Stratford, NJ 08084-1504.

sense of security for physicians faced with this dilemma.

Initial assessment

The initial evaluation of PSVT in the pregnant woman should begin with a complete history and physical examination. Excessive dietary intake of caffeine, alcohol, or tobacco, and the use of illicit drugs such as amphetamines or cocaine are all important secondary causes of PSVT.¹ Excessive dosages of prescribed medications such as β -agonists, theophylline preparations, and thyroid replacements must also be considered. Underlying endocrine disorders, such as primary hyperthyroidism, or a pulmonary pathologic process, such as pulmonary embolus, must be considered and evaluated by routine laboratory tests such as arterial blood gas and thyroid function tests.

Physical examination of the pregnant patient during an episode of PSVT is of obvious importance but seldom enables the physician to determine a specific cause. Even the click and mid- to late-systolic murmur of mitral valve prolapse may often go undetected with the pulse at such rapid rates. Physical findings of tachypnea, cyanosis, hypotension, rales, or a third heart sound have obvious implications with regard to the need for urgent resolution of the arrhythmia.

Classification

The nomenclature used to classify these tachyarrhythmias is shrouded in confusion. Tachycardias demonstrating a narrow QRS complex with regular R-R intervals and without evidence of preexcitation are grouped separately as paroxysmal atrial tachycardia or paroxysmal junctional, or nodal tachycardia. They are all, however, examples of paroxysmal supraventricular tachycardia.³

Of all the possible mechanisms responsible for a narrow complex tachycardia, paroxysmal atrioventricular (AV) (or nodal) reentrant tachycardia is by far the most common cause in pregnancy and in the general population.^{1,4} In 90% of these cases, the tachycardia involves a circus rhythm confined entirely to the AV node and is composed of anterograde conduction to the ventricle over slow (alpha) fibers

and retrograde conduction to the atrium over fast (beta) fibers.

The arrhythmia is initiated by a premature atrial complex that blocks conduction in the fast fibers. It thus establishes a pathway for reentry that uses the slower pathway for anterograde conduction and the fast pathway for retrograde conduction. Less commonly, reentry may likewise occur within the sinoatrial node or the atria, or it may involve accessory pathways to the ventricle or conduction system.³

Electrocardiographically, reentrant tachycardia in the AV node is characterized by a narrow QRS complex of 0.12 seconds or less, regular heart rates between 150 and 250 beats per minute, and abrupt onset and termination.⁴ Bar and colleagues⁵ reviewed the electrocardiographic criteria currently used in the differential diagnosis of narrow complex tachycardia. They found P wave location to be the most helpful tool among all criteria. In more than two thirds of the cases of AV nodal reentrant tachycardia reviewed, the P wave occurred simultaneously within the QRS complex. This finding was in direct contradistinction to PSVT involving accessory pathways in which the P wave was found to follow the QRS complex in the majority of cases.

Finally, there is the situation in which patients with PSVT have heart rates greater than 250 beats per minute. In these patients, the physician should suspect one of the preexcitation syndromes such as Wolff-Parkinson-White or Lown-Ganong-Levine. Standard first-line medical therapy with calcium-channel blockers or cardiac glycosides may be contraindicated in these cases. Such agents may actually promote conduction via the bypass tract, leading to higher heart rates and the potential for ventricular fibrillation.^{6,7}

Management

Vagal maneuvers

Self-induced or physician-mediated attempts at increasing vagal tone should always form the first line of therapy in the management of hemodynamically stable PSVT in the pregnant patient. Unlike pharmacologic therapy, this form of intervention precludes potentially

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Antacids containing magnesium hydroxide or aluminum hydroxide interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

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Cipro[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

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Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*,^{*} and *Shigella sonnei*^{*} when antibacterial therapy is indicated.

^{*}Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella: Microsome Test (Negative)
- E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three in vivo test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced

IN LOWER RESPIRATORY INFECTIONS CIPRO[®] MAKES A TOUGH THERAPEUTIC CHOICE EASIER.

gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSENSITIVITY: (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS). **SPECIAL SENSES:** blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccup, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

- Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).
- Cholestatic jaundice has been reported.
- Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).
- Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.
Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro[®] (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: 1. Data on file, Miles Inc. Pharmaceutical Division. 2. Barry AL, Jones RN, Thornsberry C, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother.* 1984;25:633-637. 3. Guimaraes MA, Noone P. The comparative in-vitro activity of norfloxacin, ciprofloxacin, enoxacin and nalidixic acid against 423 strains of gram-negative rods and staphylococci isolated from infected hospitalized patients. *J Antimicrob Chemother.* 1986;17:63-67. 4. Van Caekenberghe DL, Pattyn SR. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazine-substituted quinolone derivatives. *Antimicrob Agents Chemother.* 1984;25:518-521.

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serious side effects. This makes it an ideal initial therapeutic approach.

