PHARMACOTOXICOLOGIC INTERACTIONS BETWEEN DRUGS AND ANTIBIOTICS †

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†Opinions expressed and any conclusions drawn are those of the author and are not to be understood as necessarily having the endorsement or representing the viewpoints of the Food and Drug Administration.

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1. INTRODUCTION

1.1. Clinical Significance of Antibiotic Interactions

No drug is safe under all conditions of usage. A benefit-to-risk "trade off" is present in every clinical situation. There seems to be a tendency to regard the benefits of antibiotics, in particular, as paramount; such a view stems in part from the critical needs of the patient when rational antibiotic therapy is indicated and widely effective. More often, however, antibiotic use is justified by a sense of confidence that this type of drug therapy has a high safety margin and is fairly harmless. Statistical reports on the proportion of hospitalized patients receiving antibiotics during their stay and on the number of unhospitalized patients given prescriptions for antibiotics suggest that, in light of today's prescribing habits of using multiple drugs concurrently, the incidence of antibiotic interactions may be greater than the available adverse reaction reports have indicated. Karch and Lasagna /1/, in a recent critical review, reported that antibiotics were involved in a large proportion (range, 9.3 - 41.5%) of adverse reactions. The literature contains little definitive information on the overall incidence of antibiotic interactions that result in adverse drug reactions in hospital or outpatient populations.

The potential for problems and the overall incidence of adverse reactions due to antibiotic interactions in large populations is unknown at this time. A surveillance computer program at the Food and Drug Administration (FDA) was used to estimate the adverse reaction incidences and antibiotic interactions on file at this Federal Agency, which is charged with monitoring drug experience information as part of its review of the safety and efficacy of marketed drugs. In actual practice, this represents a herculean task beyond the means of manpower and monitoring resources currently available.

1.2. Analysis of Adverse Antibiotic Interactions Reported to FDA (1969-1975)

Data derived from the FDA Adverse Drug Reaction Reporting Program /2/ for the period 1969-1975 were used to assess the relative incidence of adverse drug interactions that involved antibiotics.* Information on file from earlier years was incomplete and unreliable.

* The author was assisted in this analysis by Dr. Rita A. Orzel, formerly with the Bureau of Drugs, FDA.

Table I lists the antibiotic classification taken from the *Code of Federal Regulations* that groups the various antibiotics according to chemical similarity; this classification provides a useful grouping of every antibiotic that may be involved in a drug interaction.

TABLE I *Classification of antibiotics involved in interactions*[a]

Penicillins	*Tetracyclines*
Ampicillin	Chlortetracycline
Carbenicillin	Doxycycline
Cloxicillin	Minocycline
Dicloxicillin	Oxytetracycline
Methicillin	Tetracycline
Nafcillin	
Penicillin G	*Peptides*
Penicillin V	Bacitracin
Phenethicillin	Colistin
Oxacillin	Polymyxin B
	Viomycin
Cephalosporins	
Cephalexin	*Aminoglycosides*
Cephaloridine	Streptomycin
Cephalothin	Gentamicin
	Kanamycin
Macrolides	Paromomycin
Erythromycin	Neomycin
Troleandomycin	
	Antifungal
Lincomycins	Amphotericin B
Clindamycin	Griseofulvin
Lincomycin	
Certain Other Antibiotics	
Chloramphenicol	
Rifampicin	

[a]Classification used by FDA in the *Code of Federal Regulations*.

A standard form* is used to report information about drugs to the Drug Experience Group at FDA. The system takes the form of evaluating reports (mostly voluntary) on adverse drug effects submitted

*Form 1639a, Drug Experience Report, available from Division of Epidemiology and Drug Experience, Food and Drug Administration, Rockville, Md 20857.

by drug companies, physicians, pharmacists, dentists, and other health practitioners. In these reports, the terms "drug experience," "adverse *drug experience," and "adverse reaction,"* as defined in the *Code of Federal Regulations* /3/, "...mean any adverse experience associated with the use of the drug, whether or not drug-related, and include any side effect, injury, toxicity, or sensitivity reaction or significant failure of expected pharmacological action". This definition includes suspected antibiotic interactions. The information received is stored in a computer programmed to retrieve data on the nature of the adverse interaction, the drugs involved, their doses and routes of administration, and information about the relative significance of the interaction as assigned by the reviewer. In this manner, a limited degree of objectivity is obtained from a subjective adverse drug report.

All antibiotic interactions reported to FDA can be classified according to cause and effect relationships (Table II) similar to those described by Karch and Lasagna /1/. In general, the designations "definite," "probable," "possible," and "remote" are used to standardize clinical judgments and reflect a reviewer's interpretation of the reported information. Many qualifying factors influence the information that is entered into the computer file; these include differences of opinion among reviewers, experience of the reviewers, differences in information provided in each adverse reaction report, and differences in information sources. Consequently, there is a tendency to underestimate the categories of "definite" and "probable" adverse reactions, and to overestimate the incidence of reactions in the possible and remote categories. With all the variables involved, the validity of any such computer analysis of specific interactions (*e.g.*, of antibiotics) always raises unanswerable questions.

TABLE II *Antibiotic-drug interactions reported to the FDA, 1969-1975*[a]

Interaction classification	*No. of cases*	*%*
Definite	5	0.3
Probable	12	0.6
Possible	171	7.6
Remote	2048	91.5
Total	2236	100.0

[a]Data represent 3.2% of all adverse drug reactions reported to FDA.

