Pregnant women often require medical therapy for treatment of various coexisting cardiovascular conditions. The effects of the cardiovascular drugs in pregnant women are discussed in this article.

PHARMACOLOGIC CONSIDERATIONS IN PREGNANCY

Complex physiologic changes occurring during pregnancy in the cardiovascular, pulmonary, renal, gastrointestinal, and endocrine systems may affect the pharmacokinetics of drugs, with several consequences on the fetomaternal unit. 107, 150, 173, 198 Drug absorption may be influenced by the decreased motility of the gastrointestinal tract that occurs during pregnancy. Reduced gastric motility may cause stagnation of drugs in the stomach. 170 Diminished acid secretion, combined with increased production of alkaline mucus, can affect gastric pH and, consequently, the degree of ionization and solubility of drugs. 150, 173 The prolongation of transit time through the small bowel may lead to increased metabolism of drugs in the gut wall131 or, conversely, may allow a more complete absorption with increased bioavailability. 53, 107 In addition, the administration of opiate analgesics or antacids, frequently used during labor, also may delay or decrease drug absorption. 162, 193 During pregnancy, the distribution of drugs is modified by increased plasma volume, total body water, and total body fat. 107, 150, 198 Serum concentration of albumin, the principal drug binding protein, decreases progressively throughout pregnancy. 46 This change, along with altered binding to alacid glycoprotein, 78, 254 increase in fatty acids and lipids, and hormonal changes, may lead to an increase of the unbound drug fraction. 107 Furthermore, the difference in fetal and maternal plasma binding capacity produces a complex situation that also has to be considered in the interpretation of therapeutic and toxic drug concentrations. 8, 107, 150, 198, 254

The metabolism of many drugs is altered during pregnancy; however, these changes are not necessarily clinically significant. 107 The liver has an important role in drug metabolism. Hepatic clearance is dependent on the binding affinity of drugs, hepatic blood flow, and hepatic enzymatic systems. Sex hormones may have opposite effects on the hepatic microsomal oxidase system. 42, 44, 59 For example, estrogens inhibit the microsomal oxidase system for ethylmorphine and hexobarbitone; 44; on the other hand, progesterone enhances hepatic enzymatic activity. 42, 59

The fetoplacental unit plays an active role in metabolism of various drugs. The placenta contains many enzymatic systems that transform several drugs into toxic or nontoxic products.
The fetus also participates in drug metabolism after 6 to 8 weeks of gestation. Placental transfer of drugs depends on maternal and fetal drug concentration, degree of protein binding, placental blood flow, anatomy, and metabolism; and acid-base equilibrium. The acidic pH of amniotic fluid, for example, can function as an "ion trap" for weak basic drugs. 

The excretion of drugs that primarily are cleared by the kidney may be enhanced during pregnancy. Both renal blood flow and glomerular filtration rate are increased markedly. 

Postural changes that occur late in pregnancy also may influence hemodynamics and drug clearance. A modern concept of teratogenesis has to embrace not only the anatomic malformations noted at birth, but also biochemical, physiologic, and behavioral modifications, which are more subtle and may manifest first during childhood or adult life. Teratogenic effects depend on the chemical nature of drugs, duration of exposure, dosage, genetic susceptibility, and gestational age. During blastogenesis (first 14 days), severe insults may result in abortion; however, the blastocyst is relatively resistant to teratogenic agents and there are no known viable malformations generated during this period.

The most vulnerable period of gestation is that of embryogenesis (2 to 8 weeks). Various organ systems are formed during this period and injuries to the embryo will result in morphogenetic alterations. During fetogenesis, the effect of drugs may be similar to that occurring during extrauterine life; however, the systems still in differentiation (that is, the central nervous system) might be damaged. Other effects can be nonspecific, manifested by growth retardation or system dysfunction that become evident after birth. 

As a general principle, all drugs should be avoided as much as possible during pregnancy. If a therapeutic decision has to be made, the risk-benefit ratio should be evaluated carefully. In choosing drugs, toxicity, metabolism, and gestational age are of crucial importance in avoiding untoward effects. If a condition requires drugs potentially harmful to the fetus, the best solution is to avoid pregnancy for the duration of treatment. As previously described, the pharmacokinetics of drugs is modified in pregnancy; because of a multitude of factors, these changes cannot always be predicted and, therefore, close monitoring of therapy, both clinically and by laboratory methods, is necessary.

Another source of concern is the transfer of drugs into breast milk and, consequently, to neonates. Again, this is dependent on the physicochemical characteristics of the compound. Generally, only 1 to 2 per cent of maternal dose appears in milk. Except for some drugs that clearly are contraindicated, there is not enough evidence to allow or to prohibit breast feeding in mothers undergoing drug treatment. Most data regarding drug excretion in human milk are available from case reports. Because of the complexity of mechanisms involved in drug excretion into breast milk, various models and formulas used to estimate plasma milk ratios have limited clinical value. Close monitoring of the infant's ingested dose and plasma levels, as well as close observation for adverse effects or toxicity, therefore are necessary to assure safety.

CARDIAC GLYCOSIDES

Cardiac glycosides have been known to humanity since the ancient Egyptian and Roman era. Used for centuries for different purposes, digitalis emerged as one of the major drugs in the therapy of congestive heart failure, as well as for terminating paroxysmal supraventricular tachycardia and controlling rapid ventricular rates in patients with atrial fibrillation and flutter.

Among various digitalis preparations, digoxin is the most accepted and widely used. During pregnancy, the most common maternal and fetal indications for digoxin use are congestive heart failure and/or supraventricular tachycardia and controlling rapid ventricular rates in patients with atrial fibrillation and flutter. 

68. 74. 81. 121. 130. 189. 196. 201. 211. 223 Only 60 to 80 per cent of an oral dose is absorbed, mostly in the proximal small intestine. As with other drugs, the presence of food or delayed gastric emptying that may occur in pregnancy may retard its absorption. Digoxin is only 20 to 25 per cent bound to proteins; the decreased albumin level seen during pregnancy, therefore, should not affect its serum concentration significantly. Peak level and maximal effect following oral administration are reached after 2 to 3 hours and 4 to 6 hours, respectively. The intravenous (IV) preparation has a rapid onset of action (within 5 to 20 minutes) and a maximal effect within 1.5 to 3 hours. The half life of digoxin is 36 to 40 hours. The volume of distribution (V D) is increased significantly dur
ing pregnancy. For rapid digitalization, the dosage is similar to that in the nonpregnant state—that is, 0.75 to 1.5 mg IV. Digoxin is excreted primarily by the kidneys. During pregnancy, there is a linear correlation between digoxin and creatinine clearance; the dosage, therefore, has to be adjusted when renal function is impaired. The maintenance dose has to be approximately 35 percent of total body stores; it may need adjustments throughout pregnancy in order to obtain optimal therapeutic effect.

In 1972, Rogers and coworkers96 reported that serum digoxin level at term was lower than 4 weeks post delivery in mothers treated with the same maintenance dose. These data could not be confirmed by other authors.6, 31, 130 however, who found digoxin concentration in the therapeutic range at the time of delivery. Luxford and colleagues130 demonstrated that despite increased digoxin and creatinine clearance and increased 24-hour urinary digoxin elimination, serum digoxin level was higher during the third trimester of pregnancy than during the postpartum period.

Several studies79, 104, 240 recently have demonstrated the existence of endogenous digoxin-like substances in pregnant women and neonates. These substances interfere with the radioimmunoassay for exogenous digoxin, leading to reading errors ranging from 0.1 J.Lg per L to more than 2 J.Lg per L. To complicate the situation further, the concentration of these digoxin-like substances changes with gestational age, making it extremely difficult to assess therapeutic levels.240 These data cast doubts on the utility of monitoring digoxin serum concentration during pregnancy and suggest the need to use electrocardiographic and clinical criteria to determine adequacy of digoxin dosing during gestation.

Treatment of fetal conditions is based on the ability of digoxin to cross the placenta. Although this property was well documented by numerous authors,6, 31, 68, 74, 81, 121, 189, 196, 201, 211, 223 the magnitude of digoxin transfer to the fetus is somewhat conflicting. Rogers and coworkers96 found similar concentrations of digoxin in both maternal and fetal blood at the time of delivery. Chan and colleagues31 found lower levels in fetal blood and postulated the existence of a placentental barrier or digoxin. Allonen and coworkers6 also noted lower digoxin concentration in fetuses but at a different gestational age (12 to 16 weeks). In light of the new reports on endogenous digoxin-like substances and their effect on digoxin measurement, it is difficult to interpret these data.

In a study using radioisotopes, Saarikosky and associates201 demonstrated that placental transfer of digoxin occurs fairly rapidly. Five minutes following the injection of H3-digoxin in maternal blood, radioactivity was demonstrated in umbilical cord blood, and by 30 minutes, fetal and maternal blood concentrations of radioisotopes were approximately equal. They also demonstrated that the fetal heart binds digoxin much less avidly than the infant heart. Based on these reports, the fetomaternal digoxin concentration ratio probably ranges from 0.5 to 1.0.

During the past decade, digoxin has been employed with increasing frequency to treat fetal supraventricular tachycardia and congestive heart failure.68, 74, 81, 121, 189, 223 Digoxin may be adequate alone in treating fetal tachycardia.68, 81 In refractory cases, it may be necessary to add a second drug such as verapamilP21 or quinidine.223 As in the nonpregnant state, the addition of quinidine or verapamil may increase the digoxin level significantly. The same precaution regarding drug interactions therefore applies during pregnancy as in the nonpregnant state.