Valsalva's maneuver in which expiration is forced against a closed glottis, or the diving reflex, which is elicited by immersing the face in ice water while the breath is held, are two time-tested methods of increasing vagal tone at the AV node.⁸ When these measures fail or when the patient is unable to adequately perform these maneuvers, massaging the carotid sinus or gagging the patient are often effective means of converting the heart to normal sinus rhythm.⁹

Drug therapy

Obviously, if conservative measures designed to increase vagal tone fail, the physician has no choice but to prescribe medication in the attempt to slow the ventricular response and convert the heart to normal sinus rhythm. The choice of a particular drug will depend on its relative safety in pregnancy. No drug is completely safe. However, some agents clearly have a lower risk-to-benefit ratio than others. Verapamil hydrochloride, β -adrenergic blocking agents (β -blockers), digoxin, and the type 1a antiarrhythmic agents are most commonly used for both acute and chronic conditions. Edrophonium chloride,¹⁰ a cholinesterase inhibitor, was widely used in the 1970s for PSVT in the nonpregnant population. Because there are no reports concerning its safe use in pregnancy, it will not be included in the following discussion.

Verapamil

Studies to date have yet to substantiate the safety of verapamil in pregnancy when used during the critical phase of organogenesis.^{1,2} The drug, however, has an overwhelming record of effectiveness (96%) in the treatment of PSVT. Because of this record and the fact that there is much evidence supporting its safety, verapamil is considered excellent first-line drug therapy.^{3,11} The use of verapamil is relatively contraindicated in pregnant women who have moderate to severe hypotension because of the drug's propensity for causing further maternal hypotension. To date, there have been no documented cases of fetal mor-

bidity or mortality attributed to verapamil.¹ Reports of safe and effective use of verapamil in the management of premature labor and even fetal supraventricular tachycardia in utero further support its use.^{12,13} The recommended dose is 0.075 mg/kg to 0.15 mg/kg administered intravenously (IV) over 1 to 3 minutes. This dose may be repeated in 20 to 30 minutes.¹¹

Beta-blockers

Despite the fact that there has been no large-scale controlled trial to evaluate β -blockers in the treatment of PSVT during pregnancy, a number of papers have been written regarding the use of these agents in the treatment of hypertension,^{14,15} thyrotoxicosis,¹⁶ and hypertrophic obstructive cardiomyopathy¹⁷ during pregnancy. Their excellent safety record and the rapid onset of action makes these agents desirable first- or second-line therapy for PSVT.

It is well known that β -blockers, selective or nonselective, readily cross the placenta and appear in the maternal and fetal circulations in significant concentrations.¹⁸ However, no report has ever linked a β -blocker to a fetal malformation. Conflicting reports have been written concerning an increased incidence of intrauterine growth retardation in mothers treated with propranolol hydrochloride.^{17,19} β -Blockers can also cause a delay in the onset of spontaneous respirations based on their inhibition of the autonomic response to the stress of labor. Hypoglycemia of the newborn can occur, but the etiology of this is not clear.¹⁸

Once again, the presence of moderate to severe hypotension is a relative contraindication to the use of β -blockers. Propranolol is the β -blocker that has been most widely tested. It should be given IV in 1-mg to 2-mg increments every 15 to 20 minutes for the desired effect. When delivery is imminent, medical and obstetrical personnel should be prepared to intubate and ventilate the infant until spontaneous respirations are adequate.

Cardiac glycosides

Digoxin, the mainstay of glycoside therapy in the United States, is currently considered to

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*The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or reduction of HDL-cholesterol levels on morbidity and mortality due to coronary heart disease has not been established.

¹ Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242-9553.

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CLINICAL PHARMACOLOGY: Lorelco lowers total serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probuconol exhibit a decrease in low-density lipoprotein (LDL) cholesterol. Cholesterol is reduced not only in the LDL fraction, but also in the high-density lipoprotein (HDL) fraction with proportionately greater effect on the high-density portion. Epidemiologic studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low-density lipoprotein (VLDL).

Studies on the mode of action of Lorelco indicate that it increases the fractional rate of LDL catabolism. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Lorelco also exhibits inhibition of early stages of cholesterol biosynthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Lorelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/mL (± S.D.) ranging to 78.3 mcg/mL. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/mL (± S.D.) ranging to 62.0 mcg/mL. In a separate study in eight patients, blood levels averaged 19.0 mcg/mL at the end of 12 months of treatment. Six weeks after cessation of therapy, the average had fallen by 60%. After six months, the average had fallen by 80%.

