Drug Interactions

Clinical Significance of Drug-Drug Interactions

Philip D. Hansten, *Pharm. D*

FIFTH EDITION

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PREFACE

The fifth edition of *Drug Interactions* has undergone some substantial changes. Part II (Drug Effects on Clinical Laboratory Results) has been deleted from the book; due to the steadily increasing volume of information, it has become impossible to do justice to both drug interactions and drug effects on laboratory tests. It is planned that the laboratory material will be published separately, with the help of persons who have a special interest in clinical laboratory medicine.

A great deal of information has been published on drug interactions since the last edition, and about 200 interacting pairs have been added. The concise format of previous editions has been maintained to allow rapid access of information and to keep the size of the book within reason. In an effort to maintain clinical relevance, nearly all works cited deal with studies in humans, and all statements refer to humans unless specifically stated otherwise. A basic understanding of pharmacologic and physiologic principles has been assumed in order to keep the discussions as concise as possible.

The continued acceptance of this book has been most gratifying. It has now been translated into Japanese, German, Spanish, and Portuguese. I would also like to acknowledge those persons who helped with the preparation of this edition. The bulging files of journal articles were tamed by Debbie Emrich, Margaret Fanning; Denise Hansten, and Michelle Hansten. Ms. Fanning also prepared the initial material on the smoking-drug interactions included in this edition. Dr. Edward Hartshorn provided both encouragement and invaluable updates of the drug interaction literature; Drs. Leslie Hendeles, Timothey Self, and many others contributed useful information on specific interactions.

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INSTRUCTIONS TO USERS

INDEX

The index is the key to the effective use of this book. The drug-drug interactions are arranged as much as possible by drug or drug class, but interactions for a given drug may appear in several locations in the book. For this reason, the index *must* be consulted to ensure finding the desired drug-drug interaction.

CLINICAL SIGNIFICANCE RATING:

All of the drug-drug interactions in this book have been assigned to one of three categories of clinical significance, and these are indicated by differing type faces used both in the index and in the text of the book.

Bold type—Major Clinical Significance: includes those interactions which are relatively well documented and which have the potential of being harmful to the patient.

Italic—Moderate Clinical Significance: includes those interactions for which more documentation is needed and/or the potential harm to the patient is less.

Roman—Minor Clinical Significance: includes those interactions which may occur but which are least significant because of one or more of the following factors:

1) documentation is poor.
2) potential harm to the patient is slight.
3) incidence of the interaction is quite low.

The decision as to the best category for a given drug-drug interaction was based on the severity of the potential interaction, the predictability of the adverse consequences, the amount and quality of literature documenting the existence of the interaction, and finally, the author's own opinions based on personal experience and theoretical considerations. It is important to remember that because of differences in diseases, doses of drugs, routes and duration of administration, renal and hepatic status, etc., an interaction in the "major" category may produce no ill effects, whereas an

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interaction assigned a "minor" classification may produce a severe adverse drug interaction. Thus, the unique conditions of the individual patient must always be kept in mind when evaluating the clinical significance of drug interactions.

It is important to note that the presence of an interaction in this text (especially if assigned a "minor" rating) should not necessarily be interpreted to mean that it is felt to be of potential clinical significance. Some interactions have been included specifically to demonstrate the tenuous nature of the documentation.

CONTENTS

CHAPTER 1

Antiarrhythmic Drug Interactions

AMIODARONE INTERACTIONS

DRUGS	DISCUSSION

Anticoagulants, Oral[373–377]

MECHANISM: Not established. Amiodarone may reduce oral anticoagulant metabolism. Also, since hyperthyroidism enhances the hypoprothrombinemic response to oral anticoagulants, patients who develop amiodarone-induced hyperthyroidism may develop an increased anticoagulant effect.

