Progress in Drug Research

Fortschritte der Arzneimittelforschung

Progrès des recherches pharmaceutiques

Editor:
Ernst Jucker

29

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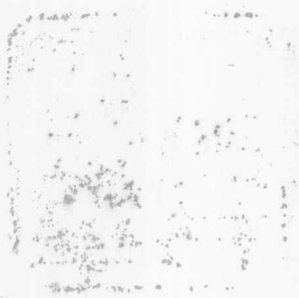

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Foreword

Volume 29 of 'Progress in Drug Research' contains 10 articles, a subject index for this volume, an alphabetic index of articles for volumes 1–29, and an author und subject index for all the volumes which have so far been published. The contributions of volume 29 are particularly concerned with drugs in general, hypertension and cardiovascular drugs, atherosclerosis, teratogenic hazards and carcinogenecity, histamine, dopamine agonists, tetrahydroquinolines and β-carbolines, and meddicinal research.

The authors have tried, and I think they have succeded, not only to summarize the current status of particular fields of drug research, but also to provide leads for future research activity. The articles of this volume will be of special value to those actively engaged in drug research, and to those who wish to keep abrest of the latest developments influencing modern therapy. In addition, it is believed that the 29 volumes of 'Progress in Drug Research' now available represent a useful reference book of encyclopedic character. The editor would like to take the occasion of the publication of this volume to express his gratitude both to the authors and to the readers. The authors have willingly undertaken the great labor of writing significant topical contributions, and many readers have helped the editor with criticism and advise. With these thanks, the editor would like to express his gratitude to the publishers, Birkhäuser Verlag Basel, particularly to Messrs. H. J. Bender, C. Einsele and A. Gomm, and their associates for the excellent cooperation.

Bâle, October 1985 Dr. E. Jucker

Vorwort

Der 29. Band der «Fortschritte der Arzneimittelforschung» umfasst 10 Beiträge sowie ein Stichwortverzeichnis dieses Bandes, ein Verzeichnis der Artikel der Bände 1–29 nach Gebieten geordnet und ein alphabetisches Register aller Autoren und Artikel der Bände 1–29. Die Beiträge des vorliegenden Bandes befassen sich mit verschiedenen aktuellen Problemen der Arzneimittelforschung sowie mit Arzneimitteln im allgemeinen. Es wurde wiederum Wert gelegt auf Beiträge mit spezifischer und gezielter Richtung sowie auf solche mit einer das gesamte Gebiet der Arzneimittelforschung tangierender Thematik.

Die Autoren auch dieses Bandes haben wiederum versucht, ihr Fachgebiet prägnant und übersichtlich darzustellen, die neuesten Entwicklungen aufzuzeigen und darüber hinaus auch in die Zukunft weisende Betrachtungen anzustellen. So dürfte auch der 29. Band der Reihe «Fortschritte der Arzneimittelforschung» dem aktiven Forscher, sei es in der Industrie oder an der Hochschule, von Nutzen sein und demjenigen, der sich über die neuesten Entwicklungen auf dem laufenden halten will, eine gute Hilfe bieten. Die vorliegenden 29 Bände stellen sicherlich ein wertvolles Nachschlagewerk mit enzyklopädischem Charakter dar.

Der Herausgeber möchte hiermit den Autoren und den Lesern seinen Dank abstatten; den Autoren für die große Arbeit, die sie bei der Abfassung der Beiträge geleistet haben, den Lesern für ihre Kritik und Anregungen. Die vielen Zuschriften und die Rezensionen helfen entscheidend mit, die Reihe auf einem hohen Niveau zu halten und den heutigen, sich stets verändernden Bedingungen der Forschung anzupassen. Dank sei auch dem Birkhäuser Verlag, insbesondere den Herren Bender, Einsele und Gomm sowie ihren Mitarbeitern für die ausgezeichnete Zusammenarbeit und für die sorgfältige Ausstattung des Bandes ausgesprochen.

Basel, Oktober 1985 Dr. E. Jucker

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Update of cardiovascular drug interactions

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1 Introduction

An increasing number of clinical studies address interactions of cardiovascular drugs in terms of both their importance in the treatment of disease and their potential to cause drug-induced toxicity. Several books and reviews are devoted to extensive listings of both observed and theoretical drug interactions [1–4]. Such listings often include extrapolation of animal data, anecdotal case reports, and interactions of questionable importance. Consequently, their literal use could result in withholding therapy or overcomplicating therapeutic decisions. Some drug interactions are critical for optimum patient care, such as combined use of drugs for their additive or synergistic effects, while others, although academically interesting, have little clinical relevance. In this review, it is not our intent to provide extensive listings of cardiovascular drug interactions but to use clinical examples to illustrate pharmacological principles which may then be extrapolated to individual patients [5].

