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CARDIOVASCULAR DRUG INTERACTIONS

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INTRODUCTION

Among the clinically important drug interactions, those involving cardiovascular agents are probably preeminent. Drug interactions change the expected relation between the dose administered and the drug's effect, whether that change is due to the amount of drug available at its site of action (pharmacokinetic), or to a change in "sensitivity" at its receptor (pharmacodynamic). Interactions that decrease a drug's effect leave the patient susceptible to the morbidity and mortality of his primary disease. Interactions that increase a drug's effect may cause toxicity. The narrow benefit:risk ratio of many of the cardiovascular agents increases the importance of drug interactions involving them, for interactions can result in subtherapeutic or toxic responses from doses that would ordinarily be therapeutic.

Though the sequelae of cardiovascular drug interactions are often serious, they often are not recognized (1–5). Many patients with cardiovascular diseases are desperately ill, and the manifestations of drug toxicity may be difficult to distinguish from those of the primary disease. For example, arrhythmias due to digitalis toxicity may be impossible to differentiate from those that are disease induced (6–9). Similarly, arrhythmias may be a toxic manifestation of antiarrhythmic drugs, and may be misinterpreted as lack of efficacy of the drug (10–14). Avoidance of and appropriate response to drug interactions requires understanding of the pharmacology of the drugs and the pathophysiology of the diseases in which they are used. We categorize drug interactions in pharmacokinetic terms and by types of drug. The breadth of this topic and editorial limitations on manuscript length allow us only to use broad outlines here. The references listed will help those who wish to pursue topics in more detail.

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PHARMACOKINETIC DRUG INTERACTIONS

Drug interactions can affect the absorption of a drug, its distribution to tissues, its elimination by metabolism and excretion, and the relationship between the amount of drug at its site of action and its effect.

Absorption

Drug interactions affecting absorption can change the rate and extent of absorption of a drug, each or both of which may be important. The rate of absorption determines the peak level of drug attained in blood and the rapidity at which the drug reaches its site of action; the extent of absorption determines the total amount of drug that is systemically available and, hence, the level of drug attained at steady state (15, 16).

Interactions affecting rates of absorption are of minor clinical importance. When a rapid onset of action is desired, as in treating arrhythmias, the agent is administered intravenously. Changes in extent of absorption, or bioavailability, however, are often clinically important, for such alterations affect the level of drug maintained at steady state.

There are a number of mechanisms by which changes in absorption can occur. Whether the drug is given as a solution, suspension, tablet, or capsule can importantly affect both the rate and the extent of absorption. In addition, the method of a tablet's formulation can change its dissolution rate and its availability for absorption, as has been observed with various preparations of digoxin (17–28).

Drug interactions of a direct physical or chemical nature are also seen. Complexing of drugs with antacids, with exchange resins, etc occurs with a variety of drugs. The in vitro dissolution of digoxin tablets is drastically decreased by antacids containing magnesium trisilicate (29). Whether these antacids impair the bioavailability of digoxin in vivo has not been reported. By interrupting the enterohepatic circulation of digitoxin, cholestyramine and colestipol enhance its elimination rate, and these resins have been advocated for treatment of digitoxin intoxication (30–32). Cholestyramine similarly increases the elimination of warfarin (33). Antacids appear not to alter the kinetics of warfarin importantly, and cholestyramine does not influence the elimination of digoxin (34, 35). Activated charcoal, on the other hand, may impair digoxin's absorption (36).

Many drugs are weak acids or weak bases. The pH of their milieu, their pK_a, and their lipid solubility determine their ability to cross cell membranes. Theoretically, therefore, a gastrointestinal (GI) pH favoring non-ionized drug facilitates absorption. For weak bases, such as procainamide, quinidine, and mecamylamine, an alkaline pH increases the amount of non-ionized drug; for weak acids, such as salicylate or phenobarbital, an acid pH increases the amount of non-ionized drug. Studies in animals verify that the acidic gastric pH facilitates movement of weak acids from the gastric lumen to blood and promotes movement of weak bases in the opposite direction (37, 38). Gastric luminal pH effects, however, are not as important as might be expected; these pH changes affect the rate of absorption of some noncardiovascular agents to a minor degree, but no important quantitative effects

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have been reported on the extent of drug absorption, perhaps, because a large intestinal surface area is available for absorption, or the mucosa is "leaky," or there are other unidentified factors important for facilitating complete absorption of drugs (39–40).