To date, few adverse effects have been observed in fetuses of mothers treated chronically with digoxin. Low birth weight infants occasionally have been born of mothers with cardiac conditions treated with digitalis. It has been postulated that digoxin may affect amino acid transport through the placenta, with consequent growth retardation.248 However, the duration of pregnancy and labor has been noted to be shorter in mothers on long term digoxin therapy.245 Therefore, it is conceivable that the low birth weight reported with digoxin treatment is secondary to prematurity rather than to intrauterine growth retardation.

Despite the above concerns, digoxin is considered a safe drug to use in pregnancy and, to date, there are no reports of teratogenesis in humans. Caution is advised in digitalis administration, however, because overdose can be detrimental to the mother and may be lethal to the fetus.211

Digoxin is excreted in the breast milk and the milk-plasma ratio ranged from 0.59 to 0.9.31.124 The total amount of digoxin ingested daily by the infant has been estimated to be approximately 1/100 of the pediatric recommended dose of 12.5 J.Lg per kg per day.124 No apparent clinical effects were demonstrated in newborns;
digoxin therapy of the mother therefore should not affect breast feeding decisions.31. 124

ANTIARRHYTHMIC DRUGS

Quinidine

Quinidine, a class Ia antiarrhythmic drug, is a dextrosteroisomer of quinine. Both alkaloids have similar properties and spectrum of action; quinidine, however, is more effective in suppressing both supraventricular and ventricular arrhythmias. It is used for cardioversion, as well as for prophylaxis against recurrences of paroxysmal supraventricular tachycardia, atrial flutter, atrial fibrillation, and re-entrant arrhythmia associated with Wolff-Parkinson-White syndrome. It is frequently employed in suppressing ventricular premature beats and ventricular tachycardia.

Quinidine has a depressant effect on the myocardium that is directly proportional to plasma concentration.77 It decreases myocardial automaticity, excitability, and conduction velocity and increases the fibrillation threshold. The diminished conduction velocity and the increased effective refractory period induced by quinidine are very useful in terminating reentry.58 Because of its vagolytic effects, the atrioventricular (A V) conduction may be enhanced in some patients. Quinidine also has (Xadrenergic blocking effects.

Approximately 70 to 80 per cent of an oral dose of quinidine is absorbed.37 Food and antacid may delay the absorption. In patients with congestive heart failure, the decreased volume of distribution (V D) may lead to higher drug levels despite diminished absorption.4o Maximum serum levels are attained within 60 to 90 minutes and the half-life is 6 to 8 hours. Eighty percent is bound to protein and the unbound fraction, therefore, increases during hypoalbuminemic conditions such as gestation.150 Quinidine is metabolized primarily in the liver and some of the metabolites are active. Ten to 20 percent is eliminated unchanged by the kidney251 and alkalinization of the urine may decrease urinary excretion.94 The therapeutic level is 0.5 to 1.6 !Jog per ml; cord blood levels, 0.5 to 1.6 !Jog per ml; and amniotic fluid level, 0.9 !Jog per ml. The low levels may be explained by the fact that quinidine was discontinued 24 hours prior to delivery. No side effects were noted; fetal development was normal and the labor was uneventful.

Quinidine has a minimal oxytocic effect144. 231 that manifests mainly after the onset of spontaneous uterine contraction.231 Fetal thrombocytopenia also was associated with quinidine treatment.135 Toxic doses may cause premature labor, 14 abortion, 141 or damage of the fetal eighth cranial nerve. 14o

However, the large clinical experience with use of this drug in pregnancy has shown an extremely low incidence of side effects and no known teratogenic effects. Quinidine use appears to be safe for both maternal and fetal indications. Quinidine is secreted in the breast milk, and the milk-plasma ratio is 0.71. 8e

Procainamide

Procainamide, synthesized from procaine by substituting an ester linkage with an amide
group, was introduced as an antiarrhythmic agent in 1951. It is very effective in abolishing premature ventricular contractions, ventricular tachycardia, and supraventricular tachycardia associated with Wolff-Parkinson-White syndrome, although it is less effective than quinidine for supraventricular arrhythmia.

It has a depressant effect on the heart, similar to that of quinidine; it decreases automaticity, excitability, conduction velocity, and contractility. The effective refractory period is prolonged and the fibrillation threshold increased. Its anticholinergic activity is less than that of quinidine.

Procainamide can be given orally and parenterally. Following oral administration, approximately 75 to 95 per cent of the dose is absorbed. The absorption may be retarded with delayed gastric emptying, decreased intestinal motility, or intestinal pH changes. Only 10 to 20 per cent is bound to plasma proteins. Peak levels are reached in 45 to 75 minutes after an oral capsule dose. Half-life is about 2.5 to 3.0 hours in patients with no evidence of heart or kidney failure. Therapeutic levels are 4 to 8 J.Lg per ml. Approximately 40 to 70 per cent of a procainamide dose is eliminated unchanged by the kidneys; renal impairment, therefore, may decrease elimination markedly, with a consequent increase in serum levels. Ten to 34 percent of the drug is metabolized in the liver to N-acetylprocainamide (NAPA) at a rate that varies depending on acetylator status. NAPA has less antiarrhythmic potency and its efficacy is limited. The treatment with NAPA probably does not induce antinuclear antibody formation or lupus syndrome, however, as does procainamide. NAPA is eliminated predominantly by the kidneys; its therapeutic range is 9.4 to 19.5 J.Lg per ml. In order to avoid toxicity, both procainamide and NAPA levels have to be monitored closely.

Procainamide can be administered intravenously as 100 mg boluses (25 mg per minute) every 5 to 10 minutes until therapeutic effects are obtained or 1 g is given. Intravenous administration may produce hypotension, QT interval prolongation, and, serious arrhythmias. Nausea, vomiting, and diarrhea are noted more frequently with the oral route but are less pronounced than with quinidine. Central nervous system (CNS) toxicity may manifest as mental depression, hallucinations, and psychosis. Hypersensitivity reaction such as drug fever, agranulocytosis, and skin rashes may occur and drug-induced lupus may develop in 20 to 40 per cent of the patients. Transplacental transfer of procainamide is well documented in two reports of treatment of fetal supraventricular tachycardia. 51, 66 Dumesic and coworkers reported successful control of fetal supraventricular tachycardia and heart failure when procainamide was administered to the mother in addition to digoxin. The fetal arrhythmia was refractory to previous treatment with digoxin alone or in combination with propranolol. After 4 weeks of treatment, the arrhythmia recurred and became more difficult to control, despite increased dose of digoxin and procainamide. Cesarean section was performed and, at delivery, although digoxin levels were equal in the maternal and neonate blood (0.8 J.Lg per ml), procainamide level was higher in maternal blood (15.6 J.Lg per ml versus 4.3 J.Lg per ml in fetus).

A similar therapeutic approach was reported by Given and coworkers. Again, fetal supraventricular tachycardia resistant to the combination of digoxin and propranolol converted with digoxin and procainamide. In this case, fetal tachyarrhythmia also recurred. But the digoxin and procainamide levels at delivery were discordant with those found by Dumesic’s team. Fetal levels were 30 per cent higher for procainamide and 50 per cent lower for digoxin.

NAPA levels in the maternal and fetal blood were 3.0 J.Lg per ml and 3.7 J.Lg per ml, respectively. In both cases, it is unclear whether the therapeutic success was because of synergistic digoxin-procainamide action or procainamide effect alone.

At the present time, there are no data available on procainamide pharmacokinetics in the maternalfetal unit. There is no evidence of teratogenic effects. In order to avoid toxicity, both procainamide and NAPA levels have to be monitored closely.

Procainamide pharmacokinetics in the maternalfetal unit. There is no evidence of teratogenic effects. In order to avoid toxicity, both procainamide and NAPA levels have to be monitored closely.

Disopyramide
Disopyramide, a relatively recent class Ia antiarrhythmic drug, was approved in the
United States in 1977 for the treatment of ventricular arrhythmias. In suppression of premature ventricular contractions, it appears equal to or better than quinidine or procainamide.75 During myocardial infarction, it is useful in reducing PVCs and the frequency of ventricular tachycardia; it is not clear if it can prevent ventricular fibrillation, however. 90 In Europe, it was found to be equal to quinidine in the treatment and prophylaxis of supraventricular arrhythmias.73, 128

Disopyramide has electrophysiologic properties similar to other class I antiarrhythmic agents; it decreases excitability, conduction velocity, automaticity, and contractility. It also prolongs the effective refractory period and action potential duration. It has marked negative inotropic effects and increases systemic vascular resistance.106, 157 These hemodynamic effects, while not clinically evident in patients with normal ventricular function, may be deleterious in patients with limited cardiac function.182 Disopyramide has 10 per cent of the anticholinergic effects of atropine.149 Approximately 80 to 90 per cent of an oral dose is absorbed; peak plasma levels are reached by 1 to 2 hours, and the half-life is about 6 to 9 hours. Approximately 30 per cent was found to be bound to plasma proteins at a concentration of 3 f.Lg per ml; the binding varies directly with serum concentration, however, and may be as high as 90 per cent.159 Forty to 90 percent is eliminated in the urine unchanged; dosage has to be adjusted in renal failure. The remainder of the drug is metabolized in the liver via dealkylation.69 Therapeutic levels are 3 to 6 f.Lg per ml. The oral dose is 300 to 800 f.Lg per day; this dose has to be reduced in hepatic, cardiac, or renal insufficiency.