Although antibiotics and drugs are widely used in combinations, only 3.2% of all adverse reactions were listed as being due to antibiotic interactions, and only about 8.5% of these reports were classed as meaningful and less than 1% as significant. Moreover, almost all reports of antibiotic interactions showed that conditions of use were uncontrolled and poorly defined clinically, and that doses, disease status of the patients, and the interacting drugs and other mitigating factors differed greatly, making an exact, objective characterization of the incidence of any adverse reaction impossible.

Table III shows an additional analysis of data from the more significant reports by sub-grouping the incidence and severity of each type of reaction according to the antibiotics involved. Numerically, this table shows more interactions than those listed in Table II because in some cases more than one antibiotic was involved in a reported interaction under each of the aforementioned categories. Essentially, 38.6% of all the antibiotic interactions in the "possible," "probable," and "definite" categories fell into the penicillin and cephalosporin groups, with the latter drug group showing the second largest incidence of the more significant interactions by categories. The lincomycins and aminoglycosides together comprise 53.7% of all the three categories of antibiotic interactions reported during the 6-year period. Interestingly, this information reflects antibiotic toxicity to a remarkably accurate degree. No significant correlation was noted between the incidence of drug reactions and the year the antibiotic was approved for use, although the newer drugs appear to be mentioned in a higher proportion of adverse reaction reports. Whether the distribution shown in Table III coincides with the actual incidence of antibiotic interactions and is representative of the frequency of antibiotic use in the general population at large is unknown at this time. Since the entire Adverse Drug Reaction Reporting Program is voluntary and reports come from all health sectors, the data seem to reflect the most accurate sampling survey currently available for analysis.

1.3. Factors Controlling Untoward Antibiotic Interactions

Antibiotics are subjected to more uncontrolled factors than are other classes of drugs. Variables associated with antibiotic interactions and adverse drug effects and the various pharmacokinetic and pharmacodynamic aspects that are interrelated with each other are shown in

TABLE III *Distribution of antibiotic-drug interactions reports (1969-1975)*[a]

Antibiotic group	*% of Total*	*Category*			*Year approved*
		Possible	*Probable*	*Definite*	
Penicillins	18.3				
Penicillin G		11	1		1945
Procaine penicillin G		5	1		1948
Benzathine penicillin		1			1954
Phenoxymethyl penicillin		2	1	1	1957
Cloxacillin		1			1965
Methicillin		2	1		1960
Nafcillin		2			1963
Ampicillin		13	3		1963
Carbenicillin		4			1970
Oxacillin		2			1962
Cephalosporins	20.3				
Cephaloridine		3			1968
Cephalothin		18	3		1964
Cephalexin		17			1971
Cephazolin		14		1	1973
Macrolides	3.3				
Erythromycin		7	1		1952
Troleandomycin			1		1960
Lincomycins	41.7				
Lincomycin		13	2		1964
Clindamycin		94	4		1970
Tetracyclines	2.5	6	1		1953
Chloramphenicol	1.8	5			1949
Aminoglycosides	12.0				
Streptomycin		4			1947
Kanamycin		7	1	3	1958
Gentamicin		16			1966
Peptides	0.7				
Colistin		2			1961
Cycloserine	0.7	1	1		1956
Total		350	21	5	

[a]From the FDA Adverse Drug Reaction Reporting Program.

Figure 1, which is an adaptation from a recent report on factors controlling untoward drug actions /4/. Three determinants interact together: the antibiotic, the patient, and the drug used in combination (which can be another antibiotic). Each determinant contributes its own set of modifying factors: pharmaceutical, clinical, or additional, for the antibiotic, the patient, and the interacting drug, respectively.

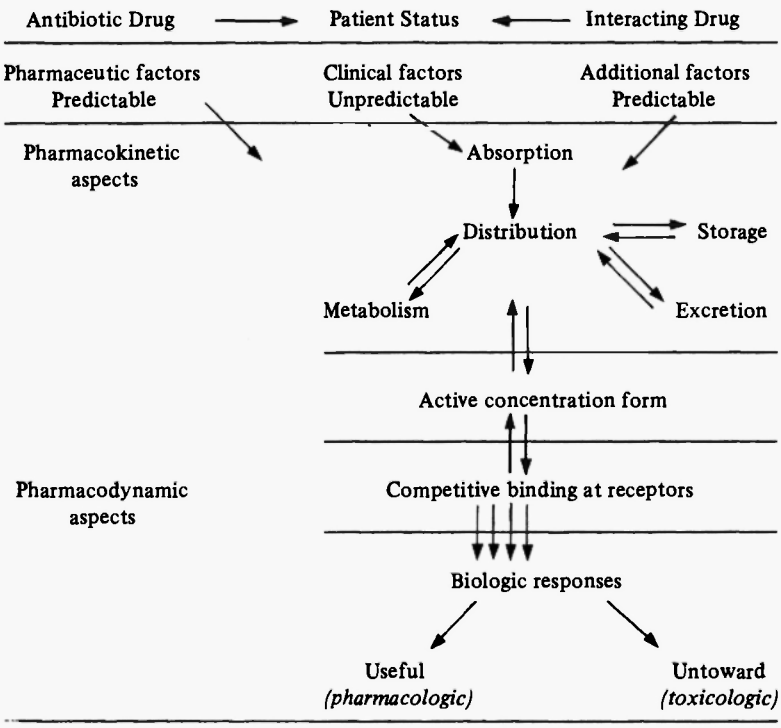

Fig. 1. Variables associated with antibiotic interactions (modified from Gysling and Heisler /4/).