The greatest amount of drug absorption occurs in the duodenum or proximal jejunum. Consequently, the rate of gastric emptying influences the time from drug administration to absorption. Drugs that delay gastric emptying, such as morphine, atropine, or meperidine can significantly decrease the rate of absorption of other drugs. Rapid gastric emptying would cause an earlier and higher peak level of drug.

Changes in GI motility can affect the extent of absorption of slowly absorbed drugs such as digoxin, guanethidine, and bishydroxycoumarin. Decreased motility provides more time for and increases the extent of absorption; increased motility has the opposite effect. With a slowly dissolving brand of digoxin, concomitant administration of metaclopramide, which increases GI motility, decreased steady state serum digoxin concentrations by one third. Propantheline, which slows GI motility, increased the steady state serum digoxin concentrations by one third (41). This effect of GI motility on the extent of absorption of digoxin was not observed when a rapidly dissolving formulation of digoxin was used (42).

Congestive heart failure or shock, release of catecholamines or vasoactive peptides, and administration of vasoactive drugs may change perfusion of the intestine or muscle, causing unpredictable absorption. In many settings in which cardiovascular agents are used, perfusion to tissue changes with time; the only certain way to know how much drug is systemically available is to administer it intravenously.

Before reaching peripheral sites, orally administered drugs pass through the intestine and the liver. Metabolism of the drug may occur in either organ and decrease the amount systemically available; this process is called the "first pass" effect. A first pass effect occurs with propranolol, alprenolol, lidocaine, reserpine, dopamine, and other sympathomimetics. This effect is clinically unimportant with reserpine; lidocaine and sympathomimetics are administered parenterally because the first pass effect is so great that insufficient levels of drug are reached systemically after oral dosing. The first pass effect on the absorption of propranolol is partly responsible for the wide variation in plasma levels of this drug that occur among patients given similar oral doses.

Changes in the liver's capacity to metabolize drugs would be expected to change the magnitude of the first pass effect importantly. By decreasing hepatic blood flow, congestive heart failure or propranolol decrease the clearance of lidocaine and other drugs (43–46).

Interference with GI muscosal function does not appear to be important with most cardiovascular agents, although diminished absorption by this mechanism may explain how heptobarbital decreases the absorption of bishydroxycoumarin (47).

Distribution

Interactions involving distribution of drugs to tissue sites of action include effects on serum protein binding and pH-dependent effects on distribution.

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Drugs bound to albumin are in equilibrium with free drug in plasma. Only the free drug is available to its site of action; consequently, changes between amounts of bound and free drug may significantly influence a drug's effect. The ability of one drug to displace another depends on the relative concentrations of each drug and their affinities for binding. The clinical significance of displacement of a drug depends on the drug's therapeutic index and its degree of protein binding. Only with drugs that are highly bound will displacement cause significantly increased amounts of free drug. Consequently, clinically important interactions have been observed only with concomitant use of highly bound drugs that have a low therapeutic index (48).

Cardiovascular agents highly bound to protein include warfarin, bishydroxycoumarin, digitoxin, phenytoin, diazoxide, clofibrate, hydralazine, and quinidine. Other highly bound drugs able to cause displacement interactions include pyrazolone derivatives, salicylates, indomethacin, chloral hydrate's metabolite, and sulfonamides. Theoretically, clinically significant serum protein displacement interactions could occur with concomitant use of any of the drugs mentioned. However, important interactions thus far have been observed only when coumarin anticoagulants are displaced from proteins by clofibrate, pyrazolones, or chloral hydrate (49–52). Displacement of coumarin anticoagulants sufficient to potentiate the anticoagulant effect has been observed in animals or in vitro with administration of diazoxide, ethacrynic acid, indomethacin, sulfinpyrazone, sulfadimethoxine, sulfaphenazole, and tolbutamide (53–56). A study in normal volunteers, however, has shown no clinically important interaction between coumarin and indomethacin (57). Pyrazolones displace digitoxin and diazoxide displaces phenytoin, but the transient increase in levels of free drug is not clinically important (58–60).