The majority of untoward effects of disopyramide are caused by its anticholinergic activity and include dry mouth, constipation, blurred vision, and urinary retention. It may precipitate congestive heart failure in patients with ventricular dysfunction and, similar to quinidine, can induce QT prolongation, ventricular tachycardia, or "torsade de pointes."139, 161

Animal studies have shown that disopyramide crosses the placenta. With very high doses, an increased incidence of low birth weight fetuses was observed, but there were no teratogenic effects. There is very little information regarding disopyramide treatment in pregnant women. Shaxted and colleagues210 described a 26-week pregnant patient treated with 600 mg per day for symptomatic ventricular tachycardia. At delivery, the maternal and fetal levels were 2.3 f.Lg per ml and 0.9 f.Lg per ml, respectively. No adverse effects were noted, and the delivery was normal. Leonard and coworkers,115 however, reported the treatment of refractory supraventricular tachycardia in a pregnant woman with mitral valve prolapse in which the administration of disopyramide initiated uterine contractions that resolved when the drug was discontinued.

Disopyramide is secreted in the breast milk in concentrations similar to those in plasma; no adverse effects were noted in the infant. 11 Because of the limited information, the use of disopyramide in pregnancy should be reserved for patients refractory to quinidine.

**Lidocaine**

Lidocaine is a local anesthetic of the amide type that has been used as an antiarrhythmic agent since 1950. During the fifties, lidocaine was employed mainly in the cardiac catheterization laboratory; today it is one of the drugs most commonly used in intensive cardiac care units. Lidocaine is very effective in suppressing ventricular premature beats and ventricular tachyarrhythmias, particularly during acute myocardial infarction, cardiac surgery, and digitalis toxicity. 65 It is of little benefit for supraventricular arrhythmias. Lidocaine depresses automaticity in Purkinje fibers and increases the threshold for ventricular fibrillation.19 The action potential duration is decreased significantly as is, to a lesser extent, the effective refractory period (ERP) in both Purkinje fibers and ventricular muscle. The effect on the ERP of A V node is variable. Lidocaine effectively decreases conduction velocity and suppresses ventricular re-entry in ischemic myocardium. There is no apparent effect on blood pressure or contractility. 165

Lidocaine is administered parenterally; oral administration is ineffective because of extensive metabolism during first pass through the liver. It has immediate onset of action and its half-life is approximately 100 minutes. A loading dose of 1 to 1.5 f.Lg per kg of body weight is followed by continuous infusion. A second dose, usually half of the first dose, may be necessary. Lidocaine is 70 per cent bound to proteins, principally to (X1-acid glycoprotein, and its clearance approximates hepatic blood flow. Any condition or drug that decreases hepatic blood flow, such as liver disease, congestive heart failure, propranolol,23 or cimetidine101; therefore, it may
decrease lidocaine clearance. Prolonged infusion of lidocaine for several days also may decrease its hepatic clearance; the dose therefore should be adjusted after 24, 48, and 72 hours. 13, 28

Lidocaine is metabolized in the liver to two compounds, glycinexylidide and monoethylglycinexylidide. Both metabolites are less active than lidocaine, but they may contribute to its antiarrhythmic activity and CNS toxicity. 20 About 10 per cent of lidocaine undergoes kidney excretion unchanged.

Lidocaine in toxic doses may produce myocardial depression and hypotension; however, CNS side effects most commonly are observed. Paresthesias, blurred vision, dizziness, drowsiness, hallucination, tremor, and seizures may manifest when levels are 5 J.l.g per ml or above. 159

Lidocaine mainly has been used during pregnancy for epidural or local anesthesia. Stokes and colleagues227 reported the use of lidocaine as an antitarrhythmic agent in an 18-week pregnant woman who suffered an acute myocardial infarction and cardiac arrest. The infant was delivered at 38 weeks of gestation with some growth retardation but had normal neurologic examination at birth and at 17 months.

The drug crosses the placenta rapidly. 17, 213 Following maternal administration, it can be detected in the umbilical cord in 2 minutes, and the maternofetal plasma concentration ratio is 0.5 to 0.7. The lower fetal drug concentration may be attributed to lower fetal concentration of (Xl-acid glycoprotein, which is approximately one-third of maternal levels. 254 This hypothesis is supported by Tucker, who has found a lower binding capacity of fetal plasma for lidocaine. Shnider and coworkers213 using ultrafiltration techniques, however, demonstrated similar binding capacities in both fetal and maternal plasma. Lidocaine's metabolism in the fetus also is hepatic.

Shnider and colleagues,212 in a study of 57 mothers treated with lidocaine, observed five infants with CNS depression at birth. Three of these infants had a lidocaine level greater than 3 J.l.g per ml. No apparent evidence of CNS toxicity was noted when the fetal level was below 2.5 J.l.g per ml. The therapeutic range of lidocaine in the nonpregnant state is 1 to 5 J.l.g per ml. If the fetal plasma concentration is 50 to 60 per cent of the maternal level, it probably is safe to have maternal levels below 4 J.l.g per ml in order to avoid maternofetal toxicity.

As a weak base, lidocaine may be trapped by the slightly acidic environment of amniotic fluid. Several studies 1, 25, 178 have shown higher fetal drug concentration during fetal acidosis. In addition, acidosis may increase the unbound fraction of lidocaine, facilitating further fetal trapping. 27

Kim and coworkers97 described a case of accidental lidocaine injection of the fetal scalp during local anesthesia or episiotomy. Fifteen minutes after birth, the newborn manifested severe toxicity, demonstrated by apnea, hypotonia, fixed dilated pupils, and then at 1 hour, seizures. The fetal lidocaine level was 14 J.l.g per ml. With appropriate treatment, the neonate recovered completely, with normal neurologic and behavioral examination at 3 days and at 7 months of age.

The Collaborative Perinatal Project surveyed 293 mothers who had exposure to lidocaine during their first trimester. 76 Lidocaine administration could not be associated with increased risk of any major group of malformations. Anomalies of the respiratory system (three cases), tumors (two cases), and inguinal hernias (eight cases), however, had greater frequency than expected.

Several studies showed that lidocaine does not have deleterious neurobehavioral effects on neonates. 2, 96 Despite the paucity of information of lidocaine's use as an antiarrhythmic agent during pregnancy, study data indicate that lidocaine is safe as long as blood levels are monitored closely.

Mexiletine

Mexiletine (see Medical Clinics of North America, Vol. 72, No.2, 1988), a class Ib antiarrhythmic drug, structurally is very similar to lidocaine. Initially studied as an anticonvulsant drug, it soon became evident that mexiletine possessed antiarrhythmic properties resembling those of lidocaine. It is efficacious in suppressing ventricular premature beats and ventricular tachycardia, but it may not prevent ventricular fibrillation during acute myocardial infarction. 229

Its antiarrhythmic activity seems to be independent of the nature of underlying cardiac condition—that is, it has equal effectiveness in acute and chronic ischemic heart disease, as well as in cardiomyopathy. 30 Mexiletine has a membrane stabilizing effect, a manifestation of its local anesthetic properties. It slows the maximal rate of depolarization of the action potential and shortens the action potential duration in Purkinje fibers. 30, 151, 163, 176, 181, 229, 236, 285
node or His-Purkinje systems, the conduction velocities are decreased and the effective refractory periods may be increased. It has no effect on the normal sinus node, but patients with diseased sinus nodes may develop sinus arrest.30 Mexiletine has no apparent hemodynamic effects, and does not significantly affect the ejection fraction in patients with left ventricular dysfunction. 225

Mexiletine is absorbed almost completely in the proximal small bowel. The delayed gastric emptying that occurs in pregnancy may retard the absorption. The peak level is reached after 1.5 hours.255 Seventy-five percent of the drug is protein bound. First pass hepatic metabolism is only 10 per cent, with bioavailability of 90 per cent following oral administration. The drug is metabolized in the liver. The renal clearance of the unchanged drug is highly dependent on urinary pH, varying from 35 per cent in acid urine to 1 per cent in alkaline urine.1~1 The half-life is 8 to 10 hours in the normal subject but may be prolonged to 15 hours in patients with myocardial infarction.176 The therapeutic range is 0.75 to 2 mg per ml, and it has a narrow toxic-therapeutic window. Following a loading oral dose of 400 to 600 mg, a daily dose of 600 to 120 mg should be sufficient to achieve therapeutic levels. The dosage has to be reduced in patients with chronic liver disease. 163

The adverse effects of mexiletine may occur in 30 to 70 per cent of the patients and are related to plasma concentration. Tremor, diplopia, nausea, and vomiting particularly are frequent. Ataxia, sleep disturbances, fatigue, headache, psychosis, seizures, fever, and rashes also have been reported. Thrombocytopenia and hepatitis are rare complications. Mexiletine also is arrhythmogenic; several authors reported induction of "torsade de pointes."34, 181

In 1980, Timis and coworkers236 reported a case of ventricular tachycardia in a 32-week pregnant patient treated successfully with a daily dose of propranolol 120 mg and mexiletine 600 mg. On this regimen, the trough plasma concentration of mexiletine was 0.3 to 0.6 j.g per L. At 39 weeks of pregnancy, the patient went into spontaneous labor and delivered a normal child. For 6 hours post delivery, however, the infant heart rate was only 90 beats per minute; thereafter, it rose to 120 beats per minute and remained stable throughout the puerperium. The fetal-maternal ratio of mexiletine plasma concentration was 1.0, indicating free transplacental transfer. Mexiletine is secreted in breast milk; however, the daily quantity ingested by the infant is minimal and, therefore, not detectable in plasma.236 Because of very limited experience with this drug, no recommendation can be made until its safety in pregnancy is documented further.