CLINICAL SIGNIFICANCE: Patients on chronic warfarin therapy have developed excessive hypoprothrombinemia following initiation of amiodarone therapy.[373–377] Several of these patients developed bleeding.[373,376,377] In nine patients on chronic warfarin therapy, the addition of amiodarone resulted in a mean increase in the prothrombin time of approximately 100%.[376] A mean decrease in the warfarin dose of one-third was necessary to maintain the prothrombin time within the therapeutic range. In ten other patients, amiodarone consistently increased the hypoprothrombinemic response to warfarin.[377] In this study the warfarin dose had to be reduced by about one-third to one-half to achieve the desired prothrombin time following the initiation of amiodarone. The increase in hypoprothrombinemic response to warfarin may last long after the amiodarone is discontinued. In four patients on warfarin, the potentiating effect of amiodarone continued for a period of 1.5 to 4 months.[376] The onset of the increased warfarin effect following initiation of amiodarone therapy has not been well studied, but available evidence indicates that enhanced hypoprothrombinemia becomes apparent within 2 to 4 days of concomitant therapy. The hypoprothrombinemia may continue to increase for several more days.[373,374] Bleeding episodes secondary to this interaction usually occur 1 to 4 weeks following the initiation of amiodarone, although bleeding could appear sooner or later.

MANAGEMENT: In patients receiving oral anticoagulants, it would be preferable to avoid the use of amiodarone. If amiodarone is used, the hypoprothrombinemic response to oral anticoagulants should be monitored carefully. Because the onset of the interaction is delayed in some patients, the prothrombin time should be monitored for several weeks following initiation of amiodarone therapy. Because the inter-

DRUGS	DISCUSSION

action may have a long duration, warfarin dosage may need to be adjusted for months following discontinuation of amiodarone.

Aprindine (Fibocil)[372]

MECHANISM: Not established.

CLINICAL SIGNIFICANCE: Two patients on chronic aprindine therapy developed increased serum aprindine levels and symptoms such as nausea, ataxia, and lightheadedness following initiation of amiodarone therapy (1200 mg daily, then 400 to 600 mg daily.)[372] The authors reported that in general patients receiving both drugs tend to require less aprindine than those receiving aprindine alone. More data are needed to establish the incidence and magnitude of this purported interaction.

MANAGEMENT: One should be alert for evidence of altered aprindine response if amiodarone therapy is initiated or discontinued.

Digitalis Glycosides[368–371]

MECHANISM: Not established. Both pharmacokinetic and pharmacodynamic interactions may be involved.

CLINICAL SIGNIFICANCE: Following the observation of unexpectedly high plasma digoxin levels and neurotoxicity in several patients who were receiving amiodarone concurrently, seven patients stabilized on chronic digoxin therapy were given amiodarone (600 mg daily).[368] The plasma digoxin concentrations were increased during the next 4 days by an average of approximately 70%. Although the plasma digoxin concentrations increased in all of the patients, only four developed symptoms consistent with digoxin toxicity. In two other patients on chronic digoxin therapy, a 0.4 and 0.7 ng/ml increase in serum digoxin occurred when the dose of amiodarone was raised from 200 mg to 600 mg daily. A control group of six similar patients receiving digoxin alone did not experience increased plasma digoxin concentrations. However, in a subsequent study of five patients receiving chronic digoxin, the administration of amiodarone (800 mg daily for 5 days, then 400 mg daily) did not affect the serum digoxin concentration.[369] The reason for the disparate results in these two studies is not clear. Nevertheless, until more conclusive data are available one should assume that amiodarone can increase serum digoxin levels. Others have noted sinus arrest in three patients receiving combined therapy with amiodarone and digoxin.[370,371] Although the sinus arrest could have been due to a pharmacodynamic and/or pharmacokinetic interaction between amiodarone and digoxin, this possibility remains largely speculative at present. In summary, the bulk of the evidence indicates that amiodarone is capable of increasing plasma digoxin concentrations.

MANAGEMENT: One should be alert for evidence of altered digoxin response if amiodarone is initiated or discontinued. Plasma digoxin determinations would be useful in following this interaction.

DRUGS	DISCUSSION

Disopyramide (Norpace), Mexiletine[121]

MECHANISM: Not established. Combined pharmacologic effects may be involved.

CLINICAL SIGNIFICANCE: Isolated cases of prolongation of the QT interval and ventricular arrhythmias have been reported in patients receiving amiodarone plus other antiarrhythmic drugs such as disopyramide and mexiletine.[121] The incidence and magnitude of this potential interaction is not known.

MANAGEMENT: Carefully monitor the cardiac status of patients receiving combined therapy with amiodarone and other agents such as disopyramide or mexiletine (especially at the beginning of combined therapy).

Lidocaine[141]

MECHANISM: Combined depression of the sinus node.