In December 1984, a National Institutes of Health Consensus Development Conference Panel¹ concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of LDL-cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probuconol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

INDICATIONS AND USAGE: Serious animal toxicity has been encountered with probuconol. See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections. Probuconol is not an innocuous drug and strict attention should be paid to the INDICATIONS, CONTRAINDICATIONS, and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important factor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension, and diabetes mellitus. Consideration should be given to the efficacy, safety, and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient. Lorelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (Types IIa and IIb hyperlipoproteinemia),² whose elevated LDL-cholesterol has not responded adequately to diet, weight reduction, and control of diabetes mellitus. Lorelco may be useful to lower elevated LDL-cholesterol that occurs in those patients with combined hypercholesterolemia and hypertriglyceridemia (Type IIb) due to elevation of both LDL and VLDL, but it is not indicated where hypertriglyceridemia is the abnormality of most concern. After establishing that the elevation in serum total cholesterol represents a primary lipid disorder, it should be determined that patients being considered for treatment with Lorelco have an elevated LDL-cholesterol as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with elevated triglycerides or with markedly elevated HDL-cholesterol values, where non-LDL fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In most patients, LDL-cholesterol may be estimated according to the following equation:

$$\text{LDL-cholesterol} = \text{Total cholesterol} - [(0.16 \times \text{triglycerides}) + \text{HDL-cholesterol}]$$

When total triglycerides are greater than 400 mg/dL, this equation is less accurate. In such patients, LDL-cholesterol may be obtained by ultracentrifugation.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels, including HDL-cholesterol, should be periodically assessed.

The effect of probuconol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

CONTRAINDICATIONS: (See also WARNINGS and PRECAUTIONS.) Lorelco is contraindicated in patients who are known to have a hypersensitivity to it. Lorelco is contraindicated in patients with evidence of recent or progressive myocardial damage or findings suggestive of serious ventricular arrhythmias or with unexplained syncope or syncope of cardiovascular origin.

Lorelco is contraindicated in patients with an abnormally long QT interval.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCONOL IN RHESUS MONKEYS FED AN ATEROGENIC DIET AND IN BEAGLE DOGS. (SEE ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION.)

Prolongation of the QT interval can occur in patients on Lorelco. Serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco alone and in patients on Lorelco and a concomitant antiarrhythmic drug. The following precautions are deemed prudent:

1. Patients should be advised to adhere to a low cholesterol, low fat diet at the start of treatment with Lorelco and throughout the treatment period.
2. An ECG should be done prior to starting treatment and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, the possible benefits and risks should be carefully considered before making a decision to continue Lorelco.
3. Lorelco therapy should be discontinued or not started if the QT interval at an observed heart rate on a resting ECG is persistently more than one of the values listed below:

Observed Heart Rate (beats/min)	QT interval in sec (15% above the upper limit of normal)*	
	Males	Females
40	0.56	0.58
50	0.52	0.53
60	0.49	0.50
70	0.45	0.47
80	0.43	0.44
86	0.42	0.43
92	0.40	0.41
100	0.39	0.40
108	0.37	0.38
120	0.36	0.36
133	0.34	0.35

*Values calculated from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia, PA: Lea and Febiger; 1958; p. 272 (Table 6).

3. Patients developing unexplained syncope or syncope of cardiovascular origin should have Lorelco therapy discontinued and should have ECG surveillance.
4. Drugs that prolong the QT interval are more likely to be associated with ventricular tachycardia after:
 - a. An increase in the dose of the drug.
 - b. Addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines).
 - c. Hypokalemia or hypomagnesemia.
 - d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
 - e. Development of recent or acute myocardial infarction, ischemia, or inflammation.

The use of Lorelco in patients receiving any of these drugs should be based on the conclusion that alternate methods of hypocholesterolemic therapy are either ineffective or not tolerated, and the potential benefits of cholesterol lowering outweigh the risk of serious arrhythmia.

The following conditions should be resolved or corrected prior to initiation of therapy with Lorelco.

- a. Hypokalemia
- b. Hypomagnesemia
- c. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
- d. Recent or acute myocardial infarction, ischemia, or inflammation.

PRECAUTIONS

General: Before instituting therapy with Lorelco, adequate baseline studies should be performed to determine that the patient has persistently elevated total and LDL-cholesterol levels representing a primary lipid disorder, and that the increased cholesterol is not due to secondary conditions such as hypothyroidism, poorly controlled diabetes mellitus, obstructive liver disease, nephrotic syndrome, or dysproteinemia. Serum lipid levels, including HDL-cholesterol, should be determined after an overnight fast before treatment, during an adequate trial of diet and weight reduction therapy prior to addition of drug therapy, and periodically during combined diet and drug therapy, including assessment during the first several months of drug treatment. A favorable trend in lipid levels should be evident during the first three to four months of administration of Lorelco, and if satisfactory lipid alteration is not achieved, the drug should be discontinued. Lorelco lowers serum total and LDL-cholesterol, and also lowers HDL-cholesterol in most patients with elevated LDL-cholesterol. Epidemiologic studies within hypercholesterolemic populations have shown that serum HDL-cholesterol is an independent, inversely correlated, risk factor for coronary heart disease. (See CLINICAL PHARMACOLOGY.) Human studies which will attempt to confirm or deny the hypothesis that drug-induced alteration in HDL-cholesterol affects cardiovascular risk are currently under evaluation. It is not known whether Lorelco-induced reduction of serum HDL-cholesterol will affect cardiovascular risk since no long-term, controlled clinical trials of Lorelco for the prevention of coronary heart disease, similar to the LRC-CPTT (see CLINICAL STUDIES), have been performed. The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of each patient receiving Lorelco treatment. If satisfactory lipid alteration is not achieved, the drug should be discontinued.