The pharmaceutical factors include the physiochemical nature of the antibiotic and its formulation, dosage, route and time of administration, duration of treatment, etc.; these factors are generally predictable or they are at least known and of a controllable nature. In contrast, the patient determinant factors are, for the most part, unpredictable and

poorly controlled. These include disease conditions; organ functions, especially those of liver and kidney, which are very important in antibiotic therapy; pH changes in various body fluids; plasma protein levels; and a multitude of pathophysiological variations. The interacting drug adds still another set of factors, mostly predictable, to this combination of ingredients. Pharmaceutical factors may be different from those of the antibiotic, the mode of action may be different, and another target organ may be involved; when the proper mechanism is added to this mixture of variables, it is almost inevitable that an interaction must occur. Indeed, there is a long list of possible antibiotic interactions and adverse effects. Some effects are of minor importance, but others are more serious because the consequences of ineffective action or enhanced toxicity of an antimicrobial agent can upset the usual benefit-to-risk equation for this class of drugs.

The pharmacokinetic aspects include the usual absorption, distribution, metabolism, storage, and excretion relationships (Fig. 1). These factors modulate the active antimicrobial concentration of antibiotics, more than other drug classes, in body fluids and tissues. The pharmacodynamic aspects are of two types: those that are directed towards antimicrobial activity and those that are certain pharmacological actions usually considered as toxic side effects, such as the neuromuscular blocking action of the aminoglycosides. The antimicrobial action is useful while the neuromuscular action is not, *i.e.*, it is adverse or toxic.

The unpredictable patient makes the most significant contribution to what can go wrong when an antibiotic or any other drug is given. Patient factors /5/ can influence antibiotic effectiveness negatively, even if prior sensitivity testing with microbial cultures has determined the proper antibiotic to use. These factors are:

Age. The requirements of the very young and the very old and their detoxification mechanisms must be considered.

Genetic factors. These factors are not usual or easy to evaluate. For example, the increased toxicity of chloramphenicol in patients with hemolytic anemia could be due to a genetic factor.

Pregnancy. All antibiotics pass the placental barrier. An example of an adverse effect is the toxicity of tetracyclines in fetal tooth development /6/.

Concurrent disease. The health status of the patient must be considered. Examples include the decreased absorption of penicillin in diabetes and, again, the increased toxicity of chloramphenicol in anemic patients.

Hypersensitivities. Allergies may be present without prior antibiotic exposure; in addition, the phenomenon of anaphylaxis may occur with many widely used antibiotics.

Central nervous system disorders. These are especially important in patients who are prone to seizures and in those with conditions like myasthenia.

Indigenous microbial flora. The presence of these flora is a special factor in antibiotic therapy. Consideration must be given to the possibility of alterations in the absorption and activation of drugs such as methotrexate and in the synthesis of vitamin K, as well as to the superinfections in the gastrointestinal and upper respiratory tracts that can follow prolonged antibiotic therapy.

Hepatic function. Metabolism, inactivation, biliary excretion, and concentrations of drugs are governed by hepatic function. A few examples of adverse effects are the enhancement of tetracycline toxicity in cirrhosis and hepatitis, the two-fold increased half-life of lincomycin and the reduced hepatic penicillin concentration in liver diseases, and the enhanced toxicity of erythromycin and rifampicin that occurs in hepatic dysfunction.

Host defense mechanism. The most important absolute predeterminant of antibiotic effectiveness is the host defense mechanism, and when it is reduced as in immunosuppression, therapeutic drug failures can result.

Renal function. The single most important determinant of antibiotic responses for penicillin, cephalosporins, aminoglycosides, peptides, and tetracyclines is renal function. Renal dysfunction, whether pre-existing or the result of kidney disease or injury, can cause serious and lethal effects when potentially toxic antibiotics and other drugs are combined to produce an enhanced nephrotoxic response. These adverse effects are common in older people who have decreased excretory capacity that is not indicated by the usual kidney function tests such as blood urea nitrogen or creatinine determinations.

These pathophysiological factors which modify antibiotic and drug response should provide ample evidence of a need for caution when antibiotics are combined with other drugs.

2. MECHANISMS ASSOCIATED WITH ANTIBIOTIC INTERACTIONS

2.1. Pharmacokinetic Aspects

2.1.1. Chemical and Physical Effects in the Gastrointestinal Tract

Antibiotic interactions can alter gastrointestinal absorption by either chemical or physical effects. The tetracyclines interact with polyvalent cations that are present in milk products and antacid preparations, especially those containing calcium, aluminum, magnesium, and bismuth salts; chelation complexes are formed and, as a result, antibiotic absorption is decreased. Tetracycline absorption is also reduced when the gastric pH is increased (achlorhydria) by sodium bicarbonate /7, 8/ or when the antibiotic forms complexes with iron salts /9/. The lincomycins are incompatible with antidiarrheal mixtures containing kaolin and pectin /10/ and with preparations containing polyvalent cations or activated charcoal /11/; even food, through a physical adsorption mechanism, can cause a decrease in the blood concentration of the antibiotic. To a lesser extent, the aminoglycosides interfere with the normal function of bile salts to cause a malabsorption syndrome /12/ that impairs the utilization of lipid-soluble drugs, vitamins, fats, iron, and glucose /13, 14/, as well as of penicillin /15/ and digitalis glycosides /16/. Pharmacologically, drugs such as the anticholinergic and ganglionic blocking agents decrease motility, resulting in increased emptying time and increased gut inactivation and thereby decreasing the absorption of antibiotics such as the penicillins and erythromycins /17/.

