Adverse Drug Reactions to Antibiotics and Major Antibiotic Drug Interactions

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Abstract. Adverse drug reaction and drug interactions represent negative consequences of pharmacotherapy A thorough knowledge of how the adverse reactions and drug interactions occur will aid in our ability to provide the best patient care possible Adverse drug reactions and drug interactions are defined and mechanisms of their occurrence are discussed, ways to identify, assess, manage, and report these reactions are presented The importance of postmarketing surveillance is highlighted A thorough understanding of the mechanism of adverse drug reactions and drug interaction is essential for the health care practitioner Improved patient care can be achieved by applying this knowledge to the individual patient When drugs are administered to patients, many things can go wrong The magnitude of this problem warrants spending sufficient resources to establish programs to identify, assess, and manage these reactions Having effective reporting programs will help prevent many reactions and will provide earlier detection of adverse reactions to new drugs

Key words: Antibiotics-adverse drug reactions — Drug interactions

Introduction

All drugs which provide a proven therapeutic benefit may cause adverse effects Nevertheless, a large number of effective drugs produce no adverse effects in the vast majority of patients who take them This is in part due to the pressures on pharmaceutical companies to produce safe and effective medicines, but is also due to increasingly stringent governmental regulations which regulate the use of new drugs, and organizations which monitor the safety of existing compounds New drugs are now subjected to a rigorous programme of preclinical and clinical testing before they are licensed for general use, and are monitored for safety following licensing

The size of the problem

Overall, approximately 10–20% of hospital inpatients experience an adverse drug reactions Up to 7% of hospital admissions are directly due to adverse drug reactions, and about 0 25–0 5 % of deaths are attributable to treatment rather than to disease for which

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the drugs were being used. Unwanted effects of drugs are more common in elderly patients, rising from 3% in 10–20 years olds to 20% in patients aged over 80 years. The likelihood of adverse reactions increases sharply with the number of drugs administered, partly because such patients are likely to be more unwell, more susceptible to a drug-host reaction, and partly because the potential for interaction between drugs increases in a factorial manner with each new drug added to the regimen (WHO 1975; Goodman and Gilman 1996).

Some have estimated that up to 15% of hospitalized patients suffer at least one adverse drug reaction during their hospital stay (Stafford 1988; Prince et al. 1992). In a study of more than 30,000 hospital records, nearly 4% of patients received disabling injuries caused by medical treatment (Roe 1984; Leape et al. 1991). Drug complications were the most common cause for injuries, accounting for 19% of the total.

Table 1 lists the drug classes responsible for adverse events in order of frequency. The most troublesome classes were antibiotics and antitumor agents, responsible for the recorded adverse effects in approximately 16% and 15% of cases, respectively. Table 2 lists the types of drug related adverse events in order of frequency. The most common complications were bone-marrow suppression (16%), bleeding (15%), central nervous system effects (15%) (Cumming and Kineberg 1993), and allergic/cutaneous reaction (14%) (De Swarte 1984).

Table 1. Drug classes responsible for adverse effects

Drug class	Frequency
Antibiotics	Most frequent
Antitumor agents	↓
Anticoagulants	↓
Cardiovascular agents	↓
Anticonvulsant agents	↓
Diabetes therapy	↓
Antihypertensives	↓
Analgesics	↓
Antiasthmatics	↓
Sedative-hypnotics	↓
Antidepressants	↓
Antipsychotics	↓
Peptic ulcer therapy	Least frequent

Table 2. Types of drug-related adverse effects by frequency

Type of Adverse Event	Frequency
Marrow suppression	Most frequent
Bleeding	↓
Central nervous system	↓
Allergic/cutaneous	↓
Metabolic	↓
Cardiac	↓
Gastrointestinal	↓
Renal	↓
Respiratory	Least frequent

Reported rates range from 2.6–50.6%, with the lower rates coming from physician data collection and the higher rates coming from patient surveys (Schneider et al. 1992; Gugler 1994; Novotný 1996; Novotný 1997). The elderly are at special risk because of the numbers of medication they often present. An estimated 75% of elderly patients are receiving prescription drugs, while 82% use nonprescription drugs regularly; polypharmacy is a particular problem in this age group (Honig et al. 1994; Novotný 1996).

The magnitude of this problem increases significantly in certain patient populations. One study documented an exponential increase in the incidence of adverse drug reactions in relationship to the number of drugs given. Average hospital stay and mortality rates were also higher in relation to the number of drugs administered. Several population groups have been singled out as having a high potential for adverse drug reactions because of the large number of drugs used. These include the elderly (D'Arcy 1982; Jankel et al.