Amiodarone

Amiodarone (see Medical Clinics of North America, Vol. 72, No. 2, 1988), a benzofuran derivative, was introduced in the late 1960s as an antianginal drug. Since introduction, however, its unusual class III antiarrhythmic properties became evident and it has been widely employed in the management of various supraventricular and ventricular arrhythmias. Amiodarone prolongs the duration of action potential and reduces the maximum rate of depolarization.218 It increases the refractory period and prolongs repolarization.217 It does not affect resting membrane potential. It depresses the sinus. node membrane (see PR, QRS, and QTc intervals. 60. 156 In patients with Wolff-Parkinson-White syndrome, it increases refactoriness in both the retrograde and antegrade pathways. 246

Amiodarone has noncompetitive a- and 13-adrenergic blocking activity, and is a potent coronary and systemic vasodilator.32 It also reduces myocardial contractility and heart rate and may lower the blood pressure. Absorption of amiodarone following oral administration is variable and unpredictable; however, it is estimated to be approximately 40 per cent. Its oral bioavailability ranges from 22 to 86 per cent. 114, 192 Peak plasma concentration is reached within 2 to 10 hours, but a therapeutic effect may take up to 21 days to occur. The metabolism of amiodarone is not fully elucidated. After absorption, the drug is widely distributed into various tissues. Being lipophilic, it accumulates mostly in adipose tissue but also is taken up extensively by the lung, the liver, and cardiac and skeletal muscle. 114 The drug undergoes hepatic metabolism and, of its metabolites, desethylamiodarone (DEA) accumulates in plasma during chronic therapy. Only 1 per cent of the dose is excreted unchanged in the urine. Biliary excretion probably plays an important role.114 Protein binding is about 96 per cent. 192 The elimination half-life ranges from 13 to 100 days, with an average of 40 to 50 days.114 To initiate oral treatment, a loading dose of 800 mg to 1600 mg per day is given for 1 to 3 weeks, then decreased to 600 to 800 mg per day for 1 month, and, thereafter, to a maintenance dose of 400 mg per day. The...
Amiodarone has numerous adverse effects;70 the most severe is pulmonary fibrosis that carries a 10 per cent mortality and may be reversible if the drug is discontinued. Amiodarone may produce sinus bradycardia, A V block, QT prolongation, and "torsade de pointes." Anorexia, nausea, vomiting, and elevation of transaminases are common. Amiodarone has a high iodide content— that is, 75 mg of elemental iodide in a 200 mg dose of drug; both hypoand hyperthyroidism may occur. Corneal microdeposits may affect the patient's vision. Photosensitivity and bluish gray discoloration of the skin develop not infrequently. CNS toxicity (tremor, ataxia, and dizziness) or peripheral neuropathy is uncommon, but reported. The adverse effects may persist months after discontinuation of drug.

Amiodarone interacts with numerous drugs; it potentiates the effects of warfarin and increases serum concentration of digoxin, diltiazem, quinidine, procainamide, and phenytoin.

Transplacental transfer of amiodarone has been documented in several reports.7, 129, 137, 179, 195 McKenna and coworkers137 treated a 34 week pregnant patient who had paroxysms of atrial flutter-fibrillation associated with Wolff-Parkinson-White syndrome and resistant to quinidine. A loading dose of 800 mg per day for 1 week was followed by a maintenance dose of 400 mg per day. At 41 weeks, the patient delivered a normal child that was slightly bradycardic for 48 hours (104 to 120 beats per minute). Amiodarone and DEA plasma levels in the infant at birth were approximately 25 per cent of the mother's levels.

Pitcher and colleagues179 also reported a case of a patient with atrial tachycardia resistant to propranolol, digoxin, and verapamil, treated successfully with amiodarone during the last 3 weeks of pregnancy. Transplacental transfer of amiodarone and DEA was 10 per cent and 25 per cent, respectively. Neither the mother nor the child had untoward effects.

Robson and associates195 described two additional cases in which amiodarone was administered during pregnancy for longer time periods. In the first case, amiodarone was given at a dose of 200 mg per day to control atrial fibrillation associated with mitral stenosis. The patient became pregnant while on treatment, and the drug was continued through the pregnancy. At 34 weeks, she delivered a healthy baby. Maternal drug levels through pregnancy were 0.5 to 0.7 mg per ml. The cord drug level was 0.05 mg per ml and the amniotic fluid level was 0.02 mg per ml. Desethylamiodarone levels in maternal plasma, cord blood, and amniotic fluid were 0.8 mg per L, 0.15 mg per Land 0.11 mg per L, respectively. In the second case, amiodarone (400 mg per day) was given in addition to metoprolol (50 mg per day) to control atrial tachycardia in a 22-week pregnant patient. At 39 weeks, she delivered a healthy child. Again, amiodarone and DEA levels in cord blood were 10 and 20 per cent of maternal levels, respectively.

Treatment of fetal supraventricular tachycardia with amiodarone during pregnancy was attempted in two cases.7, 129 Armoux and coworkers7 described a patient with fetal supraventricular tachycardia and congestive heart failure resistant to digoxin alone or in combination with either sotalol or verapamil who was successfully treated with digoxin and amiodarone. Started at 31 weeks of pregnancy, amiodarone was continued until term (38 weeks). A normal infant was delivered with an amiodarone level at 12.7 per cent of maternal level. The comparison of doses and fetomaternal levels shows a linear concentration-dosage relation. Maternal levels, therefore, may be used as an indicator for fetal levels.

The conclusion from the above reports is that amiodarone crosses the placenta; however, fetal levels are approximately 10 per cent of maternal levels. The concentration of amiodarone in the placenta is higher than in adipose tissue, but the significance of this finding is not clear.

In the previously described case reports, no harmful effects on the fetus were observed. Until more data are available, however, caution is recommended regarding the use of amiodarone during pregnancy.

Amiodarone is secreted in breast milk in quantities significant enough to be detected in infant blood.137 The effect of chronic amiodarone exposure in neonates is unknown; breast feeding, therefore, is not recommended to women who are treated with amiodarone.

Verapamil

Verapamil (see Medical Clinics of North America, Vol. 72, No.1, 1988) a papaverine derivative, initially was used in the 1960s as an antianginal agent. The drug was approved in the United States in 1981 for angina pectoris and supraventricular tachyarrhythmias. It is very effective in terminating A V nodal and
bypass tract re-entrant tachycardias. In patients with atrial flutter or fibrillation and multifocal atrial tachycardia, verapamil slows the ventricular response and sometimes causes conversion to sinus rhythm. It generally is not used for ventricular arrhythmias unless they are precipitated by coronary spasm. Other indications are angina, hypertension, and hypertrophic cardiomyopathy.

Verapamil blocks the slow influx of calcium and probably of sodium in the sinus and A-V nodes. It decreases the conduction velocity and increases the refractory period in nodal tissue. The direct effect of slowing the sinus node generally is overwhelmed by sympathetic activation secondary to peripheral vasodilation.

Oral verapamil is absorbed quite completely, is 90% per cent bound to proteins, and reaches peak levels in 1 to 2 hours. During first pass through the liver, however, it is eliminated extensively, so the drug has a bioavailability of only 10 to 20 per cent. In the liver, the drug is metabolized to several compounds, of which norverapamil is most active. The elimination half-lives of verapamil and norverapamil are 3 to 7 hours and 8 to 10 hours, respectively. The hepatic metabolism of verapamil may decrease with chronic administration. In the patient with advanced liver disease (that is, cirrhosis), the half-life of verapamil may increase dramatically, up to 14 to 16 hours or more. The onset of action with IV preparation is 10 to 15 minutes and its duration is approximately 6 hours. The usual dose employed is 0.15 mg per kg given intravenously at 1 mg per minute.

In patients with compromised sinus or A-V node, verapamil may precipitate bradycardia, asystole, hypotension, or A-V block. It may increase digoxin levels. The most frequent non-cardiac side effects are headache, dizziness, nausea, constipation, and peripheral edema. It may induce galactorrhea and hyperprolactinemia. The therapeutic indications for verapamil are varied. These agents have proven efficacious in multiple conditions occurring during pregnancy, including dysfunctional labor, hypertension, asthma, and A-V block. It may decrease uterine tone and uterine contractions. The majority of reports regarding verapamil administration during pregnancy are from Europe. The drug was used for different indications: maternal and fetal supraventricular arrhythmia, premature labor, severe pre-eclampsia, and fetal tachyarrhythmias.

Klein and colleagues described a 38-year-old pregnant hypertensive patient treated with verapamil for supraventricular tachycardia resistant to digoxin and propranolol. The arrhythmia converted to sinus rhythm after 5 mg of IV verapamil. The fetal monitoring tracing showed a transient decrease in fetal heart rate but no decelerations. One month later, the patient delivered uneventfully. Wolf et al. also studied six pregnant patients who were administered a single oral dose of 80 mg of verapamil 49 to 564 minutes prior to delivery. The umbilical vein levels were 171 to 26 per cent of maternal concentration. The same investigator also reported one case of successful cardioversion of fetal supraventricular tachycardia with digoxin and verapamil without adverse effects. Successful fetal cardioversion with verapamil also was described by other authors.

Despite several reports demonstrating no fetal side effects or teratogenesis, the experience with chronic verapamil therapy is limited. Further studies are therefore necessary in order to assess its safety. Verapamil is secreted in breast milk, but the total daily dose ingested by the baby is very small and no apparent neonatal effects have been noted.