2.1.2. Antibiotic Interactions with Intestinal Flora

By their nature, antibiotics have an antimicrobial action on the normal bacterial flora of the intestines. Microbial action is essential for the degradation and absorption of methotrexate and perhaps of other antitumor drugs; inhibition of microbial action by aminoglycosides causes reduced blood concentrations of this drug /18/. Tetracyclines, ampicillin (a broad-spectrum penicillin), and other broad-spectrum antibiotics interact with oral anticoagulants to suppress vitamin K synthesis, causing enhanced anticoagulant activity and increased prothrombin times, especially when a dietary vitamin K deficiency exists /19, 20/.

2.1.3. Antibiotic Interactions Involving Serum Protein Binding and Displacement

Combinations of penicillin and drugs such as aspirin, phenylbutazone, and probenecid displace many antibiotics, notably penicillin, from serum protein binding sites. The resulting action increases and prolongs penicillin activity, an effect that is used beneficially in therapeutics, *e.g.*, in the treatment of gonorrhea and other diseases when sustained high blood concentrations of penicillin are needed /21, 22/.

2.1.4. Antibiotic Interactions Involving Active Renal Tubular Transport and Secretion

Sulfonamides, uricosuric agents, and anti-inflammatory drugs, such as probenecid, salicylates, phenylbutazone, and indomethacin, tend to inhibit the very rapid excretion of penicillin and cephalosporins by their competitive action on the same renal tubule transport mechanism /19, 23-26/. The effect is to prolong the presence of penicillin in blood and thereby to enhance its action by achieving the high concentrations needed for treatment of endocarditis, septicemias, and gonorrhea.

2.1.5. Receptor Site Antagonism and Displacement From Tissue Sites

Probenecid and penicillin interact at various tissue sites; effects with this combination occur in blood, kidney, and brain, and biliary excretion is also affected /19/. Essentially, probenecid causes increased concentrations and a prolonged half-life of penicillin in the blood and cerebral spinal fluid (CSF) by blocking active penicillin secretion through the renal tubules and into the bile, by displacing penicillin from the brain into the CSF, and by blocking transport from the CSF into blood.

2.1.6. Antibiotic Interactions Involving Hepatic Enzymes and Metabolism

Several antibiotics interact with other drugs to cause either stimulation and induction, or inhibition of hepatic drug-metabolizing enzymes. Chloramphenicol and antidiabetic drugs (sulfonylureas) interact to cause an enhanced and prolonged hypoglycemic effect that is due to the inhibition of hepatic biotransformation of the antidiabetic drug by chloramphenicol action on the liver /27, 28/. A similar effect occurs

with diphenylhydantoin and related anticonvulsant drugs, and results in increased blood concentrations and enhanced drug toxicity /29/. The inhibitory action of chloramphenicol increases anticoagulant activity and prolongs prothrombin times and clotting times because of the decreased metabolism of oral anticoagulant drugs such as dicumarol and warfarin. The antifungal antibiotic griseofulvin also interacts with anticoagulant drugs by a mechanism of induction or enhanced drug metabolism, thus causing hypoprothrombinemia and decreased anticoagulant activity /20, 30/. Barbiturates stimulate liver enzymes and would tend to increase griseofulvin metabolism /31/ and to decrease the half-life of tetracyclines /32, 33/. Aminoglycosides and polymyxin antibiotics have inhibitory effects on the metabolism of general anesthetics, and enhancement of anesthesia can result /34-37/. Another example of hepatic interaction between an antibiotic and drugs, is the potential of the antitubercular antibiotic rifampicin to interact with halothane to enhance its hepatotoxic effect /38/, with oral contraceptives to increase their metabolism /39/, and with probenecid to increase rifampicin activity and blood concentrations /40/.

2.1.7. Antibiotic Interactions Involving the Urinary Tract

Both favorable and adverse actions can occur when antibiotics interact with other drugs in the kidney. These include the competition for renal tubular transport when penicillin and cephalosporins are used with uricosuric agents, as mentioned previously; the enhanced nephrotoxicity caused by tetracyclines interacting with methoxyflurane /41-44/; and the extreme nephrotoxicity caused by combinations of the aminoglycosides and peptide antibiotics /17, 45, 46/. Both amphotericin B and thiazide diuretics cause a loss of potassium, and when they are combined an enhanced hypokalemic toxicity results /47, 48/. Antibiotic interactions affecting the kidney also include favorable actions of certain drugs that enhance antibiotic activity by changing the urine pH. The antimicrobial activity of the aminoglycosides, erythromycin, and cephalosporins is enhanced by sodium bicarbonate and acetazolamide /49/, which alkalinize the urine, and tetracycline activity can be enhanced by concurrent administration of ammonium chloride, which acidifies the urine.

2.1.8. Antibiotic Interactions Involving Tissue Sites

Certain important antibiotics are associated with specific effects that are manifested by signs of clinical toxicity on target organs and these effects are markedly enhanced by the combined action of another antibiotic or drug with a similar tissue predilection. Some of the more important interactions of this type are listed in Table IV. Aminoglycosides and peptide antibiotics have neuromuscular blocking activity /37/.