CLINICAL SIGNIFICANCE: A 64-year-old man with sick sinus syndrome developed severe sinus bradycardia following local anesthesia with 15 ml of 2% lidocaine while on amiodarone therapy (600 mg/day).[141] He responded to cardiac massage, atropine, and isoproterenol. The authors proposed that the reaction resulted from the combined effects of amiodarone and lidocaine. More study is needed.

MANAGEMENT: Until more is known about this purported interaction, cardiac status be monitored closely if lidocaine is administered systemically or locally to patients receiving amiodarone.

Quinidine[121]

MECHANISM: Not established. Both pharmacodynamic and pharmacokinetic interactions may be involved.

CLINICAL SIGNIFICANCE: A patient on long-term quinidine therapy (1200 mg daily) developed atypical ventricular tachycardia ("torsades de pointes") and a prolonged QT interval shortly after an injection of amiodarone (150 mg in pulmonary artery).[121] These effects did not recur when quinidine was subsequently administered alone. Another patient receiving quinidine (1200 mg/day) and amiodarone (200 mg/day) developed atypical ventricular tachycardia following routine bicycle ergometry. In addition, a healthy subject was given quinidine (1200 mg daily) and 6 days later amiodarone (600 mg daily) was added. After 3 days of amiodarone administration, the plasma quinidine level was increased by about twofold, and the QT interval was prolonged in comparison to that seen the quinidine alone. In summary, preliminary evidence indicates that amiodarone may interact with quinindine on both a pharmacodynamic and pharmacokinetic basis.

MANAGEMENT: When amiodarone is added to quinidine therapy, one should monitor the cardiac status (e.g., QT interval prolongation) and, if possible, serum quinidine levels.

DRUGS	DISCUSSION

Anticoagulants, Oral[104,125,126]

MECHANISM: Not established.

CLINICAL SIGNIFICANCE: A patient stabilized on warfarin (3 mg/daily) and disopyramide developed a twofold increase in warfarin requirements when the disopyramide was stopped.[104] Other causes for the increased warfarin requirements could not be found. However, disopyramide had little effect on the hypoprothrombinemic response to warfarin in three other patients.[125] It has been proposed that disopyramide-induced hemodynamic changes could affect hepatic clotting factor synthesis,[125,126] thus affecting the prothrombin time. In summary, there is little evidence to support an effect of disopyramide on warfarin response, but one should be aware of the possibility.

MANAGEMENT: Until more information is available, monitor patients for altered anticoagulant response if disopyramide is started or stopped.

Antidiabetics[127,128,389]

MECHANISM: Not established.

CLINICAL SIGNIFICANCE: Isolated cases of hypoglycemia associated with disopyamide therapy have been reported,[127,128,389] but the incidence of this finding is not established. It has been suggested that predisposing factors for disopyramide-induced hypoglycemia may be old age, and serious impairment of renal or hepatic function.[389]

MANAGEMENT: One should be alert for evidence of enhanced hypoglycemic response to antidiabetic drugs if disopyramide is given concurrently.

Beta-Adrenergic Blockers[122–124,140]

MECHANISM: Not established. Combined pharmacologic effects may be involved.

CLINICAL SIGNIFICANCE: Two patients with supraventricular tachycardia developed severe bradycardia after receiving intravenous practolol and then intravenous disopyramide.[122] One of the patients progressed to asystole and died. In studies of healthy subjects, no pharmacodynamic interactions on left ventricular function were noted when the use of propranolol (Inderal) and disopyramide in combination was compared to either drug alone.[123,140] Further, concurrent administration of disopyramide and propranolol does not appear to affect the pharmacokinetics of either drug.[124] In summary, there is only limited clinical information indicating an interaction between disopyramide and practolol. However, the severity of the possible interaction is such (one patient died), that it cannot be ignored.

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DRUGS	DISCUSSION

MANAGEMENT: Until more clinical information is available, one should administer disopyramide (especially if given intravenously) only with caution and careful monitoring to patients receiving practolol or other beta-adrenergic blockers.

Diazepam (Valium)[124]

MECHANISM: None.

CLINICAL SIGNIFICANCE: Studies in healthy subjects indicate that concurrent use of disopyramide and diazepam does not alter the disposition of either drug.

MANAGEMENT: No special precautions appear necessary.

Digitalis Glycosides[129–131,384]

MECHANISM: None.