Interactions among the other drugs may not be important because changes in free levels are minor, or because the increase of the free level is short-lived and not detected. All protein displacement interactions are transient. Because the described drugs obey first order elimination kinetics, the temporarily increased free drug is eliminated more quickly, causing a new steady state in which the total drug in serum is decreased, but the amount of free drug is the same as before. The duration of the displacement interaction depends on the time necessary to reach the new steady state; this time period is a function of the intrinsic elimination rate of the displaced drug (61, 62). Many drug interactions previously believed to occur by protein displacement mechanisms are now felt to occur through changes in metabolism of one drug induced by another (63). These interactions would persist throughout the concomitant use of the interacting drugs, while protein displacement interactions are clearly short-lived. Concomitant administration of highly bound drugs, therefore, requires dose adjustment and close following of endpoints of drug effect only until the new steady state is reached. These interactions are clinically most important when using coumarin anticoagulants, requiring frequent determinations of the prothrombin time when starting or discontinuing other drugs.

Changes in systemic pH can affect distribution of drugs to tissues. A pH favoring the non-ionized congener of drugs that are weak acids or weak bases would facilitate its diffusion into tissues. The converse is also true. Acidemia increases the hypoten-

sive effect of mecamylamine by increasing its distribution to its extracellular site of action (64). A number of other cardiovascular agents including quinidine and procainamide are weak bases. Changes in systemic pH induced by other drugs might affect their distribution to sites of action, but this phenomenon has not been described.

Metabolism

Significant interactions among cardiovascular drugs occur with induction or inhibition of hepatic metabolism of drugs and from inhibition of monoamine oxidase (MAO). A number of different drugs can affect the hepatic microsomal enzyme system that is responsible for metabolism of various drugs. There is a great deal of interindividual variation in the capacity of this system and the degree to which it may be induced or inhibited (65, 66). This knowledge, plus the realization that many of the potential inducers and inhibitors have been studied only in animals, makes tenuous any prediction of the extent of an interaction in any individual.

Clinically important interactions due to induction of hepatic microsomal enzymes that have been observed with cardiovascular agents occur with the coumarin anticoagulants, phenytoin, and quinidine. Phenobarbital and carbamazepine can significantly increase the metabolism of phenytoin in some patients (67–70). The decreases in phenytoin levels have not resulted in increased seizure activity, presumably because of the seizure inhibiting activity of the inducing agent. A similar interaction when phenytoin is used as an antiarrhythmic could result in subtherapeutic levels of the drug. Phenytoin and phenobarbital increase the clearance of quinidine probably by metabolic induction. Both drugs decreased the half-life of quinidine in normal subjects by approximately 50%, and in two patients decreased quinidine to subtherapeutic levels (71).

Inhibition of metabolism is also important with these same drugs. Inhibition of hepatic metabolism of phenytoin, probably by noncompetitive inhibition of parahydroxylation, occurs with concomitant use of bishydroxycoumarin, disulfiram, antituberculous drugs, phenylbutazone, oxyphenbutazone, chloramphenicol, phenyramidol, sulfaphenazole, sulfamethizole, sulthiame, and methylphenidate (72–76). "Epidemics" of phenytoin toxicity have been reported when isoniazid was administered to a group of patients (77). Phenyramidol, sulthiame, and chloramphenicol doubled the serum half-life of phenytoin in studies of normal subjects (78–80).