TABLE IV *Antibiotic interactions at tissue sites*

Antibiotic	*Drug*	*Interaction*
Aminoglycosides, peptides	Skeletal muscle relaxants (surgical)	Myasthenia, apnea
Aminoglycosides	Peptides	Nephrotoxicity
Tetracyclines	Methoxyflurane	Nephrotoxicity
Aminoglycosides	Ethacrynic acid, furosemide	Ototoxicity
Cephaloridine	Ethacrynic acid, furosemide	Nephrotoxicity
Aminoglycosides	General anesthetics	Prolonged neuromuscular blockade, apnea

When they are used with skeletal muscle relaxants before surgery or with general anesthetics, a pronounced synergistic action on respiration can occur and the risk of apnea is increased /34-37, 50/. Both aminoglycoside and peptide antibiotics predispose to nephrotoxicity as well as to neuromuscular blockade /45/; combination of these agents for their possible synergistic antimicrobial effects should be avoided to prevent kidney damage and respiratory paralysis /51/. In addition, the aminoglycosides are known to be associated with ototoxicity /45, 52, 53/, especially when combined with loop diuretic drugs like ethacrynic acid and furosemide or when used in the presence of renal insufficiency. Even when given alone, these diuretics and antibiotics have been implicated with deafness in older patients who have impaired kidney function. The combined use of these agents can induce serious adverse effects and should be avoided. The same precautions hold for concurrent use of cephalosporins with these diuretics; the combinations have been

reported to cause an enhanced nephrotoxic effect /54-56/. Renal failure has been associated with the combined use of tetracyclines in patients anesthetized with methoxyflurane /41, 43/, and this combination should also be avoided. These are only a few specific examples of the pharmacokinetic liabilities between antibiotics and drugs that have been reported. It is apparent that in only a few instances can beneficial responses be attributed to the combined use of these agents on the basis of pharmacokinetic mechanisms.

2.1.9. Physiochemical Incompatibilities Involving Antibiotics and Parenteral Fluids

The antimicrobial actions of antibiotics can be altered inadvertently by mixing antibiotics with each other /57, 58/ or with parenteral solutions or vehicles in which inactivation, precipitation, decomposition, or accelerated deterioration can occur /19, 59-61/. Table V shows some of the more important restrictions governing antibiotic admixtures. Physical evidence, such as visible changes, may not always be present to indicate chemical or pharmacological inactivation. Obviously, interactions occurring without visible evidence of incompatibilities are greater hazards than those that are visible. Penicillin is inactivated in 5% dextrose or 10% sucrose when the pH is increased to 8 or above by sodium bicarbonate. Penicillin G potassium, chloramphenicol sodium, and erythromycin are inactivated when added to intravenous infusions of vitamin B complex with vitamin C. Tetracyclines form complexes with polyvalent cations in a bottle, as well as in the gastrointestinal tract, and are inactivated at a pH above 4. Guidelines for antibiotics indicate that as a general rule these therapeutic agents should not be added to or mixed with parenteral solutions containing salts or other drugs at an incompatible pH.

2.2. Pharmacologic and Toxicologic Effects

2.2.1. Antimicrobial Synergism and Antagonism of Antibiotic Combinations

Unlike other types of drugs, antibiotics are often combined to promote antimicrobial effectiveness against various types of pathogens. In general, certain guidelines for combination have been developed and are based on the antimicrobial mechanisms of action (Table VI). The antibiotics are grouped according to whether they are, (I) bactericidal inhi-

TABLE V *Physiochemical incompatibilities involving intravenous infusions*

Antibiotic	*Vehicle*
Penicillin	Dextrose or sucrose, pH above 8
Erythromycin, penicillin G potassium, chloramphenicol sodium	Vitamin B complex with vitamin C
Methicillin sodium	Saline or dextrose, pH below 7
Cephalothin sodium	Lactated Ringer's solution; calcium salts
Tetracyclines	Lactated Ringer's solution; calcium salts; sodium bicarbonate
Kanamycin	Dextrose, pH 3.5–6.5
Amphotericin B	Saline

TABLE VI *Functional or physiological antagonism of antibiotic combinations*[a]

I	Bactericidal inhibitors of mucopeptide synthesis:	II	Attacking membranes:
	Penicillins		Polymyxins
	Cephalosporins		Bacitracin
III	Bacteriostatic inhibitors of protein synthesis:		Colistin
	Tetracyclines	IV	Bactericidal inhibitors of protein synthesis:
	Chloramphenicol		Streptomycins
	Erythromycin		Kanamycin
	Lincomycins		Neomycin
			Gentamicin

[a]Types I and III are generally antagonistic when combined; types I and IV are generally synergistic when combined; and types III and IV are generally additive when combined.

bitors of mucopeptide synthesis (penicillins and cephalosporins); (II) disrupters of microbial membranes (peptide antibiotics);(III) bacteriostatic inhibitors of protein synthesis (tetracyclines, chloramphenicol, erythromycin, and lincomycins); or (IV) bactericidal inhibitors of protein synthesis (aminoglycosides). Combinations of types I and III antibiotics are generally antagonistic, while combinations of types I and IV are synergistic. In contrast, combinations of types III and IV antibiotics generally have an additive effect against most microbial pathogens /19, 51, 62, 63/. Although this scheme of combined antibiotic therapy appears simple and the subject has received much attention, there are few instances in which rational antibiotic combinations are justified on the basis of well-controlled and documented clinical reports. Most of these reports have been concerned with treatment failures of combined therapy rather than enhancement of clinical efficacy; behind the problem lies the difficulty that clinically, experimental studies in humans border on the narrow line between ethics and acceptable risk.