1.1 General principles: Pharmacokinetic interactions

For the purpose of this review, pharmacokinetic drug interactions are those which alter drug absorption, distribution, metabolism, or excretion.

Absorption of a drug has multiple determinants, including physicochemical properties of the drug, gastric pH, site of absorption in the GI tract, rate of gastric emptying, intestinal motility, surface area and mucosal function, and blood flow to the absorption site. When two or more drugs are co-administered, interactions can occur involving any of these factors.

Drug interactions can also occur by alterations in the tissue distribution of drugs. Many drugs bind reversibly to plasma proteins and this binding limits the free drug concentration that is available to tissue sites of action. When drugs are highly bound to plasma proteins, large shifts in free drug concentration can occur if the drug is displaced from binding sites by other drugs. For example, a decrease of warfarin binding from the normal 99 to 96 % may seem like a small decrement. However, the concentration of free drug, that which is available to the site of action, has quadrupled from 1 to 4 %. In most instances an increase in free drug concentration as a result of one drug's displacing another

is rapidly compensated for by an increase in metabolism and/or excretion of the free drug such that the increased free concentration is transient [6]. If, however, the patient's drug elimination is compromised by drug interactions of metabolism or by disease, the increased free concentration may be more sustained and serious consequences may result.

Drug interactions of metabolism can result in an increase or decrease in drug clearance. This change in metabolism can occur by multiple mechanisms, including: alterations in hepatic blood flow (affecting drugs for which the limiting step is delivery to metabolic enzymes), competitive inhibition at sites of metabolism, or induction of microsomal enzymes. Since many drugs are metabolized by similar pathways, there is a high probability for competitive inhibition of one or more agents. It is important, therefore, to have an idea of the metabolism of each drug administered to a patient to anticipate the possibility of an interaction's occurring. In many instances, even if drugs compete for metabolic sites, sufficient capacity remains such that the competition is of negligible importance. Since most drugs are metabolized by first order kinetics, the rate of metabolism is dependent on drug concentration, meaning the sites of drug metabolism are unsaturated. All drugs, however, are capable of saturating their metabolic sites and shifting from first order to zero order kinetics. Indeed, with some drugs this shift occurs at very low plasma concentrations. Since the limited metabolic sites are saturated, only a specific amount of drug is metabolized per unit of time. With a majority of drugs, however, the shift from first order to zero-order only occurs at extremely high plasma concentrations that are seldom attained. When two drugs are administered simultaneously, however, they may compete for the same metabolic sites, and conceivably lesser concentrations of each are needed to saturate the metabolic enzymes. Therefore, a drug interaction may result in a disproportional increase in the half-life and decreased clearance of drug if the interaction not only competes for metabolism but also causes a change from a nonsaturated to a saturated state.

Finally, pharmacokinetic drug interactions can occur at sites of drug elimination, mainly the kidney. Drug excretion can be altered by several factors depending on how the individual drug is handled, including blood flow to the kidneys, glomerular filtration rate, physical characteristics of the drug such as molecular size and pKa, urine pH and se-

cretion or reuptake of the drug. Drug interactions can occur via any of these possible mechanisms or their combination.

It is important to note that pharmacokinetic drug interactions can be exaggerated by disease states. For example, disease induced decreases in metabolic capacity of drugs (as may occur in cirrhosis) may increase the likelihood of a drug interaction that shifts metabolism from first to zero-order kinetics. Similar extrapolations can be hypothesized for many disease conditions. Therefore, additional caution should be used when examining drug interactions in patients with various diseases.

1.2 General principles: Pharmacodynamic interactions

Pharmacodynamic drug interactions are defined as those that result in an alteration of the biochemical or physiological effects of a drug. Since a wide variety of dynamic drug interactions can occur, it is important for the clinician to not only be aware of the pharmacokinetics of a drug but also its mechanism of action.

In general, pharmacodynamic drug interactions can be divided into four classes:

(1) Interactions at the drug receptor (pharmacological).
(2) Interactions via different cellular mechanisms acting in concert or in opposition (physiological).
(3) Interactions due to alterations of the cellular environment.
(4) Chemical neutralization in the body.

