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INTERACTIONS BETWEEN ANTIHYPERTENSIVE AGENTS AND OTHER DRUGS

Peter A. van Zwieten, Departments of Pharmacotherapy, Cardiology and Cardio-Thoracic Surgery, Academic Medical Centre, The Netherlands, and Csaba Farsang, 1st Department of Internal Medicine, St. Imre Hospital, Budapest, Hungary

Introduction

The vast majority of hypertensive patients is treated with antihypertensive drugs for many years. Other therapeutic agents are frequently used simultaneously, thus giving rise to the possibility of drug-drug interactions. The potential for drug-drug interactions increases with rising age, since elderly patients receive larger number of drugs, but also because the renal excretion of several therapeutic agents is impaired in the elderly, as a result of diminishing kidney function (1, 2). The interactions between *antihypertensive drugs and other therapeutic agents* will be discussed and summarized in the present issue, after a brief general explanation of the various mechanisms underlying drug-drug interactions. The combination and mutual interactions between various categories of antihypertensive agents will be dealt with by us in a separate issue of this newsletter.

Mechanisms

There are several mechanisms by which drugs may interact (3-5), and most of these mechanisms can be categorized as pharmacokinetic (involving intestinal absorption, distribution, metabolism, and elimination) or as pharmacodynamic, or as additive toxicity, respectively.

Pharmacokinetic interactions: the interaction in *intestinal absorption* is best illustrated by an example: tetracylines and other broad-spectrum antibiotics may impair the absorption of oral contraceptives (in particular those with low-dose progestogens and/or estrogens) and hence render contraception unsafe. Several drugs are subject to inactivation via *metabolic degradation* it the liver, catalysed by various liver enzymes. The formation of these enzymes can be induced or enhanced by drugs such as rifampicine, griseofulvine, and several anti-epileptics (carbamazepin, phenytoine, phenobarbital), but also by regular alcohol consumption. This process, which requires several weeks of treatment and which is indicated as enzyme induction, enhances the metabolic degradation of several drugs. In practice, enzyme induction may play a relevant role for oral anticoagulants (coumarin type), corticosteroids (glucocorticoids), oral contraceptives, or quinidine. Accordingly, these categories of drugs are metabolized/inactivated more rapidly and their doses should therefore be increased. A comparable but opposite problem is the *inhibition of liver enzymes* involved in the biotransformation by a variety of drugs, such as cimetidine, erythromycin, metronidazole, tricyclic antidepressants, phenothiazine-neuroleptics, and sulphonamides (also in co-trimoxazole). Enzyme inhibitors of this type impair the biodegradation of certain drugs and hence increase their effects. A well-known problem is the enhanced effect of anticoagulants (as reflected by bleeding) induced by additional treatment with co-trimoxazole. Certain drugs may *impair the renal excretion* (3-5) of other agents, usually at the renal tubular level. A well-known relevant example is the rise in the plasma level and toxicity of digoxin, provoked by verapamil, amiodarone, or quinidine. Similarly, thiazide diuretics may decelerate the renal elimination of lithium salts and hence reinforce their toxicity. A beneficial effect of such an interaction is the impaired excretion of penicillin antibiotics induced by simultaneously administered probenecide.

Pharmacodynamic interactions and additive toxicity (3-5: Pharmacodynamic interactions between similarly acting drugs may lead to additive or even over-additive effects (potentiation). A well-known example is the combination of i.v. verapamil and a ß-blocker, which may cause additive impairment of cardiac A-V conduction and the risk of A-V block. Another possibility is the inhibition of the therapeutic effect of a drug by an additional agent. Over-additive adverse reactions are illustrated by the following example: a most important interaction, probably caused by non-specific mechanisms, is the mutual enhancement of the central nervous depressant effects of all drugs that are known to dampen the activity of the central nervous system. This interaction holds for hypnotics, anxiolytics (minor tranquillizers), antipsychotics (neuroleptics, major tranquillizers), anti-epileptics, and opioids, but also for drugs with central nervous depressant adverse reactions, such as antihistamines, centrally acting antitussives (codeine, etc.), and scopolamine (3-5, 9). Furthermore, alcohol enhances the central nervous depressant effects of all of the aforementioned therapeutics. Accordingly, enhanced sedation, impaired psychomotor skills (driving), but also respiratory depression may occur.