As an example of the interaction that may take place with combined antibiotics; tetracycline, chloramphenicol, erythromycin, and aminoglycosides inhibit the efficacy of penicillin, but bacitracin, cephalothin, polymyxin, and colistin do not. The point should be emphasized that penicillin alone might be just as or even more effective when used alone, compared with its use in combination with certain other antimicrobial agents that are technically inhibitory or indifferent in action.

When a decision must be made to use or not to use a combination of antibiotics, the indications and circumstances that could justify a mixed antimicrobial therapy include: (a) treatment of an overwhelming undiagnosed infection, (b) treatment of mixed infections, (c) avoidance or delay of the emergence of resistant pathogenic strains and the development of cross-resistance, (d) prevention of superinfections, (e) synergistic effects of the combinations, (f) reduction of adverse or untoward reactions and (g) treatment of intracellular pathogens /5, 17, 19, 51, 62, 64/. These situations give the practitioner great flexibility in the selection of the appropriate antibiotic drug combination.

Side effects and adverse reactions with combined antibiotic therapy are very common /65/. An analysis of the most significant side effects attributable to antibiotics indicates that they are related to the mechanism(s) most often associated with adverse drug interactions.

The most important and serious side effects frequently encountered with antibiotic therapy involve the kidney and liver (Table VII). Dys-

TABLE VII *Antibiotics associated with organ dysfunction*

Nephrotoxic	*Hepatotoxic*
Aminoglycosides	Chloramphenicol
Gentamicin	
Neomycin	Macrolides
Streptomycin	Erythromycin
Kanamycin	Troleandomycin
Paromomycin	
	Penicillin G
Peptides	
Bacitracin	Rifampicin
Colistin	
Polymyxin B	Tetracyclines
Viomycin	
	Griseofulvin
Cephaloridine	
Tetracyclines	
Amphotericin B	

function, whether induced or existing in these organs, can cause atypical pharmacokinetic responses /66/. Since renal and hepatic pathways are the major routes by which antibiotics are eliminated /5/, any impaired function in these organs will result in drug accumulation and the incidence of adverse reactions can increase markedly. Moreover, many of these agents are potentially nephrotoxic and hepatotoxic and continued use could further accentuate the impaired organ function. The addition of another antibiotic or drug under these adverse conditions requires prudent judgment so that further injury is avoided.

Certain aminoglycosides (streptomycin, neomycin, kanamycin, gentamicin), peptides (polymyxin B, colistin), and possibly the tetracyclines are pharmacologically active in blocking neuromuscular transmission. This effect is enhanced by surgical skeletal muscle relaxants like tubocurarine and general anesthetics, and when these drugs are used concurrently with antibiotics, serious respiratory difficulties can result /37, 67/. For this reason, these agents are contraindicated in patients with pre-existing myasthenias. Other drugs that can interact with these antibiotics are anticholinesterases, quinine, quinidine, procainamide, and phenothiazines. The serious neurological side effects of aminogly-

coside and peptide antibiotics, in addition to those mentioned, include peripheral neuropathies, seizures and ototoxicity, and the tetracyclines have been associated with benign intracranial pressure. Many drugs such as lidocaine and phenothiazines can enhance and augment these toxic effects. Anaphylaxis, usually of an allergic-type hypersensitivity, is commonly associated with penicillin and, to a lesser extent, with tetracycline, cephalosporins, and streptomycin, and manifests itself clinically by signs and symptoms of shock, vascular collapse, dyspnea, and hypersensitive skin disorders and rashes /68/. Concurrent administration of other drugs associated with anaphylaxis can enhance this adverse drug reaction.

Clinical manifestations of adverse reactions involving antibiotics are associated with a varied list of side effects that includes dermal toxicity, hematopoietic changes, fever, diarrhea, malabsorption syndromes, respiratory difficulties, and gastrointestinal disorders (Table VIII). Penicillin and a number of other antibiotics and drugs can cause dermatitis and other dermatoses such as photodermatitis and urticaria; the drugs include sulfonamides, phenylbutazone, barbiturates, and hydantoins, which can interact by a cross-sensitizing mechanism. Blood cell diseases (aplastic anemia, hemolytic anemia, immune hemolysis, leukocytosis, thrombocytopenias) can be induced by chloramphenicol together with a great number of other drugs that enhance the toxicity of these antibiotics in blood-forming organs. Diarrhoea can be produced by many drugs, laxatives, antacids, anticholinesterases, and broad-spectrum antibiotics (tetracyclines and ampicillin). Mention should also be made of the use of antibiotics with corticosteroids, notably tetracycline, which may cause the emergence of bacterial resistance in conditions such as acne with the possibility of decreased resistance and superinfections /69/.