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast-feed their infants during therapy with Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and periodic ECGs. (See WARNINGS.)

Elevations of the serum transaminases (SGOT, SGPT), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen, and blood glucose above the normal range were observed on one or more occasions in various patients treated with Lorelco. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between Lorelco and these abnormalities is not firm, the possibility that some of these are drug related cannot be excluded. In controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with Lorelco than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, Lorelco should be discontinued.

Drug Interactions: The addition of clofibrate to Lorelco is not recommended, since the lowering effect on mean serum levels of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL-cholesterol.

Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco.

Monkeys fed a high fat, high cholesterol diet admixed with probuconol exhibited serious toxicity. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.) Prolongation of the QT interval can occur in patients on Lorelco and serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco. The addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines) may increase the risk of serious arrhythmia. (See CONTRAINDICATIONS AND WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy

Teratogenic Effects

Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probuconol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn and forthwith control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

Labor and Delivery: The effect of Lorelco on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is excreted in human milk, but it is likely, since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on Lorelco.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal

diarrhea or loose stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding

Cardiovascular

prolongation of the QT interval on ECG, syncope, ventricular arrhythmias (ventricular tachycardia, torsades de pointes, ventricular fibrillation), sudden death

Neurologic

headache, dizziness, paresthesia, insomnia, tinnitus, peripheral neuritis

Hematologic

eosinophilia, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic

rash, pruritus, ecchymosis, petechiae, hyperhidrosis, feist sweat

Genitourinary

impotency, nocturia

Ophthalmic

conjunctivitis, tearing, blurred vision

Endocrine

enlargement of multinodular goiter

Idiosyncrasies

observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain

Other

diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there evidence of psychological or physical dependence in humans.

OVERDOSEAGE: There is a single report of a 15-kg, three-year-old, male child who ingested 5 g of probuconol. Emesis was induced by ipecac. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdose with Lorelco and no specific antidote is available. Probuconol is not dialyzable. Treatment is symptomatic and supportive. Probuconol has shown no identifiable acute toxicity in mice and rats. In these animals the LD₅₀ (oral) is in excess of 5 g/kg of body weight.

DOSEAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 1000 mg daily given in two divided doses of 500 mg each (two 250 mg tablets or one 500 mg tablet) with the morning and evening meals.

HOW SUPPLIED: 250 mg round, white, film-coated tablets imprinted with either the DOW diamond trademark or the code number S1 or LRC02 250. Bottles of 100 (NDC 0068-0051-52)

500 mg capsule-shaped, white, film-coated tablets, marked LORELCO 500. Bottles of 100 (NDC 0068-0053-61)

Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well-closed light-resistant containers with child-resistant closure.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys, administration of probuconol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premortem syncope was frequently observed and was associated with a pronounced prolongation of the QT intervals (30 to 50% longer than that observed in untreated monkeys). Serum levels of probuconol greater than 20 mcg/mL were generally associated with some prolongation of the QT interval in the cholesterol-fed monkey. A 75 msec or greater increase in QT interval from control values was usually seen at 40 mcg/mL and above. Blood levels in humans receiving Lorelco average approximately 20 mcg/mL and not uncommonly reach levels of 40 mcg/mL and higher. Rhesus monkeys fed normal (low fat) chow and receiving probuconol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration. In another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probuconol, separated in time from the atherogenic meal, was carried out during the second year. Serum probuconol levels ranged 20 to 50 mcg/mL in five of ten monkeys, and less in the remaining animals. Marked prolongation of the QT interval in the ECG or syncope behavior was never observed over the entire one year treatment period. Regression of gross aortic lesions comparable to that observed in a parallel group of monkeys receiving cholestyramine was seen in animals receiving probuconol. It should be emphasized that both LDL-cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chronic study involving 32 probuconol-treated dogs (beagles), there were 12 fatalities.

Subsequent experiments have indicated that probuconol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probuconol has been studied, the dog is peculiar with respect to the phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, the incidence of epinephrine-induced ventricular fibrillation was not increased in monkeys.

In other studies, monkeys were given probuconol either before and after, or only after myocardial infarction was induced by coronary artery ligation. In these studies, there was no difference between probuconol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Probuconol has shown no identifiable toxicity in mice and rats. In these animals, the LD₅₀ (oral) is in excess of 5 g/kg of body weight. In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs, and monkeys, it is known that probuconol accumulates slowly in adipose tissue. Approximately 90% of probuconol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probuconol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probuconol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days after ligation. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary-ligated, probuconol-treated minipigs.

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPTT,³ hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol-lowering diet experienced average total and LDL-cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven-year incidence of the primary end point—combined incidence of definite CHD death and/or definite nonfatal myocardial infarction—was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (P less than 0.05, single-tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction.