Most drugs act at specific receptor sites by binding to a receptor (affinity) and that binding triggers a biochemical event or series of events that result in the drug's pharmacological action (intrinsic activity). Such drugs are categorized as agonists (those with both affinity and intrinsic activity), antagonists (having binding affinity without intrinsic activity), and mixed agonist-antagonists (with varying degrees of affinity and intrinsic activity). The overall outcome of drug interactions at receptor sites are dependent on the varying affinities and activities of the different agents involved.

For example, several antagonists are used clinically for their ability to block the actions of an agonist; e. g., β-adrenergic receptor antagonists are used extensively to block the actions of endogenous or exogenous catecholamines. In some instances, however, these interactions are un-

desirable. For example, patients with congestive heart failure or chronic obstructive pulmonary disease may be compromised by blocking β-adrenergic receptors since such drugs obviate the beneficial effects of endogenous catecholamines. The physician, therefore, needs to be aware of which drugs bind to or act at the same receptor to avoid potential toxicity or loss of therapeutic effect.

Many pharmacodynamic drug interactions occur as a result of drugs acting via different mechanisms to produce similar or opposite effects. An example of a beneficial effect is the use of β-receptor agonists with methylxanthines (theophylline) to relax bronchiolar smooth muscle. An example of a harmful interaction is the effect of aminoglycoside antibiotics to potentiate the blockade of skeletal muscle (particularly respiratory) by the neuromuscular blocking agents [7]. Physiological interactions can also occur by one drug acting in concert or in opposition to another through different mechanisms. An example of the former is use of combinations of agents with different mechanisms of action to have additive effects to lower blood pressure; a converse example is the effect of nonsteroidal anti-inflammatory drugs to attenuate the antihypertensive effects of captopril [8] and β-adrenergic antagonists [9–12] or to decrease the response to loop diuretics [13, 14].

The third type of pharmacodynamic interaction occurs when the action of one drug results in a change in the intra- or extracellular environment that modifies the action of another drug. The best example of this is the interaction between cardiac glycosides and drugs that cause potassium depletion [15, 16]. Another example is the interaction between reserpine and indirectly acting sympathomimetic agents [17, 18]. Reserpine depletes norepinephrine (NE) in nerve terminals [18]. With less NE, there is less response to drugs such as metaraminol that act by releasing the neurotransmitter.

The final type of interaction involves chemical neutralization of one drug by another. Several interactions of this type occur in the GI tract and are discussed in detail in the section on drug absorption. This type of interaction also occurs within the circulation and may be desirable as is the case with the use of protamine to neutralize heparin. They can also be deleterious as is illustrated by the inactivation of gentamicin with carbenicillin, piperacillin, and other penicillins in patients with end-stage renal disease [19–21] due to formation of an inactive complex between the penicillins and the aminoglycoside.

Table 1
Cardiovascular drug interactions at absorption sites.

Mechanism	Causative agent	Drug affected	Result of interaction	Ref.
Formation of complexes, chelation, adsorption	Activated charcoal	Digoxin	↓absorption	[29]
		Phenytoin	↓absorption	[29]
	Antacids	Bishydroxycoumarin	↑absorption	[28, 35]
		Digoxin	↓absorption	[22, 25]
		Propranolol	↓absorption	[23, 26]
	Cholestyramine	Digitoxin	↓absorption, ↑ elimination	[32]
		Digoxin	↓absorption	[31]
		Oral Anticoagulants	↓absorption, ↑ elimination	[27, 33]
	Kaolin-pectin	Digoxin	↓absorption	[22, 30]
	Sucralfate	Warfarin	↓absorption	[34]
Alterations in gastric pH affecting ionization or dissociation		NONE DESCRIBED		
Changes in gastric motility	Amitryptyline	Bishydroxycoumarin	↑absorption due to ↓GI motility	[40]
	Antacids	Phenytoin Propranolol	↓rate of absorption of each of these drugs due to delayed gastric emptying	[37, 38, 23]
	Ethanol	Propranolol	↓rate of absorption	[26]
	Metoclopramide	Cimetidine Digoxin	↓absorption of both due to ↑GI motility	[39]
	Propantheline	Digoxin	↑absorption due to ↓GI motility	[39]
Effects on GI mucosa	Neomycin	Digoxin	↓absorption	[42]
	Phenytoin	Furosemide	↓absorption (possibly due to altered transport)	[44]
	Sulfasalazine	Digoxin	↓absorption	[41]
Effects on GI metabolism	Erythromycin	Digoxin	↑serum concentrations	[43]