Antibiotics are not always the problem or cause of the adverse side effect or reaction, *i.e.*, other drugs may be responsible for certain clinical manifestations of toxicity. Few cardiovascular complications, blood pressure changes, or arrhythmias are due to antibiotic administration; an exception is the hypotension caused by tetracyclines in relapsing fever and by chloramphenicol in Gray's syndrome. Behavioral toxicity, glaucoma, and cataracts have not been associated with antibiotics, nor have gastrointestinal bleeding or ulcerations, pancreatitis (except with the tetracyclines when hepatotoxicity occurs), or cirrhosis. Similarly, blood glucose concentrations remain unchanged during antibiotic therapy unless antidiabetic drugs are administered concurrently.

TABLE VIII *Clinical manifestations involving antibiotics*

Adverse effect	*Antibiotic*
Dermal toxicity	Penicillins
	Tetracyclines
	Streptomycin
	Erythromycin
	Chloramphenicol
	Neomycin
	Bacitracin
	Griseofulvin
Hematopoietic changes	Penicillins
	Tetracyclines
	Streptomycins
	Amphotericin B
	Cephalosporins
	Chloramphenicol
	Rifampicin
Fever	Penicillins
	Cephalosporins
	Streptomycin
	Amphotericin B
Pancreatitis and bowel disorders	Tetracyclines
Diarrhoea	Tetracyclines
	Ampicillin
Malabsorption	Tetracyclines
	Neomycin
Respiratory difficulties	Polymyxins

3. CLASSIFICATION AND LIST OF CLINICALLY SIGNIFICANT INTERACTIONS INVOLVING ANTIBIOTICS

Table IX lists the reported interactions of antibiotics with drugs that are of possible clinical significance; the list may not be all-inclusive, however, because new reports continue to appear in the literature. Additional information on antibiotic interactions can be found in a number of excellent articles and reviews /19, 29, 59, 60, 62, 66, 70-78/.

TABLE IX *Clinically significant interactions involving antibiotics*

Drug	*Interaction*
a) *Chloramphenicol* +	
Antidiabetic sulfonylureas Chlorpropamide; tolbutamide; tolazamide; acetohexamide	Enhanced hypoglycemia; retarded biotransformation and inhibition of hepatic metabolism of sulfonylurea
Antianemic agents Folic acid; iron-dextrans; vitamin B_{12}	Myelotoxic action; interference with erythrocyte maturation; decreased utilization of antianemic drugs
Anticoagulants Warfarin; dicumarol	Enhanced anticoagulant activity; increased prothrombin time; increased clotting time
Penicillins	Bactericidal action of penicillins antagonized by bacteriostatic action
Anticonvulsants Diphenylhydantoin	Enhanced toxicity of anti-convulsant: inhibition of drug-metabolizing enzymes; increase in blood concentrations
Alcohol	Inhibition of alcohol metabolism: increased acetaldehyde concentrations; Antabuse-type reaction
b) *Aminoglycosides (neomycin, streptomycin, kanamycin, gentamicin)* +	
Carbenicillin	Gentamicin activity reduced by prolonged contact and high doses of carbenicillin; *in vitro* inactivation of physiochemical effect
Cephalosporins Cephaloridine; cephalothin	Enhanced nephrotoxicity: increased risk with large doses in old age and pre-existing renal disease
Peptide antibiotics Polymyxin B; bacitracin; colistin	Enhanced nephrotoxicity
Other aminoglycosides	Enhanced ototoxicity and nephrotoxicity
Penicillins	Neomycin and kanamycin markedly decrease blood concentrations of oral penicillins; malabsorption syndrome

TABLE IX (cont.) *Clinically significant interactions involving antibiotics*

Drug	*Interaction*
Lipid-soluble drugs and vitamins; glucose; iron	Malabsorption syndrome, especially with neomycin
Digitalis glycosides	Digoxin absorption inhibited by neomycin, especially with large doses in aged and young patients
Methotrexate	Neomycin inhibition of GI flora impairs metabolism and degradation, reducing absorption and increasing GI excretion
Anesthetics (general) Ether; cyclopropane; halothane; methoxyflurane; fluroxene	Synergistic action: respiratory paralysis; enhanced neuromuscular blockade; apnea
Methoxyflurane	Enhanced nephrotoxicity (synergistic)
Curariform agents (surgical skeletal muscle relaxants) Tubocurarine; gallamine; succinyl choline	Enhanced and prolonged neuromuscular blockade; increased risk of respiratory arrest; respiratory myasthenia
Diuretics Ethacrynic acid; furosemide	Enhanced ototoxicity, especially with impaired renal function (may be permanent or transient, no azotemia necessary)
Anticoagulants Warfarin; dicumarol	Enhanced anticoagulant activity; increased prothrombin times; neomycin malabsorption syndrome; decreased vitamin K absorption; decreased vitamin K synthesis if dietary deficiency exists (related to fat and bile acid absorption).
Dimenhydrinate	Masks symptoms of ototoxicity
c) *Peptide antibiotics (bacitracin, colistin, polymyxin B)* +	
Curariform agents (surgical skeletal muscle relaxants)	Prolonged action and enhancement of neuromuscular blockade; respiratory myasthenia; apnea; respiratory arrest
Anesthetics (general)	Prolonged respiratory depression; enhancement of neuromuscular blockade