The subjects included in the study were middle-aged men (35-55 years old) with serum cholesterol levels at least 265 mg/dL and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestrant, cholestyramine, was used in the above trial. Caution should be exercised in extrapolating these results to Lorelco since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency, effect on HDL-cholesterol, and possible toxicity. The effect of probuconol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

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Product Information as of June, 1988

MERRELL DOW PHARMACEUTICALS INC.

Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

O-1266 (10110) MDA087

Y342D

be safe for use in pregnancy.² However, for the emergent treatment of PSVT in the pregnant woman, its relatively slow onset of action makes it less desirable in the treatment of acute PSVT. For the hypotensive pregnant patient with PSVT, IV digoxin may be considered the drug of choice because hypotension is not one of its common side effects.

Digoxin is freely transferred across the placenta,²⁰ but, to date, it has not been shown to be teratogenic. Furthermore, no adverse effects, other than an increased incidence of prematurity, have been seen in the newborn when digoxin is administered to the mother at therapeutic levels.²¹ An entirely different picture of fetal risk arises in the face of digitalis toxicity. Reports of miscarriage and sudden fetal death are not uncommon in this setting.^{22,23} A loading dose of 1 mg to 1.5 mg of digoxin administered IV over 24 hours may be used short term to control the ventricular response. Pregnant patients, however, may require higher maintenance doses due to the normal increase in the glomerular filtration rate that accompanies pregnancy.²⁴

Digoxin remains a safe and effective treatment mode for the short-term management of PSVT, but its narrow therapeutic index and potential for toxicity make it less than desirable for long-term use in the pregnant patient.

Type 1a antiarrhythmic drugs

Quinidine sulfate, procainamide hydrochloride, and disopyramide phosphate have all been proved effective in the treatment of PSVT.¹ Unfortunately, only procainamide is available in a safe intravenous form for short-term therapy. Although adverse effects on the fetus have been documented to occur with any of these agents, no adequate clinical or epidemiologic studies have been completed to date.^{2,25} In addition to the well-known cardiac and noncardiac side effects of these drugs, both quinidine and disopyramide have been reported to cause premature labor.^{26,27} As a group, these medications are of greatest value for maintenance therapy. Their use in pregnancy should be reserved for only the most refractory arrhythmias.

Electric cardioversion

The indications for synchronized, direct-current (DC) cardioversion in the pregnant woman with PSVT are identical to those for the general population. Evidence of syncope, hypotension, angina pectoris, or pulmonary edema mandates immediate conversion to normal sinus rhythm before any drug is administered.³ Also, in patients in whom all of the aforementioned pharmacologic agents fail, DC cardioversion must be considered even in the absence of hemodynamic compromise.

Since the introduction of electric cardioversion in 1962, there have been several reported cases of its use in pregnancy. The rhythm disturbances have ranged from PSVT to ventricular fibrillation, and the gestational ages of the fetuses at the time of cardioversion have ranged from 7 to 36 weeks.²⁸

Electric cardioversion during pregnancy has never been shown to adversely affect the fetus in the short term, and no permanent fetal abnormalities have ever been detected. Fetal heart monitoring during and after cardioversion has revealed a decrease in fetal heart rate and a transient loss of the normal beat-to-beat variability in a number of cases.²⁸

The proper use of DC cardioversion is not the subject of this article, but it would be well to mention that there are three principles to which one must adhere in following this procedure: (1) The shock must be synchronized with the mother's QRS complex in order to avoid the "R-on-T" phenomenon and subsequent induction of ventricular fibrillation. (2) If time allows, the patient must be properly sedated. (3) The initial energy delivered should be as small as possible (in the range of 50 J) and increased thereafter in 50- to 100-J increments until successful cardioversion is attained.³ Also, the physician must be prepared to intubate the patient and temporarily pace the heart following cardioversion should the need arise.

Summary

The treatment of PSVT in the pregnant patient is similar to treatment of PSVT in the general population. Physicians encountering pregnant patients with PSVT need to under-

stand that those measures that are effective in the general population can be safely used in the pregnant patient under monitored conditions. The approach should be systematic. Hemodynamic compromise usually warrants electric cardioversion in a closely monitored setting. Otherwise, the initial treatment should begin with vagal maneuvers followed by pharmacologic therapy. Such therapy may include the use of verapamil, β -blockers, digoxin, or type 1a antiarrhythmic agents. Physicians must be aware of the risk-to-benefit ratios of these drugs in the pregnant patient. Communication lines between the obstetrician and the cardiologist must also be established and maintained during PSVT episodes and, indeed, throughout the pregnancy.

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*"I feel like
I'm about to die...."*

PANIC DISORDER

A DISEASE WITH

Panic attacks are discrete, time-limited episodes that are characterized by a sudden, unexpected, and often overwhelming feeling of terror and intense fear, accompanied by severe physical symptoms. Later in the course of the disturbance, certain situations may become associated with having a panic attack. Many patients believe they are experiencing a heart attack or other life-threatening event and seek emergency attention.