**~ADRENERGIC BLOCKERS**

The therapeutic indications for ~adrenergic blocking drugs are varied. These agents have proven efficacious in multiple conditions occurring during pregnancy, including dysfunctional labor, hypertension, asthma, and A-V block. It may decrease uterine tone and uterine contractions. The majority of reports regarding verapamil administration during pregnancy are from Europe. The drug was used for different indications: maternal and fetal supraventricular arrhythmia, premature labor, severe pre-eclampsia, and fetal tachyarrhythmias. With some exceptions, however, the treatment of fetal tachyarrhythmias has been rather disappointing.

The desire to ensure both maternal health and normal fetal growth has led to questions regarding the safety of ~blocker use during pregnancy. In this article, the world experience with ~adrenergic blockers in pregnancy is reviewed and recommendations regarding their clinical use are proposed. The effects of ~blockers on the fetus and neonate are reviewed elsewhere in this issue (see article by Kornbluth and colleagues) and the drugs themselves are discussed extensively by Frishman in the *Medical Clinics of North America* (Vol. 72, No.1, 1988).

**Adrenergic Influences on Maternal-Fetal Physiology**

~Adrenergic activity during pregnancy assumes physiologic importance because of the direct effects the sympathetic nervous system has on umbilical blood flow and uterine tone and contractility (Table 1). Because of the diff...
Cardiovascular Drugs in Pregnancy

Table 1. Adrenergic Influences on Maternal-Fetal Physiology

<table>
<thead>
<tr>
<th>STIMULATION</th>
<th>BLOCKADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-Receptor</td>
<td>f-Receptor</td>
</tr>
<tr>
<td>Fetal heart rate</td>
<td>-</td>
</tr>
<tr>
<td>Maternal heart rate</td>
<td>-</td>
</tr>
<tr>
<td>Umbilical blood flow</td>
<td>-</td>
</tr>
<tr>
<td>Uterine activity</td>
<td>t</td>
</tr>
</tbody>
</table>

No effect; t increases; ! decreases.

difficulty in studying humans and the need to separate direct from indirect sympathetic effects, most experimental work on umbilical blood flow has been conducted in the pregnant ewe. Oakes and coworkers\(^{165}\) studied the effects of propranolol and isoproterenol in nonlaboring, anesthetized pregnant sheep that were near term. During fetal or maternal infusion of the j3-blocker, there was a significant decrease in umbilical blood flow and in the maternal and fetal heart rates. Uterine blood flow and systemic blood pressure remained unchanged. With isoproterenol infusion, there was an increase in umbilical blood flow and only a small increment in fetal heart rate. It, therefore, may be concluded that j3-adrenergic tone affects basal umbilical blood flow and a disturbance in sympathetic inputs potentially could be harmful to the developing fetus.

a-Agonists influence umbilical blood flow indirectly through their action on uterine blood vessels. When a low dose of norepinephrine was infused directly into a uterine artery, a profound reduction in uteroplacental blood flow developed.\(^{110}\) A direct action of norepinephrine on the umbilical circulation has not been demonstrated.\(^{3,33}\)

In the myometrium, there are adrenergic receptors of the a- and j3-types. Stimulation of the j3-receptor results in myometrial relaxation, whereas increased a-adrenergic stimulation potentiates contractility.\(^{136}\) In animal studies, propranolol has been shown to reverse the myometrial depressant action of j3-stimulation.\(^{242}\) Barden and colleagues\(^{70}\) also demonstrated this effect of propranolol in pregnant humans. In their study, pregnant women at term were selected for elective induction of labor. Maternal and fetal heart rates, maternal blood pressure, and intrauterine pressure were measured in all patients. After an infusion of oxytocin to eight patients, epinephrine was administered and caused a consistent inhibition of uterine activity, while accelerating maternal heart rate. These effects were completely reversed by prior propranolol treatment. Norepinephrine infusion potentiated uterine activity, while decreasing maternal heart rate and increasing blood pressure. Prior propranolol treatment had no effect, whereas the a-adrenergic blocker, phentolamine, significantly attenuated the actions of norepinephrine. After these studies, all of the subjects had normal term vaginal deliveries.

The influence of the autonomic nervous system on normal fetal circulation also has been studied in the fetal lamb preparation. In a report by J oelson and Barton,\(^{91}\) isoproterenol administered to the fetus caused an increase in heart rate and a decrease in blood pressure, whereas propranolol caused only a slight drop in heart rate. It was apparent that the effects of j3-adrenergic blockade in the unstressed and undisturbed fetus were minimal. When the fetus is stressed, however, stimulation of the j3-receptor may provide an important reserve for neonatal adaptation. Thus, maternal treatment with j3-blockers may impair the response to fetal distress.

Clinical Experience

Different j3-adrenergic blocking drugs have been used in pregnancy. Despite their growing use, several adverse reactions have been reported (Table 2).

**Propranolol.** Propranolol, the oldest of the available nonselective j3-blockers, has been studied the longest in pregnancy. The drug is a class II antiarrhythmic agent, and j3-blockade appears to be the main mechanism for its antiarrhythmic effect.\(^{81}\) 159 A membrane stabilizing effect also may be involved, however, particularly at higher concentrations.\(^{8,65}\)

During pregnancy, propranolol can affect uterine contractility (see Table 1). Barden and coworkers\(^{166}\) have demonstrated that propranolol...
101, given to pregnant women, blocks the inhibitory effects of epinephrine on myometrial activity. The administration of propranolol therefore may facilitate an increase in uterine contractility. 

The pharmacokinetics of propranolol during pregnancy are similar to those in the nonpregnant state. O'Hare and colleagues169 administered propranolol to six healthy pregnant volunteers between 32 and 36 weeks of gestation. There were no significant changes in elimination half-life, clearance, VD, and bioavailability. Perruca and coworkers,142 however, found that the protein binding of propranolol decreased during pregnancy.

Propranolol readily crosses the placenta39. 43, 67. 112, 184, 233 and, at delivery, the fetal serum concentration is equal to or less than the maternal concentration. The unbound fraction of propranolol is higher in fetal plasma, how ever, probably because of low concentration of X1-acid glycoprotein. Because of decreased hepatic metabolism and altered protein binding, the serum concentration of propranolol may be increased in the neonate during the first days of life. 67. 184

Several fetal and neonatal adverse effects were reported.21. 43. 54. 132. 166. 184. 232. 239 Pruyn and associates184 noted that 10 to 11 neonates from mothers treated chronically with propranolol had intrauterine growth retardation. Extrapolating data from an animal study,165 they suggested that propranolol may decrease umbilical blood flow and, consequently, fetal nutrition. While reported by many other authors21. 43. 54. 132. 166. 187. 232 the true incidence of intrauterine growth retardation is unclear. In some prospective studies,21, 54. 166. 232 the incidence of intrauterine growth retardation was only 3 to 4 per cent (4 of 94 pregnancies). Furthermore, two of these four mothers who had small babies delivered normal babies in subsequent pregnancies, despite continuous treatment with propranolol. 166 Redmond,187 in an extensive review of human and animal literature, concluded that the evidence implicating propranolol in growth retardation is suggestive but inconclusive.

There are many hypothetical mechanisms by which propranolol may induce growth retardation. A decrease in cardiac output combined with plasma volume contraction and increased systemic vascular resistance occurring during hypertension in pregnancy may decrease uterine blood flow.187 Propranolol has been shown to reduce umbilical blood flow in pregnant ewes.165 Other postulated mechanisms may involve a decreased peripheral conversion of T4 to T3 and a theoretical effect on neurotransmitters that may affect the brain's influence on fetal growth. 187

Turnstall and colleagues239 described a delay in the onset of respiration of newborns when propranolol was administered to the mother prior to cesarean section. Another major source of concern is the effect of propranolol and of 13-blockade therapy in general on the fetal response to hypoxia. During asphyxia, several hormonal, metabolic, and circulatory adaptive mechanisms are activated. Most responses are mediated through catecholamines and 13-receptors. As has been demonstrated in experimental animal studies,85. 91 propranolol therapy may be particularly deleterious during these circumstances of fetal distress. 13-blockade also may be responsible for lack of fetal heart acceleration provoked by sound stimulation166 and persistently negative throughout the nonstress test and contraction stress test. 132

To date, propranolol has not been demonstrated to be teratogenic. However, three cases of congenital malformations have been associated with propranolol therapy during pregnancy; for example, pyloric stenosis, crepitus of the hip, and tracheoesophageal fistula. 22. 29. 167 It is not clear at all if this is a casual occurrence or a true teratogenic effect of propranolol. In any case, if the last hypothesis is correct, these malformations probably are very rare.

Although the information concerning use of propranolol during pregnancy has expanded steadily, its safety is still somewhat controversial. Despite favorable reviews,123. 199 there is a potential for side effects29, 184. 187. 205 that should be anticipated by the clinician.

Propranolol is excreted in breast milk. 12. 93. 116 Karlberg and coworkers93 showed that propranolol is secreted into the breast milk in a dosedependent manner and the milk-plasma ratio is approximately 1.0. Bauer and colleagues12 found a milk-plasma ratio of 0.4 to 0.6; they estimated that the daily dose ingested by the infant probably is 1 per cent of the recommended pediatric daily dose. No adverse effects were observed in infants breast fed by mothers treated with propranolol. However, the newborn hepatic microsomal enzyme systems are immature and propranolol may accumulate. Careful observation of these infants is therefore recommended.