TABLE IX (cont.) *Clinically significant interactions involving antibiotics*

Drug	*Interaction*
Cephalosporins	Enhanced nephrotoxicity
Aminoglycosides	Enhanced nephrotoxicity; prolongation of neuromuscular blockade
Heparin	Incompatibility in intravenous solutions
d) *Tetracyclines* +	
Antacids, polyvalent cations (calcium, magnesium aluminum, bismuth)	Inhibition of absorption; decreased blood tetracycline concentrations; formation of chelation complexes
Sodium bicarbonate	Achlorhydria; increased intragastric pH; decreased tetracycline absorption; increased pH in GI tract
Iron salts	Impaired tetracycline absorption; formation of chelation complexes; binding to proteins in GI tract; decreased blood tetracycline concentrations
Methoxyflurane	Enhanced nephrotoxicity, decreased renal function; renal azotemia; increased tetracycline toxicity; increased blood tetracycline concentrations
Neuromuscular blocking agents	Weak myasthenic effect; enhanced action in myasthenia patients
Anticoagulants Warfarin	Enhanced anticoagulant effect; hypoprothrombinemia; suppression of vitamin K synthesis
Barbiturates and carbamazepine	Induction and stimulation of hepatic drug-metabolizing enzymes; decreased half-life of doxycycline; decreased effect of tetracyclines
Corticosteroids	Emergence of bacterial resistance to antibiotics (especially with prolonged therapy); decreased resistance and possible superinfections

TABLE IX (cont.) *Clinically significant interactions involving antibiotics*

Drug	*Interaction*
Penicillins	Antagonistic, reduced effectiveness of penicillin against pneumococci (meningitis) and hemolytic streptococci; bacteriostatic action of tetracycline interferes with bactericidal action of penicillin
Streptomycin	Synergistic in brucellosis
Macrolide antibiotics; anticonvulsants; chlorothiazides; isoniazid; *p*-aminosalicylic acid; phenothiazines; phenindone; methyltestosterone; chlorpropamide	Enhanced hepatotoxic effect
e) *Penicillins* +	
Probenecid and other uricosuric agents	Inhibition of rapid penicillin excretion by competition for same renal transport system, prolonging penicillin concentrations in blood (combination used in treatment of gonorrhea, endocarditis, and septicemias)
Aspirin and other salicylates	Decreased serum protein binding of penicillin; increased antibacterial action
Chloramphenicol; erythromycin; tetracyclines	Bactericidal action of penicillin antagonized by bacteriostatic action
Neomycin	Malabsorption syndrome; decreased blood penicillin concentrations
Sulfonamides	Displacement of penicillin from protein binding sites
f) *Lincomycin and clindamycin* +	
Antidiarrheal mixtures Kaolin and pectin; bismuth; magnesium; aluminum; charcoal	Physical adsorption of antibiotic; decreased GI absorption and decreased blood concentrations
Erythromycin; chloramphenicol	Antagonistic, reduced effectiveness of lincomycins; interference with bacterial protein synthesis in ribosomes (affinity for protein binding sites in cell walls is greater than that of lincomycins)

TABLE IX (cont.) *Clinically significant interactions involving antibiotics*

Drug	*Interaction*
Curariform agents Tubocurarine; succinyl choline	Enhanced neuromuscular blockade
g) *Griseofulvin* +	
Phenobarbital and other barbiturates	Decreased griseofulvin efficacy; decreased absorption and decreased blood concentrations (not due to metabolism)
Anticoagulants Warfarin	Decreased anticoagulant effect; reduced hypothrombinemia; induction and stimulation of liver drug-metabolizing enzymes by griseofulvin
Alcohol	Reduced alcohol tolerance; possible inhibition of alcohol metabolism
h) *Amphotericin B* +	
Digitalis glycosides	Increased risk of digitalis toxicity due to hypokalemia induced by amphotericin B
Corticosteroids	Enhanced potassium depletion and sodium retention with possible cardiac enlargement and failure
Thiazide diuretics	Possible enhancement of hypokalemic effects
Curariform agents Tubocurarine; gallamine; succinyl choline	Enhanced neuromuscular blocking effects due to hypokalemia
i) *Cephalosporins (cephaloridine, cephalexin, cephalothin)* +	
Diuretics Ethacrynic acid; furosemide	Enhanced nephrotoxicity
Peptide antibiotics Colistin	Enhanced nephrotoxicity Enhanced nephrotoxicity
Aminoglycosides Probenecid	Increased blood concentrations, reduced renal clearances, and prolonged effects of cephalosporins (combination used in treatment of gonorrhea, endocarditis, and septicemias); possible cephalosporin toxicity

TABLE IX (cont.) *Clinically significant interactions involving antibiotics*

Drug	*Interaction*
j) *Macrolides (erythromycin troleandomycin)* +	
Lincomycins	Antagonistic, effectiveness of lincomycins reduced
Penicillins	Synergistic for staphylococci and streptococci
Tetracyclines	Enhanced hepatotoxicity
Urinary alkalinizers Acetazolamide; sodium bicarbonate	Enhanced macrolide effectiveness in urinary tract infections involving *Klebsiella* and *E. coli*
k) *Rifampicin* +	
Anticoagulants aspects	Decreased anticoagulant effect; induction and stimulation of hepatic drug-metabolizing enzymes
Oral contraceptives	Decreased contraceptive effect; increased estrogen metabolism
Probenecid	Increased rifampicin activity; increased blood concentrations; decreased hepatic uptake
Halothane	Enhanced hepatotoxicity
p-Aminosalicylic acid	Decreased blood rifampicin concentrations; decreased absorption from GI tract
Barbiturates	Decreased blood refampicin concentrations due to induction of hepatic microsomal enzymes

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