Recent NIMH epidemiologic survey data estimate the lifetime prevalence of panic disorder at 1.6% of the general population.¹

DIAGNOSING PANIC DISORDER

A diagnosis of panic disorder, according to the DSM-III-R,² requires that a patient experience at least four panic attacks within a 4-week period or one or more attacks followed by a month of persistent fear of having another attack.

*"I can't breathe...
I have to get
out of here!"*

MANY DISGUISES

Panic attacks involve four or more of the following characteristic associated symptoms (see Table).

These symptoms develop suddenly, with no apparent organic cause, and build in intensity within 10 minutes of the onset of the first symptom.

Symptoms associated with panic attacks²

- Tachycardia or palpitations
- Chest pain or discomfort
- Sweating
- Shortness of breath (dyspnea) or smothering sensations
- Flashes (hot flashes) or chills
- Dizziness, unsteady feelings, or faintness
- Nausea or abdominal distress
- Choking
- Trembling or shaking
- Depersonalization or derealization
- Numbness or tingling sensations (paresthesias)
- Fear of dying
- Fear of going crazy or losing control

PANIC DISORDER AND PHOBIC AVOIDANCE

Most cases of panic disorder are accompanied by some degree of agoraphobia—the fear of being in places or situations from which escape might be difficult (or embarrassing) or in which help might be unavailable in the event of a panic attack.²

This fear often causes the panic-disorder patient to restrict daily activities dramatically, occasionally to the point of never leaving home.

Please see last page for references and brief summary of prescribing information.

PANIC DISORDER

A NEW INDICATION

The effectiveness of XANAX Tablets (alprazolam) for the treatment of panic disorder with or without agoraphobia was conclusively demonstrated in three short-term, placebo-controlled trials (up to 10 weeks); however, patients with panic disorder have been treated successfully for up to 8 months. The largest of these studies, the Cross-National Collaborative Panic Study, involved more than 500 patients in eight centers in the United States, Canada, and Australia.³

*"Doctor, please.
I need
your help."*

XANAX USUALLY BLOCKS PANIC ATTACKS WITHIN 1 WEEK

Percentage of patients free of panic attacks³

WEEK 1

Placebo (n=259)	16.9%
--------------------	-------

XANAX (n=267)	33.2%*
--------------------------	---------------

WEEK 4†

Placebo (n=259)	27.1%
--------------------	-------

XANAX (n=267)	46.8%*
--------------------------	---------------

10% 20% 30% 40% 50% 60%

* $P < .001$

†End-point analysis involving all patients

FOR XANAX[®] TABLETS

XANAX produced significant relief from panic attacks compared with placebo by the end of the first week of therapy.³

XANAX REDUCES PHOBIC AVOIDANCE

In the same multicenter study, XANAX was significantly more effective than placebo in reducing overall phobic symptoms, as measured on an 11-point physician assessment scale.³

Mean overall phobic-symptom rating^{3}*

*Zero to 10 scale, where 0=no phobias and 10=extremely distressing
†End-point analysis involving all patients

XANAX REDUCES SOCIAL AND WORK DISABILITY

When patients in the Cross-National Collaborative Panic Study were asked to indicate the extent to which their social life and work abilities were impaired by their disorder on a scale from 0 (not at all) to 10 (very severely, cannot work), those who received XANAX showed significantly greater improvement than those who took placebo.³

Mean work impairment rating^{3}*

*Zero to 10 scale, where 0=not at all, 5=moderately, and 10=severely impaired
†End-point analysis involving all patients

Please see last page for references and brief summary of prescribing information.

Tablets
Xanax[®]
alprazolam [Ⓢ]
FIRST FOR PANIC

"I'd forgotten how enjoyable life could be without those attacks...."

PANIC DISORDER

PROPER DOSING

The usual starting dose for panic patients is 0.5 mg t.i.d. Depending on the patient's response, the dose can then be adjusted upward in increments no greater than 1 mg every 3 to 4 days to a maximum of 10 mg/day. Some patients may require a slower dosage titration. In clinical studies, the average daily dose after 8 weeks was 5.7 mg. The risk of dependence and its severity appear to be greater in patients treated with relatively high doses (above 4 mg/day) and for long periods (more than 8 to 12 weeks), as required by panic patients.

Continue incremental dosage adjustment until adequate control of panic attacks is achieved and phobic symptoms are reduced.

SIDE EFFECTS

Most treatment-emergent symptoms and side effects reported by patients who received XANAX Tablets were those generally associated with benzodiazepine therapy, such as drowsiness/sedation and ataxia/impaired coordination. At least mild sedation was reported by 77%

OF XANAX®: ESSENTIAL TO SUCCESS

of patients who received therapy with XANAX Tablets and by 43% of patients who received placebo. Side effects are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

MAINTENANCE AND TAPERING

The necessary duration of treatment for panic-disorder patients responding to XANAX is unknown. After a period of extended freedom from attacks, a carefully supervised, tapered discontinuation may be attempted. Dosage reduction must be individualized according to patient response, and the length of time will depend in part on the dosage level attained. There is evidence that discontinuation may be exceedingly difficult for some patients to accomplish without recurrence of panic-disorder symptoms or the development of withdrawal phenomena.