Metoprolol. Metoprolol is a 13-specific blocking agent. It is similar in its effectiveness to other nonselective 13-adrenoreceptor blocking drugs used in the treatment of angina pectoris4 or essential hypertension. 15 Because of its primary 131-selective properties, the drug
theoretically would not interfere with 132-mediated peripheral vasodilatation or 132 effects on uterine tone.

In pregnancy, metoprolol has been used primarily to control hypertension61, 84, 202, 203 or tachyarrhythmias.24 Its metabolism during pregnancy is increased and, therefore, half-life, serum concentration, and bioavailability are decreased.83 The most plausible explanation is that steroid hormones increase the activity of the hepatic mono-oxygenase system, which is involved in metoprolol metabolism.83 Protein binding is not altered during pregnancy.

Metoprolol crosses the placenta, and the fetal/maternal serum concentration ratio is approximately 1.0.122,203 Because of redistribution and/or relative immaturity of hepatic enzymatic systems in the newborn, the serum concentration of metoprolol increases four-fold during the first hours of life, but then declines over 5 to 20 hours.122

Metoprolol alone or combined with hydralazine was studied in 101 pregnant hypertensive patients.203 The metoprolol group experienced lower perinatal mortality (2 per cent versus 8 per cent) and a lower incidence of intrauterine growth retardation (11.7 per cent versus 16.3 per cent). Theoretically, this might be explained by metoprolol's lack of action on uterine tone (132 effect) and 13-mediated vasodilatation. No differences in Apgar score, gestational age, or birth weight were noted.

Hogstedt and colleagues,84 in a recent controlled trial, compared the combination of metoprolol and hydralazine with non pharmacologic management of hypertension in 161 pregnant patients. The outcome for the neonates with respect to birth weight, head circumference, Apgar score, incidence of respiratory distress, bradycardia, and hypoglycemia was similar in both groups, confirming the results previously reported.220 There was one case of fetal malf ormation in each group. This may be an unrelated event because the combination metoprolol-hydralazine was started during the second and third trimesters. To date, no cases of fetal malformation induced by metoprolol have been reported, but experience during the first trimester is lacking.

Sandstrom204 has shown the combination of metoprolol and hydralazine to be superior to hydralazine and thiazide for the treatment of pregnant hypertensive patients with regard to maternal well-being, fetal intrauterine growth, 10-minute Apgar scores, and perinatal mortality.

Despite encouraging data, caution is recommended. Kjellmer and associates,98 in an animal study, showed that 131-adrenoreceptor blockade is potentially dangerous in cases of fetal asphyxia. These data are in agreement with previous experimental results obtained with the nonselective 13-blocker propranolol. 29, 85

Metoprolol is secreted in breast milk,119 but the daily fetal quantity ingested by the neonate is very small. Unless hepatic function in the newborn is markedly impaired, breast feeding should not be discouraged.

Finally, metoprolol appears to be safe in pregnancy, but the data are still limited. Pending further studies assessing metoprolol's safety in pregnancy, caution is recommended.

Atenolol. Atenolol is another relatively selective 13-adrenergic blocking agent used to treat hypertension during pregnancy. 113, 127, 138, 200, 220. 238 Its fetal effects are described in the article by Kornbluth and colleagues in this issue.

Like metoprolol, atenolol has negative inotropic and chronotropic activity. However, it has insignificant partial 1–1 mimetic activity and weak membrane stabilizing properties. 194

Transplacental transfer of atenolol is well documented. 113, 138 Although there is a three- or six-fold individual variation in plasma atenolol concentration in each patient studied, its concentration was found to be equal in maternal and fetal blood (ratio 1.0). 138 Atenolol is secreted in breast milk and no effects were noted in atenolol-exposed babies; breast feeding, therefore, need not be discontinued. 119

Pindolol. Pindolol is a 13-adrenergic blocking agent that has partial intrinsic sympathomimetic activity. It also has some membrane stabilizing effects, but much less than propranolol's. 8

The potential advantage of intrinsic agonist activity in a 13-blocker is that the decrease in heart rate and cardiac output at rest is not as pronounced as with nonagonistic 13-blocking drugs. The exercise-induced increase in heart rate and cardiac output still is blunted, however.204 This may be of particular benefit in patients with ventricular dysfunction or those prone to bradycardia.65

Theoretically, pindolol may be particularly advantageous in pregnancy because the lack of effects on resting heart rate and cardiac output, combined with a direct vasodilator effect, are not expected to compromise uterine blood flow197 or to decrease basal fetal heart rate. 87

Pindolol crosses the placenta, and the fetomaternal concentration ratio is less than 1.0. 71

Elimination half-lives in fetus and mother are 1.6 hours and 2.2 hours, respectively. Dubois and coworkers compared acebutolol, pindolol,
and atenolol in 56, 38, and 31 pregnant hypertensive patients, respectively. In the pindolol group, the birth weight was significantly higher than in the atenolol group (3345 g versus 2745 g). Apgar score, gestational ages, fetal heart rate, and frequency of hypoglycemia were not affected by pindolol treatment. Two cases of malformation were reported in the pindolol group, however: cleft palate (pindolol started at 29 weeks of gestation) and vesicoureteral reflux (second full pregnancy on pindolol in a mother with asymmetrical segmental renal hypoplasia).

In another study, pindolol was compared with methyldopa in 32 consecutive patients with pregnancy-induced hypertension. Maternal blood pressure was controlled better in the pindolol group. Furthermore, a drop in creatinine levels and an increase in creatinine clearance was noted in mothers treated with pindolol. No difference was observed between the two groups in regard to intrauterine growth. Apgar score, or fetal morbidity. The birth weight was similar in the two groups (2850 g).

Nonstress tests were normal and no bradycardia was observed in the pindolol group.

Rosenfeld and coworkers randomly assigned 44 consecutive pregnant hypertensive patients to two treatment groups: hydralazine alone (21 patients) or hydralazine and pindolol (23 patients). These investigators found a lower incidence of maternal side effects such as dizziness or headaches in the combination therapy group. No differences were noted in the two groups concerning birth weight, gestational ages, hypothermia, hypoglycemia, Apgar score, or mode of delivery. Two major malformations were noted in the hydralazine group and neonatal thrombocytopenia was noted in the combination group.

Although preliminary reports are favorable for recommending the use of pindolol in pregnancy, the information available is still limited. Additional experience is needed to confirm the safety of pindolol during pregnancy.

Labetalol. Labetalol, like propranolol, blocks both β and α-adrenergic receptors. But labetalol is unique in that it also has both α-adrenergic blocking properties and direct vasodilatory activity. Labetalol crosses the placenta. The fetomaternal concentration ratio is 0.5. Its clearance and volume of distribution are not altered during pregnancy.

There have been a number of favorable reports describing the safe use of labetalol in pregnancy.

Lamming and coworkers randomized 26 patients with pregnancy-induced hypertension in two groups: one treated with labetalol (14 patients) and one treated with methyldopa (12 patients). Improvement of renal function and a better control of blood pressure were observed in the labetalol group. The incidence of spontaneous labor and Bishop score also were higher in the labetalol group. Theoretically, the higher incidence of spontaneous labor could be caused by myometrial relaxation induced by a-blocking and the 132-mimetic activity of labetalol. Furthermore, Nyland and colleagues dem onstrated that uterine blood flow was not affected despite significant reduction in blood pressure. There also is evidence that labetalol may promote fetal lung maturation. Michaep45 observed higher than expected lecithin-sphingomyelin ratio in amniotic fluid as early as 31 weeks of gestation in patients treated with labetalol. This effect probably is mediated by 132-mimetic activity because salbutamol has similar effects. Several studies showed that no fetal adverse effects were associated with labetalol treatment.

Labetalol also is useful in the management of severe pre-eclampsia or eclampsia. Michaep47 randomly assigned 90 patients with severe hypertension (diastolic blood pressure greater than 105 mm Hg) to receive IV labetalol (45 patients) or IV diazoxide (45 patients). The control of blood pressure was better in the labetalol group. A precipitous drop in blood pressure (60/40 mg Hg) was noted only in the diazoxide group (eight patients). No fetal bradycardia, hypoglycemia, hypothermia, or malformations were noted. There was a higher operative delivery rate in the diazoxide group. The results obtained in several studies regarding the use of labetalol for all types of hypertension during pregnancy, including hypertensive emergencies, are very encouraging. However, more information concerning its safety is warranted and, therefore, caution is recommended.

Labetalol is secreted in breast milk and no adverse effects were noted in neonates. The nursing babies should be monitored closely, however.

Other l3-Blockers. The experiences with acebutolol, oxprenolol, and sotalol are reviewed in the article by Kornbluth and coworkers.

Recommendations

The evidence currently available regarding the safety of l3-blocking agents in pregnancy is inconclusive. It, therefore, appears preferable to offer other effective drugs already proven
safe during pregnancy, prior to using ~-blockers. If a ~-blocker is to be used, the following guidelines may be useful.

1. Consider the pregnant woman (and the fetus) receiving ~-blockers to be a high-risk patient, deserving special care during both pregnancy and labor.

2. Whenever possible, avoid the use of ~-blocker therapy during the first trimester.

3. Use the lowest possible therapeutic dose; combinations of low doses of ~-blockers and other agents may be the optimal drug therapy.

4. When possible, taper drug therapy at least 2 to 3 days prior to delivery, both as a way of limiting the effects of ~-blockers on uterine contractility and of preventing neonatal complications secondary to ~-blockade.