CLINICAL SIGNIFICANCE: Three studies involving a total of 24 patients indicated that disopyramide does not affect the disposition of digoxin.[129–131] A subsequent study found a reduction in digoxin half-life in five healthy men given 600 mg/day of disopyramide.[384] However, this was balanced by a reduction in digoxin volume of distribution resulting in no change in the steady-state serum digoxin concentration.

MANAGEMENT: No special precautions appear necessary.

Lidocaine[132]

MECHANISM: Combined cardiodepressant effects.

CLINICAL SIGNIFICANCE: Isolated cases have been reported of impaired intraventricular conduction and ventricular asystole in predisposed patients receiving combined therapy with disopyramide and lidocaine.

MANAGEMENT: Patients receiving combined therapy with disopyramide and lidocaine should be monitored closely, especially in the presence of preexisting impairment of myocardial function of conduction disturbances.

Phenytoin (Dilantin)[132–135]

MECHANISM: The hepatic metabolism of disopyramide may be enhanced by phenytoin-induced enzyme stimulation. Also, disopyramide and phenytoin may exert additive cardiodepressant effects.

CLINICAL SIGNIFICANCE: Data from several patients indicate that phenytoin increases the elimination of disopyramide.[133–135] The magni-

DRUGS	DISCUSSION

tude of the reductions in serum disopyramide appear large enough to reduce the response to disopyramide. However, serum levels of the major metabolite of disopyramide (mono-N-dealkyldisopyramide) are increased, and there is some evidence that this product may have antiarrhythmic activity.[133–134] Thus, it is not yet clear whether the therapeutic response to disopyramide would be reduced by concurrent use of enzyme inducers such as phenytoin. A pharmacodnamic interaction between disopyramide and phenytoin has also been proposed based on a patient who developed an idioventricular rhythm and atrial standstill while receiving both drugs.[132] It should be noted that any pharmacodynamic interaction between phenytoin and disopyramide would occur as soon as sufficient serum levels of both drugs are achieved, while the stimulation of disopyramide metabolism by phenytoin would occur gradually over a period of about 7 to 10 days.

MANAGEMENT: One should be alert for evidence of altered disopyramide response if phenytoin is given concurrently.

Potassium Salts[136]

MECHANISM: The cardiovascular toxicity of disopyramide may be increased by elevated potassium levels.

CLINICAL SIGNIFICANCE: A patient developed conduction disturbances and hypotension which was attributed to the combined effects of disopyramide and potassium supplementation.[136] The serum disopyramide level was 10.8 μg/ml (about twice the upper limit of the therapeutic range), and the serum potassium was 6.9 mEg/L. The degree to which elevated serum potassium levels would predispose to disopyramide toxicity in patients with therapeutic serum levels of disopyramide is not established. The likelihood of elevated serum levels of both disopyramide and potassium would increase in a patient with serious renal impairment, and such patients may be at greater risk of this interaction.

MANAGEMENT: One should be alert for electrocardiographic evidence of disopyramide toxicity (e.g., QRS widening) if potassium supplementation is also given, especially if large doses of disopyramide and potassium are used or if renal function is impaired.

Quinidine[124,137]

MECHANISM: The mechanism for the small changes in serum levels of disopyramide and quinidine is not established. Combined cardiodepressant effects may occur since both drugs are type I antiarrhythmic agents.

CLINICAL SIGNIFICANCE: In healthy subjects quinidine administration has been shown to produce small increases in serum disopyramide levels, while disopyramide produces small decreases in serum quinidine levels.[124,137] Also, anticholinergic effects such as dry mouth,

DRUGS	DISCUSSION

blurred vision, and urinary retention were more common with concurrent therapy with both drugs than with either drug alone.[137] It seems unlikely that the degree of increase in serum disopyramide following quinidine would be sufficient to produce toxicity unless the preexisting disopyramide level was at the upper end of the therapeutic range. Significant additive electrocardiographic effects from disopyramide and quinidine were not noted in healthy subjects,[137] but this does not rule out such effects in patients with cardiac disease.

MANAGEMENT: One should be alert for evidence of enhanced disopyramide effect and anticholinergic side effects if quinidine is given concurrently.

Rifampin (Rimactane, Rifadin)[134]

MECHANISM: Rifampin stimulates the hepatic metabolism of disopyramide.