Dosage should be reduced gradually, never abruptly, by not more than 1 mg/week until a total daily dose of

4 mg is achieved; by 0.5 mg/week until a total daily dose of 2 mg is reached; and by 0.25 mg/week thereafter. Some patients may require an even slower tapering of dosage. Withdrawal reactions may occur when dosage reduction occurs for any reason. This not only includes purposeful tapering but also inadvertent reduction of dose. Therefore, the dosage of XANAX should be reduced or discontinued gradually.

NEW XANAX 2-mg TABLETS FOR PANIC

- Greater convenience in maintenance dosages
- Scored to allow incremental dosing (0.5 mg, 1 mg, or 2 mg)
- New tablet strength more economical for patients

Please see last page for references and brief summary of prescribing information.

Tablets
Xanax
alprazolam [®] ^{IV}
FIRST FOR PANIC

XANAX® Tablets
(alprazolam, © Upjohn)

INDICATIONS AND USAGE

Generalized anxiety disorder, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic.

Panic disorder, with or without agoraphobia.

Effectiveness has been established for up to 4 months for anxiety disorder and 4 to 10 weeks for panic disorder; but panic disorder has been treated open label for up to 8 months with no apparent loss of benefit. The usefulness should be reassessed periodically.

CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines and in acute narrow-angle glaucoma.

WARNINGS

Dependence and withdrawal reactions, including seizures

Physical dependence to XANAX can produce certain adverse clinical events, some life-threatening. These include a spectrum of withdrawal symptoms—the most important is seizure. Even after relatively short-term use at 0.75 to 4 mg per day, there is some risk of dependence; but the risk and severity seem to be greater in patients treated with doses above 4 mg/day for more than 8 to 12 weeks.

Treatment of panic disorder: Dose and risks of XANAX

Panic-disorder patients often need doses greater than 4 mg/day, hence the risk of dependence may be greater than in patients treated for less severe anxiety. Based on studies involving 641 patients, the most frequent symptoms seen during discontinuation were:

Neurologic: Insomnia, light-headedness, abnormal involuntary movement, headache, muscular twitching, impaired coordination, muscle-tone disorders, weakness.

Psychiatric: Anxiety, fatigue and tiredness, irritability, cognitive disorder, memory impairment, depression, confusional state.

Gastrointestinal: Nausea/vomiting, diarrhea, decreased salivation.

Other systems: Weight loss, decreased appetite, sweating, tachycardia, blurred vision. It has not yet been determined if these symptoms are clearly related to dose and duration of therapy. In two controlled trials of the discontinuation of XANAX lasting 6 to 8 weeks, 71% to 93% of patients treated with XANAX compared with 89% to 96% of placebo patients tapered completely off medication. The ability of patients to completely discontinue after long-term therapy has not been reliably determined.

Seizures were reported in 8 of 1,980 patients who took more than 4 mg XANAX daily for over 3 months, generally during abrupt dose reduction. There have been occasional reports of seizures during gradual taper; the risk seems to be greatest 24 to 72 hours after discontinuation.

Status epilepticus and its treatment: Discontinuation of XANAX has been associated with seizures. In most cases a single seizure was reported; however, multiple seizures and status epilepticus have been reported. Treatment is the same as that for status of any cause.

Interdose symptoms: Early morning anxiety and emergence of anxiety symptoms between doses have been reported in panic patients taking XANAX. It can usually be managed with more frequent administration of the same total daily dose or by increasing total dosage.

Risks of dose reduction: Withdrawal reactions may occur with dosage reduction for any reason; dosage should be reduced gradually. (See DOSAGE AND ADMINISTRATION.)

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. (See DRUG ABUSE AND DEPENDENCE AND DOSAGE AND ADMINISTRATION.)

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See DRUG INTERACTIONS.) Use the usual precautions in patients with impaired renal, hepatic, or pulmonary function and regarding prescription size in depressed and suicidal patients. Use the smallest effective dose to avoid ataxia or oversedation, which may be a particular problem in elderly or debilitated patients. Alprazolam plasma half-life may be prolonged in obese patients or those with alcoholic liver disease. There have been rare reports of death in patients with severe pulmonary disease shortly after the start of therapy with XANAX. Episodes of mania and hypomania have been reported in depressed patients. Alprazolam is weakly uricosuric.

Information for patients: For all users of XANAX. Alert patients about:

(1) consumption of alcohol and drugs, (2) not taking any benzodiazepine during pregnancy or while nursing, (3) operating machinery or driving, (4) not increasing the dose due to risk of dependence, (5) not stopping the drug abruptly.