5. The use of ~-blockers with ~1-selectivity or intrinsic sympathomimetic activity, or the use of an ~-blocker (that is, labetalol) may be preferable, in that these. drugs theoretically would be less likely to interfere with ~2-mediated uterine relaxation and peripheral vasodilation.

A comprehensive recommendation regarding the use of ~-blockers is extremely difficult to state because of the absence of any large scale clinical use of these agents in pregnant patients. Further studies are needed to define drug pharmacokinetics in mother and fetus. Future trials hopefully will address these questions and further clarify the role ~-blocking agents should play in therapy in controlling maternal disease states, as well as their effects on fetal and neonatal well-being.

**SODIUM NITROPRUSSIDE**

Sodium nitroprusside (SN) is one of the most potent drugs available for treatment of hypertensive emergencies. It was approved in the United States in 1974. Chemically, sodium nitroprusside is disodium pentacyanonitrosylferrate. The hypotensive component of sodium nitroprusside is the free nitroso (NO) group which interferes with calcium influx and activation, producing relaxation of vascular smooth muscle but not of uterine smooth muscle. SN directly relaxes arteriolar and venous smooth muscle, decreasing preload and afterload. Blood pressure decreases and heart rate increases slightly. Renal blood flow and glomerular filtration rate are preserved; plasma renin activity is increased. Nitroprusside reacts rapidly with hemoglobin, yielding methemoglobin and cyanide. The latter compound undergoes metabolism in the liver or kidney to thiocyanate, which is excreted in the urine. Cyanide also may be eliminated as cyanomethemoglobin or cyano-cobalamin. In case of liver diseases, hepatic immaturity, and excessive administration, cyanide ions may poison the cytochrome oxidase system, leading to anaerobic metabolism and, clinically, metabolic acidosis.

SN is given intravenously in light-protected tubing. The initial rate of infusion should be 0.1 to 0.2 J.Lg per kg per minute and slowly increased (5 to 10 J.Lg every 5 to 10 minutes) until the desired effect is obtained or a dose of 10 J.Lg per kg per minute is reached. Cyanide, thiocyanate, methemoglobin level, and arterial pH should be monitored periodically.

Prolonged use of SN and/or renal failure may result in excessive thiocyanate formation and/or accumulation that initially manifests with CNS symptoms (tinnitus, blurred vision, confusion, psychosis). Plasma thiocyanate above 10 mg per 100 ml is toxic ana above ~O mg per 100 ml, fatal. Other adverse effects are methemoglobinemia, increased intracranial pressure, headache, rash, nausea, abdominal pain, and muscle twitching.

During pregnancy, SN has been used to control the blood pressure during intracranial aneurysm surgery9, 249 or severe gestational hypertension1, 74. SN was demonstrated to cross the placenta in both human21, 226 and animal studies56, 115, 156, 191, 247.

The experimental data concerning the pharmacodynamic effects of SN in pregnant animals still are conflicting. 56, 115, 156, 191, 247. Ring and coworkers191 compared SN with hydralazine in phenylephrine-induced hypertension in nearterm pregnant ewes. Both agents were equally effective in lowering the blood pressure. However, only hydralazine counteracted the effects of phenylephrine-that is, increasing uterine blood flow, heart rate, and cardiac output. Wheeler and associates247 found that nitroglycerin and nitroprusside have similar effects on uterine flow, that is, mostly increased or, in a few cases, unchanged. Ellis and coworkers156 found that SN increases uterine blood flow in pregnant ewes, whereas Lieb and coworkers115 noted a significant (25 to 35 per cent) decrement. Naulty and colleagues156 observed a decrease in blood pressure without any changes in uterine blood flow.

Paul and coworkers174 described four severe pre-eclamptic patients with hypertension resistant to diazoxide and other "conventional methods" treated successfully with nitroprusside. The only fetus alive at the onset of therapy was...
delivered uneventfully. Four other patients with severe pregnancy-induced hypertension and refractory congestive heart failure were treated successfully with SN. One premature infant expired. The other infants were free of side effects or malformations. The infusion rate varied from 0.013 /Lg per kg per minute to 2.75 /Lg per kg per minute. Measurements made in one case showed equal but negligible (0.1 ILg per ml) concentrations of cyanide in maternal and fetal blood.

Shoemaker and coworkers described a 24-week pregnant patient with severe pre-eclampsia not controlled by hydralazine and magnesium sulfate. Blood pressure was controlled with SN and labor was induced with pitocin. Fifteen hours after the onset of SN therapy, the patient delivered a 478 g stillborn infant. The nitroprusside dose was 3.9 /Lg per kg per ml. The level of cyanide in the fetal liver was less than 10 /Lg per ml, with toxic levels reported to be 30 to 40 /Lg per ml. The authors speculate that fetal death was caused by severe eclampsia.

In summary, nitroprusside is a very effective but toxic drug. Until further studies clarify its pharmacodynamics, kinetics, and safety during pregnancy, caution is recommended.

**HYDRALAZINE**

Hydralazine has been used extensively during pregnancy since the early 1950s. It is one of the agents of choice in the management of hypertensive emergencies as well as for maintenance therapy, alone or in combination with other antihypertensive drugs.

It has a direct relaxing effect on arteriolar vascular smooth muscle, producing a decrease in systemic vascular resistance and vasodilatation. The hydralazine effects appear to be mediated through guanosine 3' ,5' -monophosphate (cyclic GMP).

Peripheral vasodilatation triggers compensatory sympathetic discharge, which increases the heart rate and cardiac output. Plasma renin activity is increased and, consequently, sodium and water retention may lead to edema formation. Regional vasodilatation is not equal; splanchnic, cerebral, coronary, and renal vascular beds are more dilated than skin and muscle vascular beds. Venous dilatation is minimal and, therefore, postural hypertension is infrequent.

When given orally, the drug is absorbed almost completely from the gastrointestinal tract. The systemic bioavailability of hydralazine after its first pass through the liver depends on acetylator type. Obviously, slow acetylators will have a higher blood level and will be more prone to toxicity. Peak plasma concentration is reached within 0.5 to 2 hours, and the hypotensive effect lasts 6 to 8 hours. Parenteral administration is less influenced by acetylator type; onset of action is within 10 to 20 minutes and may last 2 to 4 hours. For the treatment of hypertensive emergency during pregnancy, Pritchard and colleagues suggested an initial IV dose of 5 mg that can be increased by 5 to 10 /Lg every 20 minutes.

With IV administration, flushing, headache, dizziness, and palpitations may be prominent. Nasal congestion, nausea, vomiting, diarrhea, fatigue, and sleep disturbances also may be common. Approximately 5 to 10 per cent of the patients may develop a lupus erythematosus-like syndrome. The syndrome is more common in slow acetylators and when doses of more than 200 mg per ~ day are used. It may become evident after 2 months of treatment and resolve slowly (6 months to years) after withdrawal of drug. Other rare complications are blood dyscrasias, rash, and fever.

Experimental data from animal models concerning the effect of hydralazine on uterine blood flow have been controversial. Ring and associates reported an increase in uterine blood flow in pregnant hypertensive sheep, whereas Ladner and coworkers showed the opposite effect in normotensive pregnant sheep. Several studies investigated the effects of drugs on intervillous blood flow in hypertensive pregnant women. In all of these studies, the administration of IV hydralazine did not change the mean intervillous blood flow significantly. Looking at individual results, however, uterine blood flow was decreased in 9 of 13 patients in the Lunell study, in contrast to the Suomo study, in which the flow decreased in only 4 of 10 patients.

Vink and coworkers investigated the effect of IV administration of dihydralazine on maternal blood pressure, uterine activity, fetal heart rate, and growth retardation in 33 hypertensive pregnant patients. Dihydralazine, 12.5 mg, lowered the diastolic blood pressure from more than no mm Hg to 70 to 90 mm Hg in 5 minutes in 30 of 33 patients. Nineteen fetuses had deceleration in fetal heart rate concomitantly with the decrease in blood pressure; 13 of these 19 fetuses had intrauterine growth retardation; and three fetuses were stillborn. Only one fetus from the group without deceleration had intrauterine growth retardation.
Uterine activity was not influenced by hydralazine administration. According to the authors, fetal deceleration was caused by inability of the uteroplacental unit to compensate for the acute reduction in blood pressure.

Spinnato and colleagues27 also observed a higher incidence of cesarean section deliveries secondary to fetal distress in pre-eclamptic or eclamptic patients treated with hydralazine.

Kuzniar and coworkers108 observed that the hemodynamic effects of hydralazine are more pronounced in patients with pregnancy-induced hypertension than in those with essential hypertension. These observations indicate that lower doses and a gradual decrease in blood pressure are particularly beneficial in the high risk group of patients with pre-eclampsia.

In summary, the use of IV hydralazine in hypertensive emergencies such as pre-eclampsia and eclampsia is very effective in lowering the blood pressure and preventing hypertensive encephalopathy or intracranial hemorrhages. Hydralazine therapy is associated with the risk of fetal distress, however, particularly in patients with a reduced uteroplacental reserve. In these patients, a precipitous decrease in blood pressure clearly is associated with fetal distress and should be avoided. Some authors11 believe that the reduction in uterine blood flow is caused by catecholamine-induced vasoconstriction rather than a reduction in perfusion pressure alone. They suggest that the concomitant administration of antiadrenergic agents, such as methyldopa, as well as avoidance of unnecessary reduction in blood pressure may explain the low incidence of fetal distress noted in their patients.