A number of drug interactions due to inhibition of MAO are well known (81). Their significance is only lessened by the appropriately infrequent use of these agents. However, procarbazine, a drug used in treating Hodgkin's disease, has MAO inhibitory activity (82). Concomitant use of sympathomimetic agents requires awareness of this potential effect of procarbazine. MAO metabolizes sympathetic neurotransmitters at the synaptic cleft. During inhibition of this enzyme, administration of catecholamines or agents that release catecholamines such as tyramine, ephedrine, amphetamines, and some antihypertensive agents like reserpine and guanethidine can cause fatal hypertensive crises. Conversely, the effects of some antihypertensive agents such as diuretics may be potentiated and prolonged (81).

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Inhibitors and inducers of the metabolism of coumarin derivatives are presented in the section on anticoagulants.

Excretion

The kidney excretes many drugs. A drug that changes the glomerular filtration rate might alter excretion of another drug, but changes of sufficient magnitude to be important have not been reported. Active secretion of a variety of drugs occurs at the pars recta of proximal tubules. There appear to be two nonspecific transport systems, one for organic acids and one for bases; any of the secreted drugs can compete for transport with another drug within its group (83–85). Cardiovascular agents for which this effect might be important, but which have not been reported, include the bases, procainamide and quinidine, and the organic acids, thiazides or thiazide derivatives. Spironolactone decreases the renal excretion of digoxin by competing for active secretion. This probably occurs at a site in the distal tubule, and concomitant administration can significantly increase the serum level of digoxin (86).

Passive renal tubular transport of drugs is related to urine flow rate and pH (87). High rates of urine flow induced by diuretics or fluid loading increase excretion of phenobarbital, but this effect has not been observed with cardiovascular agents. Carbonic anhydrase inhibitors or bicarbonate administration causing an alkaline urine, and ammonium chloride, potassium depletion from diuretics etc, inducing acid urine can affect passive transport of weak acids and bases. Alkaline urine decreases excretion of weak bases like amphetamine while acid urine decreases excretion of weak acids like salicylate by increasing the amount of non-ionized drug that can be reabsorbed from the tubular lumen (88). Procainamide, a weak base, follows urine pH-dependent excretion in dogs, but not in man (89, 90). A case of quinidine toxicity has been reported in a patient with renal tubular acidosis receiving "normal" doses of quinidine and has been attributed to accumulation due to a persistently alkaline urine (91). However, the increment of change in quinidine excretion that occurs with changes in urine pH is not of a magnitude that should be clinically important.

PHARMACODYNAMIC INTERACTIONS

Relationship Between Drug Amount and its Effect

Drugs and disease states can alter the effect seen from a known amount of drug; that is, they change the dose-response relationship. Systemic acidemia decreases the expected response to catecholamines (92). Potassium depletion increases the toxicity of digitalis glycosides. This interaction is particularly easy to overlook because substantial decreases in intracellular potassium can occur with normokalemia. Use of digitalis with guanethidine or propranolol can result in profound bradycardia as a result of the "vagal" activity of digitalis during sympathetic blockade (93). In addition, disease states can also affect the relation between drug dose and effect. A pharmacology or clinical pharmacology text, or the *Index Medicus,* should be referred to when unusual responses to a drug are observed.

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Drug Interactions at the Receptor Site

Clinically important drug interactions at the receptor site include those involving drugs that have direct and indirect effects on the autonomic nervous system. Interactions among drugs primarily used for their effects on the autonomic nervous system are well known and include blockade of the β-agonist effects of isoproterenol and epinephrine by propranolol, or of the α-agonist effects of norepinephrine by phentolamine or phenoxybenzamine. Less commonly anticipated interactions are those occurring with concomitant administration of drugs that have secondary effects on the autonomic nervous system. For example, phenothiazines, tricyclic antidepressants, and butyrophenones are α-sympathetic antagonists, accounting for the enhanced activity of other α-blockers used concomitantly and the rationale for the use of directly acting α-sympathomimetics to reverse the α blockade of phenothiazines.