Additional advice for panic patients:

Use of more than 4 mg per day of XANAX for long periods of time may cause severe emotional and physical dependence in some patients, and these patients may find it difficult to stop treatment. In two studies lasting 6 to 8 weeks, 7% to 29% of patients treated with XANAX did not completely taper off therapy. The ability of patients to completely discontinue therapy has not been determined. Also, extended use of high doses appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally minor, but seizure, which can be life-threatening, can occur, especially if dose is reduced too rapidly or stopped abruptly.

Laboratory tests: Not ordinarily required in otherwise healthy patients.

Drug interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine and oral contraceptives can delay clearance of benzodiazepines. **Drug/laboratory test interactions:** No consistent pattern. **Carcinogenesis, mutagenesis, impairment of fertility:**

No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See WARNINGS. **Nonteratogenic effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity, and respiratory problems. **Labor and delivery:** No established use. **Nursing mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric use:** Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or light-headedness.

Central nervous system: Drowsiness, light-headedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. Impaired coordination, irritability, memory impairment, cognitive disorder, dysarthria, anxiety, abnormal involuntary movement, changed libido, muscular twitching, weakness, muscle-tone disorders, agitation, disinhibition, paresthesia, talkativeness, vasomotor disturbances, derealization, dream abnormalities, fear, feeling warm.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, increased salivation, decreased salivation, and abdominal distress.

Cardiorespiratory: Tachycardia/palpitations, hypotension, nasal congestion, chest pain, hyperventilation, upper respiratory infection.

Other: Blurred vision, rigidity and tremor, tinnitus, muscular stiffness and cramps, sweating, skin disorders, rash, change in appetite, micturition difficulties, menstrual disorders, sexual dysfunction, edema, incontinence, infection, dermatitis/allergy, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See WARNINGS.)

To discontinue treatment, dosage must be reduced slowly by no more than 0.5 mg every 3 days.

The following adverse events have been reported with benzodiazepines: dystonia, concentration difficulties, anorexia, slurred speech, jaundice, pruritus, diplopia.

Untreated panic disorder has been associated with depressive disorders and suicide. When treating panic patients, the same caution must be used as in treating patients with depression or suicidal ideation.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia, and galactorrhea have been reported, but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE

Physical and psychologic dependence: Withdrawal symptoms like those noted with sedative/hypnotics and alcohol have been seen after discontinuance of benzodiazepines. Symptoms can range from mild dysphoria and insomnia to a major syndrome including abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The distinction between withdrawal symptoms and recurrence of illness is difficult. Withdrawal typically includes new symptoms, occurs toward the end of taper or shortly after discontinuation, and decreases with time. Recurrent panic disorder recurs early or late, with persistent symptoms similar to the initial presentation. When necessary XANAX should be restarted in adequate dosage.

Withdrawal symptoms, including seizures, may occur after brief therapy with doses of 0.75 to 4 mg/day, but severity and incidence are apparently increased after doses above 4 mg/day, after rapid decrease of dosage or abrupt discontinuation. Dosage should be gradually tapered under close supervision, especially in patients with a history of seizures or epilepsy.

Psychologic dependence is a risk with all benzodiazepines, increasing at higher doses, with long-term use, and in patients with a history of alcohol or drug abuse. Addiction-prone patients should be closely supervised when receiving XANAX and repeat prescriptions limited.

Controlled Substance Class: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported with overdosage of benzodiazepines by themselves or in combination with overdosage of alcohol.

DOSAGE AND ADMINISTRATION

Dosage should be individualized, using the lowest effective dose. The need for treatment should be reassessed frequently.

Anxiety: The usual starting dose is .25 to 0.5 mg t.i.d. Maximum daily dose is 4 mg. Patients who are elderly or debilitated, or have advanced liver disease, may be especially sensitive to benzodiazepines, and the starting dose is 0.25 mg b.i.d. or t.i.d. Reduce dosage gradually, by no more than 0.5 mg every 3 days, or more slowly.

Panic disorder: Many patients required more than 4 mg daily. Mean dosage in studies was 5 to 6 mg/day, with a maximum of 10 mg/day. Treatment may be initiated with 0.5 mg t.i.d. Depending on the response, dose may be increased every 3 or 4 days by up to 1 mg daily. After extended freedom from attacks, dosage should be carefully tapered by, at most, 0.5 mg every 3 days. Some patients may be resistant to all discontinuation regimens.

HOW SUPPLIED

XANAX Tablets are available in 0.25-mg, 0.5-mg, 1-mg, and 2-mg strengths.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

References:

- Regier DA, Boyd JH, Burke JD Jr, et al. One-month prevalence of mental disorders in the United States: based on five epidemiologic catchment area sites. *Arch Gen Psychiatry*. 1988;45:977-986.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987:236-238.
- Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial, I: efficacy in short-term treatment. *Arch Gen Psychiatry*. 1988;45:413-422.

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