Antihypertensive agents and other drugs

The most relevant interactions between antihypertensive and other drugs have been listed in the *Table 1*, and the effect of these interactions on blood pressure in the *Table 2.* A few comments may be made: it goes without saying that a combination of two or more antihypertensive agents may be expected to cause an additive blood-pressure lowering effect, to be dis-

cussed in more detail in a forthcoming issue of this newsletter. Central nervous depressant effects of all drugs suppressing the activity of the central nervous system enhance the side effects of centrally acting antihypertensives (reserpine, alpha-methyldopa, guanfacine, clonidine) (3-5, 9). More recently, a great deal of attention has been paid to the interaction between antihypertensive drugs and NSAID's. Example: indomethacin and other nonsteroidal antiinflammatory drugs (NSAID's) may counteract the antihypertensive effects of thiazide diuretics, ß-blockers, ACE-inhibitors and AT_1-receptor antagonists, as a result of sodium and fluid retention as well as of decreased formation of vasodilatory prostaglandins (6,7). It has been clearly demonstrated, however, that low-dose acetylsalicylic acid (ASA; Aspirin®, 75 mg daily) does not interfere with the antihypertensive activity of ACE-inhibitors and other types of antihypertensive drugs (8).

Table 1. Interactions between antihypertensive and other drugs

Drugs (class)	Interaction with	Mechanism	Effect
β-Blockers	verapamil diltiazem	Additive effects	A-V conduction impaired; risk of A-V block
	oral antidiabetics	β_2-receptor blockade	symptoms of hypoglycaemia are suppressed
	broncho-spasmolytic agents	β_2-receptor blockade	suppression of the bronchospasmolytic effect
	dobutamine	β_1-receptor antagonism	the inotropic action of dobutamine is inhibited
Thiazid diuretics	digoxin	Hypokalaemia	digoxin becomes more toxic (arrhythmogenic)
	lithium ions	renal excretion of lithium ions impaired	accumulation of lithium ions
α-Blockers	noradrenaline	α_1-receptor blockade	noradrenaline shows less vasoconstrictor activity
Calcium antagonists			
Verapamil, diltiazem	β-Blocker	additive effect	A-V conduction impaired; risk of A-V block
	digoxin	renal excretion of digoxin	digoxin may accumulate; arrhythmogenic effect
	protease inhibitors (HIV-treatment)	inhibition of hepatic degradation	accumulation of verapamil or diltiazem
	cimetidine	ibid.	ibid.
DihydropyridineCa-antagonists	β-blocker	β-receptor blockade	suppression of reflex tachycardia (favourable)
Felodipine	Grapefruit Juice	Enzymic inhibition (Cyt.L450 system)	accumulation of felodipine
ACE-inhibitors	diuretics (thiazide)	additive effect	strong hypotensive action
	Diuretics (K^+-sparing)	reduced renal excretion of K^+	hyperkalemia
	NSAID´-s including high dose ASA	retention of Na^+ and H_2O	reduced antihypertensive effects
	lithium ions	Reduced excretion of lithium ions	lithium ions accumulate
AT_1-receptor antagonists	virtually the same as ACE-inhibitors	interactions as ACEi-s (see above)	described before
Centrally acting antihypertensives			
α-methyl-DOPA	Fe^{2+}-ions	enteral absorption of α-methyl-DOPA	reduced antihypertensive action
clonidine	tricyclic antidepressants	antagonism of central α_2-adrenoceptors	Ibid.
	β-blockers	unknown	the clonidine rebound phenomenon is more frequent
both clonidine and α-methyl-DOPA	centrally acting depressant agents (hypnotics, tranquillizers, neuroleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)	additive effect, non-specific	sedation,fatigue

Table 2. Effect of drug interactions on blood pressure

Drugs	Mechanism of action	Increase in BP	Interferes with antihypertensive effect
Sympathomimetics	Nasal decongestants (α-rec.)	YES	NO
Ergot alkaloids	Antimigraine drugs (5HT) Bronchodilators ($ß_2$ rec.)	YES	NO
NSAIDs	Sodium retention Inhibition of vasodil. PGs	YES	YES
Oral contraceptives	Estrogens and progesterone	YES	NO
Corticosteroids	Sodium retention	YES	YES
Psychotropes	Chlorpromazine, Tricyclics, MAO-inhibitors etc.	YES	NO
Erythropoietin	Increase in blood viscosity	YES	NO
Cyclosporine	Hypothetical (via NO)	YES	NO
Resin	Inhibition of GI Absorption of anti-HT drugs	YES	YES
Anabolic steroids	Sodium retention	YES	NO

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