Tricyclic antidepressants and guanethidine block neuronal uptake of catecholamines at the synaptic cleft. Because reuptake of catecholamines is a major mechanism of attenuation of their effect, exogenously administered catecholamines may have an increased effect if used with them. In studies of normal subjects who had taken imipramine (25 mg TID) for five days, there was potentiation of the pressor effects of phenylephrine by two to three times, norepinephrine by four to eight times, and epinephrine by two to four times (94). In a similar study in subjects administered debrisoquin, an antihypertensive agent that also blocks the catecholamine reuptake system, the circulatory effects of phenylephrine were markedly potentiated and prolonged (95). Indirectly acting sympathomimetics would not be expected to have an enhanced effect with guanethidine-like drugs, and would more likely have a decreased effect, since guanethidine, debrisoquin, and bethanidine deplete endogenous catecholamines.

Another set of important cardiovascular drug interactions involving the catecholamine reuptake mechanism is that occurring between quanethidine, bethanidine, and debrisoquin and a number of psychoactive agents. The former drugs are taken into the synaptosomes by the catecholamine reuptake system. They then cause release and depletion of endogenous catecholamine stores. A reversal of their effect by tricyclic antidepressants is predictable since the tricyclics would inhibit their uptake to this site of action (96–103). A similar reversal of effect that probably occurs by inhibition of uptake or displacement from the site of action occurs with amphetamine, ephedrine, methylphenidate, doxepin, phenothiazines, butyrophenones, thiothixene, and possibly reserpine (103–109). This interaction has also been seen with use of a nasal decongestant containing chlorpheniramine, isopropamide, and phenylpropanolamine (110). This last interaction is probably not clinically important in most patients, but use of over-the-counter "cold" remedies should probably be avoided in patients on guanethidine-like drugs.

Reversal of the antihypertensive effect of clonidine by desipramine is well documented (111, 112). The site of action of clonidine appears to be central. This observed interaction may imply uptake of clonidine into CNS neurons as integral to its mechanism of action. This interaction requires caution in using other tricyclic antidepressants and psychoactive drugs in patients receiving clonidine.

Drugs, like reserpine, or diseases, like congestive heart failure, that deplete endogenous catecholamine stores can blunt the response to metaraminol and ephedrine, whose major effect depends on release of catecholamines at the nerve ending (113, 114).

Unanticipated but predictable interactions may occur with use of agents that have multiple effects. For example, epinephrine is both an α- and β-sympathetic receptor agonist; the α effect predominates in most instances, causing arteriolar vasoconstriction. However, concomitant use of an α-receptor antagonist not only will attenuate the vasoconstriction, but also may unveil the vasodilation caused by the β effect. Similarly, the use of propranolol for the treatment of hypertension rarely exacerbates the hypertension by blocking β-induced vasodilation and potentiating preexisting α-mediated vasoconstriction, especially in patients with a pheochromocytoma (115–118).

A number of drugs affect the parasympathetic limb of the autonomic nervous system. These agents may unexpectedly antagonize or potentiate the effects of cardiovascular agents used to affect the parasympathetics. Phenothiazines, antihistamines, and tricyclic antidepressants have clinically significant parasympathoplegic effects (119, 120).

Another type of drug interaction that is less clearly defined, but which we categorize as occurring at the receptor, is effects of psychotherapeutic agents on the myocardium. Phenothiazines and tricyclic antidepressants have quinidine-like effects on conductivity and automaticity (121–123). These effects can be manifested as QRS widening, QT prolongation, and arrhythmias. Because of the mechanism of these cardiac effects, concomitant use of quinidine and procainamide may have additive effects. Similarly, treatment of arrhythmias due to this effect of phenothiazines or tricyclic antidepressants requires agents that would not further depress conduction; these include lidocaine, phenytoin, and sympathomimetics. Some arrhythmias caused by these psychoactive agents are due to this quinidine-like effect rather than the parasympathoplegic effect (124). Inappropriate use of physostigmine for arrhythmias due to the quinidine-like effect can result in worsening of the arrhythmias and death.