2 Cardiovascular drug interactions

2.1 Drugs interacting at sites of absorption

Drug interactions can alter the rate and/or the extent of drug absorption. The rate of absorption determines how fast drug enters the blood and the peak concentrations attained. Extent of absorption affects the total amount systemically available. A decreased extent of absorption can result in a substantial decrease in circulating drug concentrations, thereby compromising therapy. On the other hand, an increase in absorption could subject the patient to drug toxicity. Since oral absorption of drugs is dependent on many factors, it is not surprising that potential drug interactions occur that involve a number of mechanisms. Though the ensuing discussion will focus on oral absorption, the clinician should remember that the same principles apply to IM drug administration. For our purposes, we classify absorption interactions (table 1) as follows:

(1) Formation of drug complexes due to adsorption, chelation, or binding.
(2) Alterations in gastric pH.
(3) Changes in GI motility.
(4) Alterations in GI mucosal function.
(5) Effects on GI metabolism.
(6) Effects on membrane absorption sites.
(7) Alterations in GI perfusion.

Antacids interact with many drugs to alter absorption by formation of complexes with magnesium, aluminum or calcium ions. Usually, the complex formed between drug and ion is less soluble, and/or less absorbable than the parent drug, resulting in a decrease in the extent of absorption [22–26]. In unusual instances, however, the complexes may be more soluble and, thus, antacids may occasionally result in increased absorption. For example, bishydroxycoumarin chelates with magnesium in the stomach to form a more absorbable complex [27, 28]. Thus, patients administered this anticoagulant with antacids may develop higher serum concentrations and a greater anticoagulant effect. Several other interactions occur via a similar mechanism usually to decrease bioavailability. These include binding or adsorption of digoxin and phenytoin by activated charcoal [29], of digoxin by Kaolin-pectin

[30], of a variety of cardiovascular drugs by the hypocholesterolemic agents, cholestyramine and colestipol [27, 31–33], and of warfarin by sucralfate [34]. Cholestyramine binds bile acids in the gut and, thus, decreases absorption and enterohepatic reabsorption of cholesterol. The resin can also bind other compounds in the intestine, thus accounting for decreased absorption of chlorothiazide, cardiac glycosides, and anticoagulants [27, 31–33, 35]. To avoid the interaction rather than compensate for it, patients requiring these drug combinations should be administered the drug (digoxin, digitoxin or warfarin) 1 hour before or 4 hours after ingesting cholestyramine or colestipol.

The interaction between digitoxin or warfarin and cholestyramine can also be used to clinical advantage in patients toxic with either of these agents. Both are excreted in the bile and reabsorbed by enterohepatic circulation. Administration of cholestyramine sequesters drug in the gut, thereby resulting in less reabsorption and decreasing serum concentrations [27, 32].

Antacids can also affect drug absorption by altering gastric pH [35], since drug absorption is, in part, dependent on dissolution of drug and on extent of ionization. In the acidic milieu of the stomach, drugs that are weak acids are less ionized, and thus more rapidly absorbed. The opposite is true for weak bases. Thus, alteration in gastric pH by antacids, and/or cimetidine can affect drug absorption though important interactions by this mechanism have not been described for cardiovascular agents.

Drug interactions can also affect the rate of absorption. Since most drugs are absorbed in the small intestine, changes in gastric emptying can alter delivery to absorption sites and, thereby, alter the rate of absorption. Thus antacids, alcohol and narcotic analgesics [36], which slow gastric emptying, decrease the rate of absorption of several cardiovascular drugs, including phenytoin [37, 38] and propranolol [23, 26].

Drugs that alter intestinal transit time can also affect both rate and extent of drug absorption. The anticholinergic, propantheline, slows GI motility and, thus, increases absorption of poorly soluble drugs such as some of the older preparations of digoxin [39]. Amitryptyline increases absorption of bishydroxycoumarin presumably by the same mechanism [40]. A variety of drugs such as phenothiazines, antidepressants and antihistamines (H_1 receptor antagonists) have anticholinergic side effects and might importantly influence GI transit, emphasizing the importance of understanding the spectrum of a drug's phar-