1994), critical care patients (Zarowitz et al 1985), and patients undergoing complicated surgical procedures (Nagashima 1983) Not only do drug interactions represent a danger to the patient, but they also can greatly increase health care costs Patients on the combination also required more laboratory tests Certainly, an important goal in health care should be to maximize therapeutic outcomes using the fewest number of drugs possible

Early recognition of a drug's potential adverse reaction profile is critical During safety and efficacy studies (before a drug is introduced to the market), an attempt is made to identify any adverse reaction Unfortunately, only a relatively small number of patients are evaluated Exclusion criteria for many of these studies eliminate patients with multiple disease state or other complicating factors Also, the very young and the very old are often not well studied To complicate matters further, most of the studies are short term, thus eliminating the ability to recognize any adverse reactions associated with longterm use This process sets up the potential for long lag times between the commercial release of a drug and the emergence of a true picture of its adverse reaction profile

Types of adverse drug reactions

There are two main types of adverse drug reaction
- **dose-dependent** (also called type A, augmented, predictable)
- **dose-independent** (type B, bizzare, unpredictable, idiosyncratic)

Dose-dependent reactions

These often result from the known pharmacological effect of the drug and are increasingly likely as the dose increases Good examples of such reactions are gout resulting from treatment with a thiazide diuretic, or bone marrow suppression following therapy with methotrexate As a general rule, dose-dependent reactions are less serious and rapidly resolve on stopping the drug However, some dose-dependent reactions such as nerve VIII damage with aminoglycoside antibiotics, or myocardial damage following doxorubicin therapy, are serious and largely irreversible They are due to mechanisms that are not completely understood

Dose-independent reactions

In these reactions there is a large variability between individuals in their susceptibility to an adverse effect, many different mechanisms are operative, most of which are not understood The adverse reactions are often serious and life-threatening, patients should be warned about particular symptoms suggestive of such an adverse reaction

Anaphylactic reactions (type I hypersensitivity)
These reactions are most common in patients with a history of anaphylaxis with drugs, foods (such as nuts) or insect stings, and in atopic individuals with a history of asthma and eczema

Typically, anaphylaxis occurs on the second or third exposure to the drug, and may occur following administration of only very small amounts The mechanism involves recognition of the drug (or a drug-protein complex) by IgE molecules on the surface of mast cells and subsequent degranulation with release of histamine and other inflammatory mediators The onset of the clinical syndrome of anaphylaxis is often dramatic and rapid Prompt recignition and treatment can be lifesaving

Penicillin antibiotics are notorious for causing anaphylaxis, even though the incidence of severe reactions is very low Other likely causes are radioopaque contrast media, local anaesthetics and streptomycin

Type II reactions
These reactions occur owing to interaction between the drug and a circulating or membrane-bound protein (drug-induced hemolytic anemia) to cause production of a circulating antibody of the IgG ot IgM class with subsequent complement activation The most common target for this type of immune-mediated damage is the haematological system, resulting in Coomb's positive hemolytic anaemia (e g with methyldopa and penicillin) or thrombocytopenia (e g with quinine) It is likely that some examples of agranulocytosis or marrow aplasia are due to this mechanism of adverse reaction

Type III (arthus, serum sickness or immune complex) reaction
This type of reaction used to occur most commonly following injection of foreign serum to treat infectious diseases (e g antitetanus serum) It also occurs with antibiotics such as penicillins, streptomycin and sulphonamides, as well as the antithyroid drugs propylthiouracil and carbimazole It is thought to be caused by the formation of antibody-antigen complexes which lodge in the small blood vessels of the skin, kidney and joints, and may mimic systemic lupus erythematosus, in which such complexes are also found

The classic clinical presentation occurs several days following the start of therapy and includes fever, urticaria,arthropathy, lymphadenopathy and proteinuria Eosinophilia is a common and diagnostically useful feature Other skin rashes, particularly maculopapular in type, are also characteristic

Type IV reactions (cell-mediated hypersensitivity)
The typical example of a type IV reaction is contact dermatitis which is sometimes produced following application of antibiotics or other topical therapy on the skin Again it is thought to be due to the formation of hapten-protein complexes which triugger a lymphocytic cellular immune reaction

Pseudoallergic reactions
These reactions mimic those detailed above, but are not thought to involve immune recognition Rather, they are due to the release of immunological mediators by other mechanisms They typically occur on first-time exposure to the drug rather than after previous sensitization Examples of this type reaction include