CARDIOVASCULAR AGENTS

In this section, we discuss drug interactions involving specific types of cardiovascular agents.

Digitalis Glycosides

The effects on absorption of digitalis preparations by tablet formulation, changes in intestinal motility, and possible physiochemical interactions have been discussed. Digitoxin is metabolized by the liver, while the other glycosides are excreted by the kidney. Phenobarbital, phenytoin, phenylbutazone, and spironolactone enhance the metabolism of digitoxin, but this effect is of a clinically important magnitude only with phenobarbital with which the serum half-life of digitoxin is halved (58, 59, 125, 126). Digitoxin is highly bound to serum proteins and is displaced by phenylbutazone, but this interaction does not appear to be clinically important (59). Inhibi-

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tion by spironolactone of digoxin's secretion by the renal tubule has been mentioned.

The most frequent interactions involving cardiac glycosides are those due to effects of other drugs on electrolyte balance. Increased sensitivity to the toxicity of digitalis occurs with potassium depletion, hypomagnesemia, and hypercalcemia, all of which may be secondary to diuretic therapy. Coadministration of sympathomimetic drugs also appears to increase the sensitivity to the toxic effects of digitalis.

Antiarrhythmic Agents

The different antiarrhythmic agents can have additive or antagonistic effects toward each other (10–14). Their effects on conductivity and the relative refractory period may differ (Table 1). Drugs with opposite effects on these electrophysiologic parameters can antagonize each other; drugs with similar effects can be additive. For example, phenytoin may antagonize the effects on conduction of quinidine, while procainamide predictably potentiates those effects. Understanding the diverse electrophysiologic effects of the different antiarrhythmic drugs increases the potential for their rational use as single agents or in combination.

Table 1 Effects of antiarrhythmic agents on the transmembrane action potential of isolated cardiac tissue[a,b]

Agent	Type of tissue[c]	Resting potential	Amplitude	*dv/dt*	Membrane responsiveness	Conduction velocity	Duration	Refractory period	Automaticity
Quinidine	Canine PF	0	↓	↓	↓	↓	↓	↓	↓
Procainamide	Canine PF	0	↓	↓	↓	↓	↑	↑	↓
Lidocaine	Canine PF	0	↓	↓	↓	↓	↓	↓	↓
Propranolol	Canine PF	0	↓	↓	↓	↓	↓	↓	↓
Phenytoin	Canine PF	0	0	0, ↓[d]	↓[d], 0, ↑[e]	0, ↓[f]	↓	↓	↓
Phenytoin	Rabbit AM and VM	0	0	↓	↓	↓	0	?	↓
Disopyramide	Canine PF	0	0	↓	↓	↓	↑	↑	↓
Ajmaline	Canine PF, AM, and VM	0	↓	↓	↓	↓	↑[f], ↓[g]	?	↓
Mexiletine	Rabbit AM and VM	0	↕	↓	↓	↓	0	↓	0
Aprindine	Canine PF	↕	↓	↓	↓	↓	↓	↑	↕
Verapamil	Canine PF	0	0	0	0, ↓	?	0, ↑[d]	0, ↑[d]	↓
Amiodarone[h]	Rabbit AM and VM	0	0	0	0	0	↑	↑	↓
Dimethyl quaternary propranolol[i]	Canine PF	0	↓	↓	↕	↓	↓	↓	↓
Bretylium	Rat AM and VM	0	↓	↓	↓	?	↕	↕	?

[a] Reprinted with permission from Morgan, P. H., Mathison, I. W. 1976. Arrhythmias and antiarrhythmic drugs: mechanism of action and structure—activity relationships I. *J. Pharm. Sci.* 65:468–82.

[b] 0 = no effect, ? = not reported, ↓ = decrease, ↑ = increase, and ↕ = questionable or slight effect.

[c] PF = Purkinje fiber, AM = atrial muscle, and VM = ventricular muscle.

[d] At high concentration only.

[e] In acutely depressed fibers.

