

# Drug Interactions in Hypertension

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**SUMMARY** Interactions between drugs and antihypertensive agents can result in either increased or decreased antihypertensive effects. These interactions may be pharmacokinetic or pharmacodynamic in type, resulting in either altered plasma drug concentrations or altered drug effects at similar plasma concentrations. Drugs may limit the absorption of antihypertensive agents, alter their metabolism through either enzyme inhibition or induction, or change renal excretion. In addition, by altering cardiovascular and volume homeostasis, changes in antihypertensive response may be produced. (Hypertension 11 [Suppl II]: II-1-II-3, 1988)

**KEY WORDS** • hypertension • drugs • drug interactions • adverse effects

**D**RUG interactions occur when the effect of one drug is altered by the coadministration of another. Such alterations may result either from changes in the drug's concentration (pharmacokinetic interaction) or from changes in the drug's effect independent of concentration (pharmacodynamic interaction). This report discusses some of the general implications of drug interactions in the management of hypertension and is restricted to interactions other than those produced by nonsteroidal anti-inflammatory agents and oral contraceptives, which are discussed elsewhere in this monograph.

## Pharmacokinetic Drug Interactions

Pharmacokinetic interactions may result from alterations in drug absorption, drug distribution, drug metabolism, or drug excretion by nonmetabolic routes. Alteration of drug delivery to the systemic circulation may occur because of a reduction in the drug's absorption from the gastrointestinal tract following oral administration. Perhaps the best recognized of such interactions are produced when cholestyramine is given to treat hyperlipidemia. Cholestyramine resin adsorbs many substances, including drugs, and reduces the absorption of thiazide diuretics. Hunninghake and Hibbard<sup>1</sup> have shown that following a single 8-g dosage of cholestyramine given 2 hours before or after hydrochlorothiazide administration there was a significant reduction in the amount of hydrochlorothiazide absorbed. This reduction was 65% when the cholestyramine was administered before the hydrochlorothiazide.

From evaluation of multiple dosing regimens, these authors concluded that cholestyramine was best given 2 to 4 hours after the administration of hydrochlorothiazide. But even in this setting, a reduction of 30 to 35% could be expected in the absorption of hydrochlorothiazide. Cholestyramine is, therefore, likely to reduce the absorption of thiazides, resulting in lower plasma drug concentrations and reduced drug effect.

Additional interactions involving alteration in drug entry into the systemic circulation occur when highly metabolized  $\beta$ -blockers are coadministered with the vasodilator hydralazine. Hydralazine produces a considerable increase in the area under the propranolol concentration-time curve, indicating greater propranolol entry into the systemic circulation. When propranolol is given with 50 mg of hydralazine, the increase in propranolol's area under the curve was almost 100%.<sup>2</sup> The explanation for these changes is not yet completely clear but seems likely to be due to a reduction in the proportion of propranolol being metabolized in its first pass through the liver before its entry into the systemic circulation. This may be due to transient changes in liver blood flow and hence in the rate of delivery of drug to the liver.

Alterations in the rate of drug metabolism through either inhibition or induction of drug metabolizing ability are important determinants of drug concentration. For highly metabolized drugs such as propranolol and metoprolol, the effects of potent enzyme inducers on their kinetics are clear. The administration of the enzyme inducer rifampin causes a twofold to threefold increase in propranolol's clearance, with a concomitant reduction in propranolol concentrations in plasma.<sup>3</sup> This reduction in concentration occurs relatively slowly during rifampin administration, taking as long as 10 to 20 days to reach maximum effect. When the administration of the enzyme inducer is stopped, return to baseline occurs again over a period of at least 10

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to 20 days.<sup>3</sup> Although not tested, it is likely that the reduction in propranolol concentrations associated with the coadministration of rifampin will reduce its antihypertensive effect.<sup>5</sup>

Inhibition of drug metabolism, particularly by the hepatic drug metabolism inhibitor cimetidine, results in an increase in drug concentration and effect. Cimetidine has been shown to result in a 50% reduction in the clearance of propranolol, with a resultant doubling of propranolol concentrations.<sup>4,5</sup> These increased concentrations result in increased  $\beta$ -blockade<sup>4</sup> and perhaps increased antihypertensive effect. Chlorpromazine also reduces drug metabolizing ability, resulting in decreased propranolol clearance and increased plasma propranolol concentrations.<sup>6</sup> These increased drug concentrations have resulted in adverse drug effects in individuals who received both propranolol and chlorpromazine.<sup>6</sup>

Alteration in the excretion of drugs whose principal route of elimination is renal may also occur because of drug interactions. The active tubular secretion of captopril is decreased when probenecid is coadministered. This interaction causes a fall in total captopril clearance of about 20%, which is due principally to a reduction in the renal clearance of captopril.