- itching, bronchospasm and vasodilatation following treatment with intravenous morphine,
- flushing, urticaria, bronchospasm and even circulatory shock caused by aspirin,
- bronchospasm and hypotension caused by N-acetylcysteine used in the treatment of paracetamol poisoning – this occurs in approximately 5% of patients and responds to intravenous antihistamines

Long term adverse effects of drugs

Adverse effects which occur months or even years after the institution of a particular drug therapy may not obviously be connected with the agents responsible and will only be discovered by taking a careful drug history Some of these long-term effects are dose-dependent and can be anticipated Table 3 details some of the more common or important long-term effects of drugs (the lag time, in years, until the adverse reaction was first reported (Venning 1983)) This table illustrates how long it can take until the medical community is alerted to an adverse reaction via medical literature Recognition at this point depends on the information reaching the medical community Many people were exposed to the risk of this adverse reaction because of the lag time

These examples should point out the importance of reporting adverse drug reactions Upon a drug's commercial release, postmarketing surveillance – whether formally organized or through spontaneous individual practitioner reports – is critical to gaining

Table 3. Summary of the time lags before adverse drug reactions were widely recognized

Adverse Reaction	Drug	Time Lag (yr)
Pulmonary embolism	Oral contraceptives	3
Myocardial infarction	Oral contraceptives	5
Deaths from asthma	Sympathomimetic aerosols	4
Jaundice	Halothane	7
Colitis	Lincomycin	6
Colitis	Clindamycin	5
Aplastic anemia	Phenylbutazone	6

a rapid picture of a drug's true adverse reaction profile Clinical trials can detect adverse events with a frequency of 1 per 1000 patients or higher (Norrby and Lietman 1993), less common effects will not likely be identifiable until after marketing Once the drug reaches the market, patients may be taking other drugs in combination with the new drug, resulting in interactions not detected in premarketing studies (Peck et al 1993)

Factors predisposing to adverse effects

Drug-drug interactions

An important type of adverse drug reaction is drug interaction Thousands of drug-drug interactions have been described in the literature, but only a relatively small number are clinically important *The three categories of drug-drug interactions – pharmacokinetic, pharmacodynamic,* and *pharmaceutic* – are described and clinically relevant examples are given (Table 4)

Pharmacokinetic interactions

A pharmacokinetic interaction may occur by several mechanisms Generally, one drug alters the absorption, distribution, metabolism, or elimination of another drug, resulting in a change in drug concentration in the body and an altered response Numerous controlled studies have described various types of pharmacokinetic interactions, however, such controlled trials are typically performed in healthy volunteers and do not always give a true perspective of the potential for an interaction Data from pharmacokinetic or epidemiologic studies of actual patients are generally more helpful in determining the clinical importance of a pharmacokinetic interaction

Absorption

Absorption interaction results in an increase or decrease in the relative rate of absorption or in the amount of the drug absorbed A decrease in the rate of absorption may result in failure of a drug to reach therapeutic concentrations even if the total amount of the drug absorbed is unchanged Absorption rate can be slowed down by any drug that slows gastric motility, such as anticholinergic drugs (e g , propantheline) and opiates (e g , codeine) Because the small intestine provides the largest surface area for absorption, it is the major site of absorption for most orally administered drugs Any drug that decreases the speed at which another drug passes from the stomach to the small intestine will induce a decrease in absorption rate However, drugs that increase gastric motility, such as metoclopamide, can increase the absorption rate Interactions resulting in a decrease in the total amount of one drug's absorption are usually more important clinically

A decrease in the amount of a drug absorbed may be caused by the formation of insoluble complexes or by changes in gastrointestinal pH Tetracycline's interactions with