CLINICAL SIGNIFICANCE: Twelve patients with recently diagnosed tuberculosis were given disopyramide (200 to 300 mg as a single dose) before and 2 weeks after starting therapy with rifampin.[134] Serum disopyramide levels were reduced to about 50% in the presence of rifampin, and the amount of disopyramide excreted unchanged in the urine (% of dose) fell to about one-fourth of that seen without rifampin. The study was complicated by the fact that some of the patients were given isoniazid in addition to the rifampin. In summary, it appears that rifampin is capable of lowering serum disopyramide to subtherapeutic levels in at least some patients.

MANAGEMENT: One should be alert for evidence of altered disopyramide effect if rifampin is started or stopped. Serum disopyramide levels would be useful in monitoring this interaction.

LIDOCAINE INTERACTIONS

DRUGS	DISCUSSION

Ajmaline[2]

MECHANISM: Lidocaine and other antiarrhythmic agents such as ajmaline can exert a combined cardiac depressant effect.

CLINICAL SIGNIFICANCE: One case has been briefly reported in which a 67-year-old woman developed a worsening of her cardiac failure following combined therapy with ajmaline and intravenous lidocaine.[2]

MANAGEMENT: Combined therapy with antiarrhythmic drugs is sometimes necessary but should be accompanied by increased vigilance toward detection of adverse effects.

Aminoglycosides, Polymyxin B[159]

MECHANISM: Enhanced neuromuscular blockade.

DRUGS	DISCUSSION

CLINICAL SIGNIFICANCE: In-vitro studies indicate that neomycin and polymyxin B enhance the neuromuscular blocking activity of lidocaine, but the clinical significance of these findings are not clear.

MANAGEMENT: Until clinical information is available one should be alert for evidence of neuromuscular blockade (e.g., impaired respirations) in patients receiving systemic lidocaine plus aminoglycosides or polymyxin B.

Barbiturates[4,5,143–145]

MECHANISM: Barbiturates appear to enhance the disposition of lidocaine. Although this has been assumed to be due to induction of hepatic microsomal enzymes, hepatic blood flow is probably the primary determinant of lidocaine disposition. Thus, the observed effect might be related to barbiturate-induced increases in hepatic blood flow.

CLINICAL SIGNIFICANCE: Barbiturates markedly reduce the bioavailability of oral lidocaine,[143,144] but lidocaine is seldom given by that route. Studies of intravenous lidocaine administration in man[4,143] and dogs[5] have indicated that lidocaine disposition is slightly enhanced by pretreatment with phenobarbital. Thus, it has been proposed that patients receiving barbiturates might be more tolerant to the effects of lidocaine. However, since lidocaine is usually titrated to achieve the desired response, it does not seem likely that patients would frequently be adversely affected. Administration of pentobarbital (30 mg/kg I.V. over 1 minute) to six dogs which had received lidocaine infusions resulted in apnea in all six, and four of them died.[145] The author proposed that the two drugs had additive effects on the respiratory center. However, large doses of pentobarbital were used, and the clinical importance of these findings is not clear.

MANAGEMENT: Until more information is available, patients receiving lidocaine and intravenous barbiturates should be monitored for excessive respiratory depression.

Beta-adrenergic blockers[80,96,146–151]

MECHANISM: Beta-blockers tend to reduce cardiac output and hepatic blood flow, which would in turn reduce hepatic lidocaine metabolism.[146,148] There is also evidence that beta-blockers may inhibit the activity of hepatic microsomal drug metabolizing enzymes.[80,149,151] This effect may be greater for the more lipid-soluble beta-blockers such as propranolol, labetalol, oxprenolol, timolol, and metoprolol than for those which are more polar, such as atenolol, nadolol, and sotalol.[149] Finally, lidocaine may enhance the negative inotropic effect of propranolol (and possibly other beta-blockers).[150]

CLINICAL SIGNIFICANCE: In 11 healthy volunteers, pretreatment with propranolol (80 mg tid for 3 days) substantially reduced the plasma clearance of intravenous lidocaine, resulting in a 30% increase in

DRUGS	DISCUSSION

steady-state serum lidocaine levels during continuous lidocaine infusions.[146] In another study, six healthy subjects were given three single doses of lidocaine (2.5 to 3.0 mg/kg IV over 10 minutes): one alone, one following 1 day of pretreatment with propranolol (40 mg orally every 6 hours), and one following 1 day of pretreatment with metoprolol (50 mg orally every 6 hours).[148] Propranolol reduced lidocaine clearance by 47%, and metroprolol reduced lidocaine clearance by 31%. The magnitude of the changes in lidocaine disposition found in these studies appear sufficient to increase the danger of lidocaine toxicity. Two cases of toxicity which may have been due to this interaction have been reported.[147] The clinical importance of the additive negative inotropic effect of lidocaine and beta-blockers[150] is not yet established.