[f] Atrial muscle and ventricular muscle.

[g] Purkinje fiber.

[h] After 6 weeks of treatment of whole animal.

[i] UM-272.

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Antihypertensive Agents

Interactions involving antihypertensive agents that occur at the receptor have been discussed. The most important interactions with these agents, however, are those used therapeutically for rational use of combinations of drugs in the treatment of hypertension. Blood pressure has a number of physiologic components as schematized in Figure 1. Successful treatment of hypertension often requires use of different drugs to treat the different physiologic components. For example, a patient treated with therapeutic doses of vasodilators to reduce peripheral vascular resistance, β-blockers to decrease heart rate, and ganglionic blockers to decrease venous return may still have hypertension if the patient's blood volume is expanded. Combination therapy for hypertension should use drugs acting on the different physiologic determinants of blood pressure. The various antihypertensive agents in Figure 1 are listed according to their dominant cardiovascular effects.

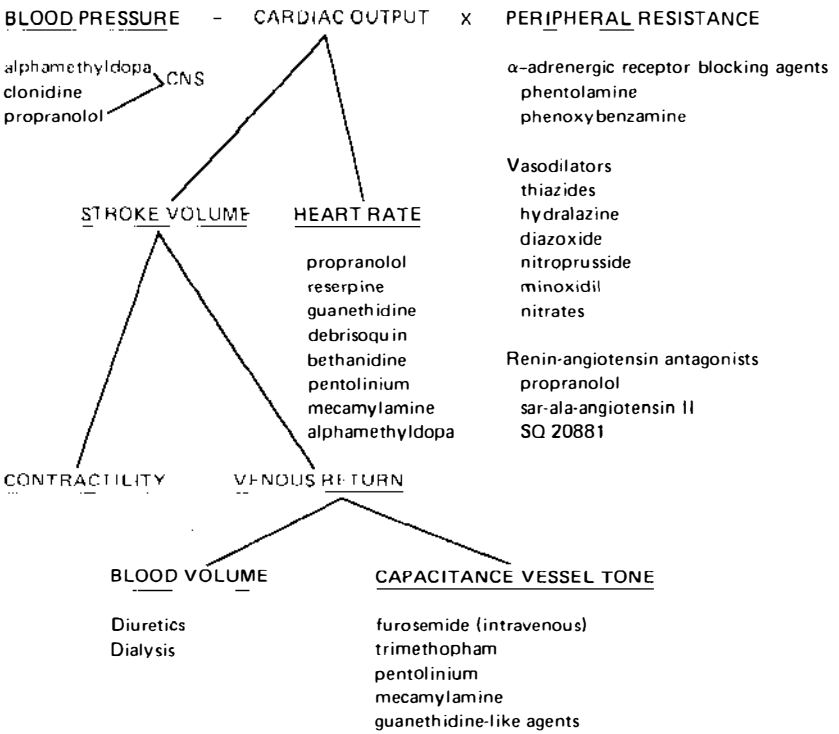

Figure 1 Antihypertensive agents as they affect the physiologic determinants of blood pressure.

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Diuretics

Rational therapy with combinations of diuretics requires knowledge of the physiology of sodium, chloride, and water reabsorption by the kidney. Different diuretics affect different segments of renal tubules, and various agents or combinations of diuretics will cause different, but usually predictable effects on extent of volume and electrolyte loss. For example, by avidly reabsorbing chloride, the loop of Henle reclaims more sodium than does the distal tubule; agents acting at the loop are predictably potent. Sodium and potassium are both reabsorbed proximally, while potassium is secreted as sodium is reabsorbed distally. Consequently, the effects on excretion of different electrolytes of drugs used singly or in combination often can be predicted by knowing the tubule segments affected and the pathophysiology of the patient's disease at a given time. The sites of action of the different diuretics are shown in Table 2. Salicylates have been reported to attenuate the diuretic effects of spironolactone (127).