Hydralazine crosses the placenta freely and also appears in small amounts in milk.15 To date, no teratogenic effects of hydralazine have been reported.

NITRATES

Organic nitrates, esters of nitric acid, have been used extensively for more than a century for the treatment of the symptoms of ischemic heart disease. Their use more recently was extended to congestive heart failure. Nitrates are very potent dilators, predominantly of venous vessels; arterial dilatation increases at high doses. Nitrate effects lead to a decrease in venous return and, consequently, to lower right and left ventricular end diastolic pressures. Systemic vascular resistance is not changed significantly, heart rate is unchanged or increased, and cardiac output usually is unchanged. In higher doses, nitrates may lower the blood pressure and cardiac output, which triggers a compensatory sympathetic activation with reflex tachycardia and vasoconstriction.

Nitroglycerin also decreases pulmonary vascular resistance. The antianginal effects mostly are because of a decrease in myocardial oxygen requirements by reducing pre- and afterload. Nitrates are metabolized in the liver. Nitroglycerin metabolites have only 10 per cent of nitroglycerin’s potency and their half-life is approximately 40 minutes. Following sublingual administration, the peak plasma concentration is reduced in 4 minutes and half-life is 1 to 3 minutes. Intravenous administration is used mostly in acute ischemic syndromes and congestive heart failure.89 It also is used to control systemic hypertension after and during coronary artery bypass surgery.

Continuous exposure to nitrates may lead to early development of tolerance.1, 171, 172, 188, 234 These problems probably may be avoided by increasing the dosing interval and allowing nitrate-free intervals of at least 10 hours over 24 hours.11, 171, 172 Most common side effects are headache, dizziness, and postural hypotension; syncopal episodes are not common. During pregnancy, IV nitroglycerin was used to control severe pregnancy-induced hypertension.86, 219 Having a very small molecular weight and being unchanged, nitroglycerin easily crosses the placenta.38 Experimental data in pregnant ewes47 showed a fetomaternal arterial blood concentration ratio of 0.15. The authors advanced the hypothesis that the low fetal levels probably are caused by rapid metabolism, poor placental transfer, or widespread binding.

Snyder19 and Hood86 and their colleagues used nitroglycerin to control the elevation of blood pressure that occurs during tracheal intubation in pre-eclamptic patients. Nitroglycerin not only successfully lowered the basal blood pressure, but also blunted the hypertensive response to intubation. No evidence of fetal compromise was noted.

Cotton and colleagues38 studied the hemodynamic effect of IV nitroglycerin coupled with
blood volume expansion in six pre-eclamptic patients. The mean gestational age was 37.3 ± 3.6 weeks. Nitroglycerin alone effectively reduced the mean arterial blood pressure by 27.5 per cent. The hypotensive effect was blunted by volume expansion. In two patients in whom blood pressure was lowered suddenly, fetal deceleration and bradycardia were observed. In the other three patients, a flat fetal heart rate with an average beat-to-beat variability of less than 5 beats per minute was noted. The authors suggested that this probably is because of a loss of cerebral autoregulation and increased intracranial pressure induced by nitroglycerin.

In summary, it appears that nitrate treatment is not free of side effects, and the information available regarding their use during pregnancy is very limited. Of particular concern are the effects on uterine blood flow, oxygen delivery, and fetal hemodynamics. Further studies are needed to clarify their effects and safety during pregnancy; therefore, no recommendation can be made at this time.

CONCLUSION

There are many clinical situations that require the use of cardiovascular medications in pregnancy. It is hard to evaluate drugs during pregnancy, so the safety experiences with many medications are limited, but certain drugs (digoxin, quinidine, b-blockers, a-methyldopa, hydralazine) have been used with relative safety to both mother and fetus. It always is best to avoid medications in pregnancy but, when necessary, drugs for cardiovascular disease may be used when the risk-benefit ratio is favorable.

REFERENCES

27. Burney RG, DiFazio CA, Foster JH: Effects of pH on
68. Golichowski AM, Caldwell R, Hartsough A, et al: Pharmacologic cardioversion of intrauterine supra-
ventricular tachycardia. J Reprod Med 30:139-144, 1985
69. Grant AM, Marshall RJ, Ankier SI: Some effects of
disopyramide and its N-dealkylated metabolite on
isolated nerve and cardiac muscle. Eur J Pharmacol
70. Greene HL, Graham EL, Werner JA, et al: Toxic and
therapeutic effects of aniodarone in the treatment of
cardiac arrhythmias. J Am Coll Cardiol 2:11141128,
1983
of pindolol across the placenta in hypertensive
72. Habib A, McCarthy JS: Effects on the neonate of
propranolol administered during pregnancy. J Pediatr
91:801-811, 1977
73. Hartel G, Loughia A, Kontinnen A: Disopyramide in the
prevention of recurrence of atrial fibrillation after
electroconversion. Clin Pharmacol Ther 15:551-555,
1974
74. Heaton FC, Vaughan R: Intrauterine supraventricular
tachycardia: Cardioversion with maternal digoxin.
Obstet Gynecol 60:749-752, 1982
75. Heel RC, Brogden RN, Speight TM, et al: Disopyramide:
a review of its pharmacologic properties and
therapeutic use in treating cardiac arrhythmias. Drugs
15:331-368, 1978
76. Heinenon OP, Slone D, Shapiro S: Birth Defects and
Drugs in Pregnancy. Littleton, MA, Publishing
Sciences Group, 1977
effects of six clinically used antiarrhythmic agents. Ann
Intern Med 91:229-238, 1979
78. Herengren L, Ehrnebo M, Boreus LO: Drug binding to
plasma proteins during human pregnancy and in
the perinatal period. Dev Pharmacol Ther 6:11a
124, 1983
79. Hicks JM, Brett EM: Falsey increased digoxin con
centrations in samples from neonates and infants.
Ther Drug Monit 6:461-464, 1984
80. Hill LM, Malkiasian GD: The use of quinidine sulfate
in the perinatal period. Dev Pharmacol Ther
15:331-368, 1978
treatment of fetal atrial flutter and congestive heart
82. Hoffman BF, Rosen MR, Wit AL: Electrophysiology and
pharmacology of cardiac arrhythmias. VII. Cardiac
effects of quinidine and procainamide. Am Heart J
90:117-122, 1975
increase in metoprolol metabolism. Clin Pharmacol Ther
37:688-692, 1985
controlled trial of metoprolol-hydralazine treatment in
hypertension during pregnancy. Acta Obstet Gynecol
Scand 64:50-10, 1985
in the fetal lamb during asphyxia in relation to j3-
adenoreceptor stimulation and blockade. Acta Physiol
Scand 105:195, 1979
nitroglycerin in preventing the hypertensive response to
tracheal intubation in severe pre-eclamptics (abstract).
Anesthesiology 59:A423, 1983
rate during treatment of maternal hypertension with j3-
118(Suppl):95-97, 1984
88. Inoue H, Unno N, Quc MC, et al: Level of verapamil in
89. Jaffe AS, Roberts R: The use of intravenous nitroglycerin
in cardiovascular disease. Pharmacotherapy
2:273-280, 1982
disopyramide in prophylaxis of arrhythmias following
91. Joelson I, Barton MD: The effect of blockade of the j3-
receptors of the sympathetic nervous system of the
fetus. Acta Obstet Gynecol Scand 3(Suppl)48:75-79,
1979
92. Jouppila P, Korkinen P, Koivula A: Effect of antiht yp-
ertensive drugs on placental and fetal blood flow. In
Kurjak A, Kossoff G (eds): Recent Advances in
Ultrasound Diagnosis. Amsterdam, Elsevier Science
Publishers, 1984, pp 68-74
93. Karlberg B, Lundberg D, Aberg H: Excretion of
propranolol in human breast milk. Acta Pharmacol
Toxicol13:222-224, 1974
macology of antiarrhythmic agents. Cardiovasc Clin
16:287-305, 1985
elimination in patients with Congestive heart failure or
epidural anesthesia for cesarean section with lidocaine
and bupivacaine. Anesthesiology 57:A403, 1983
97. Kim WY, Pomerance J, Miller AA: Lidocaine intoxication
in a newborn following local anesthesia for episiotomy.
Pediatrics 64:643-645, 1979
adrenergic blockade reduces fetal tolerance to asphyxia.
Acta Obstet Gynecol Scand 118:75-80, 1984
99. Klein V, Repke JT: Supraventricular tachycardia in
pregnancy: Cardioversion with verapamil. Obstet
of fetal supraventricular tachyarrhythmias. J Clin
Ultrasound 13:265, 1985
37:688-692, 1985
nal heart disease. Pharmacotherapy
16:287-305, 1985
angina pectoris with pindolol: The significanc e of
intrinsic sympathomimetic activity of j3-blockers. Am
Heart J 104:496, 1982
106. Kotter V, Linderer T, Schroder R: Effects of disopyramide
on systemic and coronary hemodynamics and
myocardial metabolism in patients with coronary artery
disease: Comparison with lidocaine. Am J Cardiol
46:469-475, 1980
107. Krauer B, Krauer F, Hytten F: Drug prescribing in
pregnancy. In Lind T (ed): Current Reviews in
Obstetrics and Gynecology. Edinburgh, Churchill
Livingstone, 1984
Cardiovascular Drugs in Pregnancy


193. Roberts RB, Shirley MA: The obstetrician's role in

Cardiovascular Drugs in Pregnancy

673
and sustained therapy. Am J Cardiol 49:411-419, 1982