#### Environmental Factors

In addition to the obvious effects of prescribed medications on the pharmacokinetics and pharmacodynamics of other prescription agents, the patient's life-style and other subtle factors are also important determinants of antihypertensive drug effects. For example, the hypotensive effect of meals may obscure the hemodynamic effects of cardiovascular drugs.<sup>7</sup>

Alcohol consumption appears to have a direct pressor effect that lessens the effect of coadministered antihypertensive agents.<sup>8</sup> The effect of alcohol is not major, producing a rise of systolic blood pressure of about 4 mm Hg and producing smaller changes in diastolic blood pressure. However, significant benefits can be obtained in blood pressure control by convincing hypertensive patients who are regular alcohol users to either reduce or abstain from alcohol consumption.

Cigarette smoke causes induction of drug metabolizing ability in animals. In addition, there is now considerable evidence to suggest that drug metabolizing ability is increased in chronic smokers.<sup>9,10</sup> Cigarette smokers have blood propranolol concentrations that are only 50% as high as those of nonsmokers. In the Beta-Blocker Heart Attack Trial, plasma propranolol concentrations were found to be 37% lower in smokers compared with nonsmokers.<sup>10</sup> The overall effect of these reductions is unclear; however, it is of some interest to note that in the recent United Kingdom Medical Research Council's trial on the treatment of mild hypertension, some of the beneficial effects of propranolol were evident only in nonsmokers.<sup>11</sup> Although the reason for the differences is unclear, it is at least conceivable that nonsmokers derive greater benefit because of their higher concentrations of propranolol.

When the highly metabolized  $\beta$ -blockers propranolol or metoprolol are taken with meals, increased amounts of drug enter the systemic circulation, resulting in as much as a 50% increase in drug concentrations.<sup>12-14</sup> These increased concentrations may be due to the transient changes in portal blood flow produced by meals. Theoretical calculations have supported the concept that for highly metabolized drugs, such changes in bioavailability might be produced by the alterations in liver blood flow produced by feeding.<sup>15</sup>

#### Effects of Antihypertensive Agents on Other Drugs

Following the demonstration of quinidine's effect on serum digoxin concentrations, considerable effort has been made to evaluate the effects of other drugs on the disposition of digoxin. When verapamil was administered to 49 patients with chronic atrial fibrillation, serum digoxin levels rose from 0.76 to 1.31 ng/ml.<sup>16</sup> The greater the dose of verapamil administered, the greater was the rise in serum digoxin concentrations, implying that there is a dose-response relationship between the verapamil dose and the change in digoxin kinetics. Renal digoxin clearance was significantly decreased in patients who received verapamil<sup>15</sup> and provided part of the explanation for the change in digoxin concentrations. Interestingly, an additional study has suggested that the short-term effects of verapamil on digoxin concentrations are not maintained during long-term verapamil administration.<sup>17</sup> In this study, the serum digoxin levels that initially rose during verapamil administration, concomitant with a reduction in renal digoxin clearance, gradually fell over the following 6 weeks in spite of continuing verapamil administration. In fact, the renal digoxin clearance and the plasma digoxin level had returned to pretreatment levels by 6 weeks after starting verapamil. Nifedipine has also been shown to alter plasma digoxin concentrations.

A recent study has shown that verapamil administered in the dosage of 120 mg three times daily resulted in an almost 50% increase in carbamazepine concentrations in plasma.<sup>18</sup> This increase in concentrations was due to a reduction in the metabolism of carbamazepine to the carbamazepine epoxide.<sup>18</sup> In a number of patients who received verapamil and carbamazepine simultaneously, symptoms and signs of carbamazepine neurotoxicity developed, suggesting that this interaction had pharmacodynamic consequences.

#### Pharmacodynamic Drug Interactions

The interaction between tricyclic antidepressants and guanethidine has been well studied and is due to the tricyclics inhibiting the entry of guanethidine into the sympathetic nerve. A large body of literature has shown that this interaction causes a loss of blood pressure control and sometimes results in catastrophic clinical consequences. However, because guanethidine is now rarely prescribed, this interaction is probably of less importance than in the past. However, although not well studied, guanadrel is an adrenergic

neuron blocker whose pharmacological effects are similar to those of guanethidine, and it is likely that similar interactions will be seen when guanedrel is coadministered with tricyclic antidepressants.

An important interaction that is frequently not recognized clinically is the fluid retention and weight gain caused by almost all vasodilators. This increase in intravascular volume results in loss of blood pressure control, which can be readily reversed by the simple administration of appropriate diuretics.

Subsequent papers in this monograph will discuss the importance and mechanism of the interaction between a number of antihypertensive agents and non-steroidal anti-inflammatory drugs as well as the hypertensive effects of oral contraceptives. However, from this short review, it is clear that the antihypertensive effects of a number of agents may be altered through drug interactions produced by the concomitant administration of other drugs. Frequently, recognition of this problem with appropriate adjustment of therapy will allow the physician to continue to manage the patient satisfactorily without having to produce an unnecessary increase in the complexity of the patient's antihypertensive regimen.

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