Anticoagulants

Interactions affecting anticoagulants have been partly presented; those affecting coumarin derivatives are summarized in Table 3. Excellent, current reviews of the coumarin anticoagulants are available (128, 129). Effects on coagulation from interactions with other components of the clotting pathway are also clinically important. Acetylsalicylic acid, phenylbutazone, sulfinpyrazone, indomethacin, dipyridamole, and other drugs interfere with platelet function by poorly defined

Table 2 Site of action of commonly used diuretics

Diuretic	Site of action
Carbonic anhydrase (CA) inhibitors:	Proximal tubule by inhibiting CA-mediated $NaHCO_3$ reabsorption
acetazolamide benzolamide	Minor effect more distally
Osmotic agents: mannitol glycerol glucose urea	Main effect at the loop of Henle; also blocks Na^+ and H_2O reabsorption proximally
"Loop" diuretics: furosemide ethacrynic acid	Block active reabsorption of Cl^- in the ascending limb of the loop of Henle—both cortical and medullary portions
Thiazides	Inhibit Na^+ reabsorption at the cortical segment of the ascending limb of the loop of Henle
Spironolactone	Competitive inhibition of aldosterone-mediated Na^+ reabsorption in the distal tubule
Triamterene, amiloride	Noncompetitive inhibition of Na^+ reabsorption in the distal tubule

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Table 3 Interactions affecting the coumarin anticoagulants[a]

Drug	Mechanism
Inhibition of the hypoprothrombinemic action of coumarins	
Barbiturates	Acceleration of coumarin metabolism
Carbamazepine	Acceleration of coumarin metabolism
Cholestyramine	Inhibition of coumarin absorption
Diphenylhydantoin	Acceleration of coumarin metabolism
Ethchlorvynol	Acceleration of coumarin metabolism?
Glutethimide	Acceleration of coumarin metabolism
Griseofulvin	Inhibition of coumarin absorption?
	Acceleration of coumarin metabolism?
Oral contraceptives	Increase of clotting factor synthesis
Rifampin	Acceleration of coumarin metabolism?
Vitamin K	Increase of clotting factor synthesis
Enhancement of the hypoprothrombinemic action of coumarins	
Allopurinol	Inhibition of coumarin metabolism
Anabolic steroids	Decrease in circulating vitamin K?
	Direct depression of clotting factor synthesis?
	Increase in clotting factor catabolism?
Chloral hydrate	Decrease in coumarin albumin binding
Chloramphenicol	Inhibition of coumarin metabolism
Clofibrate	Decrease in circulating vitamin K?
	Decrease in coumarin ablumin binding?
	Inhibition of coumarin metabolism?
Dextrothyroxine	Decrease in circulating vitamin K?
	Increase in clotting factor catabolism?
Diazoxide	Decrease in coumarin albumin binding
Disulfiram	Inhibition of coumarin metabolism
Ethacrynic acid	Decrease in coumarin albumin binding
Glucagon	Decrease in clotting factor synthesis?
Nalidixic acid	Decrease in coumarin albumin binding
Neomycin	Decrease in vitamin K absorption?
Nortriptyline	Inhibition of coumarin metabolism
Phenylbutazone	Decrease in coumarin albumin binding
Quinidine	Direct depression of clotting factor synthesis?
Salicylate	Direct depression of clotting factor synthesis?
Sulfonamides, long-acting	Decrease in coumarin albumin binding
Thyroid drugs	Increase in clotting factor catabolism
Tolbutamide	Decrease in coumarin albumin binding
Triclofos	Decrease in coumarin albumin binding

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mechanisms manifested as decreased secondary release by platelets of ADP (130, 131). Combined platelet inhibition and impairment of the vitamin K–dependent clotting pathways or intrinsic but latent genetic coagulation defects can contribute to a bleeding diathesis.

In summary, there are a wide variety of mechanisms responsible for a large number of clinically relevant drug interactions. Importantly, these interactions are often predictable; if the primary, secondary, or even tertiary effects of the drugs are known and considered, these interactions can be categorized in a way that makes them easier to conceptualize and remember.

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