MANAGEMENT: One should be alert for the need to lower lidocaine dosage in patients who receive concurrent therapy with beta-blockers. The magnitude of the reduction in lidocaine elimination appears to be less with metoprolol than with propranolol, but still may be clinically important.

Cephalosporins[152]

MECHANISM: None.

CLINICAL SIGNIFICANCE: Reconstitution of cefoxitin with 0.5% or 1.0% lidocaine does not appear to affect the disposition of cefoxitin.[152]

MANAGEMENT: No special precautions appear necessary.

Cimetidine (Tagamet)[153–157,380]

MECHANISM: Cimetidine is known to inhibit hepatic microsomal drug metabolism, and there is some evidence that it may reduce hepatic blood flow.[155] Also, cimetidine may alter the distribution and protein binding of lidocaine.[153] Combined effects of cimetidine and lidocaine on cardiac function and mental status are also possible, but little is known about such mechanisms.

CLINICAL SIGNIFICANCE: Six healthy subjects received lidocaine (1 mg/kg body weight I.V. over 10 minutes) with and without pretreatment with cimetidine (300 mg qid for 1 day).[153] Lidocaine clearance was reduced by about 25%, and peak serum lidocaine levels were increased by 50%. Five of the six subjects developed symptoms of lidocaine toxicity (light-headedness, intoxication, paresthesias) during the lidocaine infusions when pretreated with cimetidine. Similar results were found in a subsequent study of 21 patients receiving lidocaine infusions.[154] Cimetidine (300 mg every 6 hours) given to 15 of the 21 patients produced substantial increases in serum lidocaine levels: six had lidocaine levels in the toxic range and two had symptoms of lidocaine toxicity (confusion, lethargy). Lidocaine serum levels did not increase in the six controls who did not receive cimetidine. However, another study in seven patients did not find an effect of intrave-

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nous cimetidine (2 mg/kg body weight then 0.75 mg/kg body weight/hour) on the disposition of lidocaine given as a continuous intravenous infusion.[380]

MANAGEMENT: One should be alert for evidence of excessive lidocaine effect if cimetidine is given concurrently; reductions in lidocaine dose may be necessary. Ranitidine may be a good alternative to cimetidine since it does not appear to affect lidocaine disposition.[156,157] It also seems unlikely that antacids or sucralfate would affect lidocaine disposition.

Diazepam (Valium)[6,158]

MECHANISM: None.

CLINICAL SIGNIFICANCE: Since diazepam appeared to antagonize the central nervous system toxicity of lidocaine, it was feared that the antiarrhythmic effect of lidocaine might also be antagonized by diazepam. However, studies in dogs indicated that diazepam actually *enhanced* the antiarrhythmic effect of lidocaine.[6] In another study of cats given large doses of lidocaine, diazepam protected against lidocaine-induced seizures but did not enhance the cardiovascular toxicity of lidocaine.[158]

MANAGEMENT: No special precautions appear necessary.

Digitalis glycosides[158]

MECHANISM: None.

CLINICAL SIGNIFICANCE: In three patients receiving digoxin, the mean serum digoxin was 0.60 ng/ml before and 0.83 ng/ml during lidocaine administration.[158] The increase was not statistically significant, but too few patients were studied to determine whether an interaction occurs.

MANAGEMENT: No special precautions appear necessary at this point.

Diphenhydramine (Benadryl)[142]

MECHANISM: None.

CLINICAL SIGNIFICANCE: Diphenhydramine (dose not stated) did not affect serum lidocaine levels in three patients.

MANAGEMENT: No special precautions appear necessary.

Isoproterenol (Isuprel)[85]

MECHANISM: It is proposed that isoproterenol may increase hepatic blood flow, thus enhancing lidocaine disposition.

CLINICAL SIGNIFICANCE: Studies in monkeys have demonstrated enhanced lidocaine disposition when an isoproterenol infusion is given.[85] The significance to human therapy remains speculative.

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