Table 4. Clinically important antibiotic drug interactions

Antimicrobial	Other Agent(s)	Results of Interaction
Aminoglycosides	Neuromuscular blocking drugs	Increased neuromuscular blocade
	Other nephrotoxins or ototoxins (e.g., cisplatin amphotericin B, ethacrynic acid, vancomycin, cyclosporine)	Increased nephrotoxicity or ototoxicity
	Penicillins	Inactivation of both drugs (a particular problem in renal failure and when obtainig drug levels)
Sulfonamides	Sufonylureas	Hypoglycemia
	Phenytoin	Increased serum concentration of phenytoin leading to toxicity
	Procaine	Decreased sulfonamide effect
	Oral anticoagulants (warfarin derivates)	Enhanced hypoprothrombinemia
Chloramphenicol	Phenytoin, tolbutamine, ethanol	Increased serum concentration of other agents and enhanced pharmacologic effect or increased toxicity
	Warfarin	Decreased warfarin metabolism and inhibition of vitamin K-producing gut bacteria, thus increasing prothrombin time
Metronidazole (also cefamandole, moxalactam, cefoperazone)	Ethanol (including ethanol-containing mediators)	Disulfiram-like reaction
	Disulfiram	Psychosis
Macrolides, azalides	Theophylline	Increased serum theophylline concentration
	Terfenadine	Cardiac arrhytmias
Amphotericine B	Curariform drugs	Increased curare-like effect
Fluconazole	Phenytoin, warfarin	Inhibits metabolism of these drugs
	Rifampin	Enhances metabolism of fluconazole
Itraconazole	Astemizole, terfenadine	Cardiac arrhythmias
	Phenytoin, warfarin	Inhibits metabolism of these drugs
	Rifampin	Enhances metabolism of itraconazole
Quinolones (norfloxacin, ciprofloxacin,ofloxacin, lomefloxacin, enoxacin)	Multivalent cations (antacids, iron, sucralfate, zinc)	Decreased absorption of quinolone
	Theophylline	Inhibits metabolism of theophylline (ciprofloxacin and enoxacin)
Rifampin	Coumarin anticoagulants	Decreased anticoagulant effect (increased metabolism of drug)
	Isoniazid	Additive hepatotoxicity
	Methadone	Withdrawal symptoms
	Quinidine	Decreased effect of quinidine
	Digoxin	Decreased effect of digoxin
	Methadone	Narcotic withdrawal
	Propranolol	Decreased effect of propranolol
	Oral contraceptives	Decreased effect (pregnancy)
	Steroids	Decreased steroid effect
	Fluconazole; ketoconazole	Decreased antifungal effect
Tetracyclines	Antacids, iron, calcium	Inhibit intestinal absorption of tetracycline
Penicilins and cephalosporins	Uricosuric agents (probenecid, high-dose aspirin, etc.)	Block excretion of β-lactams, causing higher serum levels
	Cooper reduction test for Glycosuria (Clinitest tablets)	False-positive test for glycosuria (not seen with glucose oxidase method)
	Ethanol	Disulfiram reaction
Isoniazid	Phenytoin	Increased serum concentrations of both
	Warfarine	Increased risk of toxicity by decreased drug metabolism

anacids and dairy products are well known Divalent or trivalent cations (aluminium, calcium, iron, and magnesium) combine with tetracycline to form a nonabsorbable complex, greatly reducing serum tetracycline concentrations These interactions can be prevented by separating administration time of the interacting agents by 2 hours The absorption of ketoconazole appears to be reduced when the gastrointestinal pH is increased (Van der Meer et al 1980) A significant reduction in plasma ketoconazole concentrations occurred when it was given concurrently with antacids or cimetidine

Distribution

Two types of distribution interactions are most common protein-binding/displacement interactions and cellular distribution interactions Once absorbed, drugs are distributed via the blood as both free and plasma protein-bound drug Because only the free or unbound fraction of the drug is active, any change in the percentage bound can lead to a change in the drug's availability to receptor sites and its metabolism and excretion When two or more highly protein-bound drugs are administered concurrently, competitive binding by one may increase the free fraction of the other Drug-drug interactions in this class are complex and probably in some cases overstated Rolan (1994) challenged the clinical importance of most protein-binding/displacement interactions Displacement produces a minor transient increase in free drug, and the mean steady-state concentration remained unchanged Drugs most likely to result in clinically important interactions were protein bound to more than 90%, had a narrow therapeutic index, had a high hepatic extraction ratio, and were given intravenously Still, caution should be exercised when administering any two highly protein bound drugs when one or both have a narrow therapeutic index

Metabolism

Many interactions involve the effect of one drug on the metabolism of another drug, and these can be clinically important Certain drugs, such as barbiturates, are known to induce hepatic enzymes, resulting in shortened plasma halflives for some drugs A well-documented and clinically important example is seen with administration of barbiturates and warfarin (O'Reilly 1980), higher than usual dosages of warfarin are needed to produce suitable anticoagulation When a patient stabilized on warfarin discontinues barbiturate therapy, hemorrhage often results Other drugs that may act as enzyme inducers include carbamazepine, phenytoin, rifampin, and phenylbutazone (Gugler 1994)

Many drugs are metabolized in hepatic microsomes by an enzyme system called the mixed-function oxidase system (cytochrome P-450 system) This type of interaction has also been reported with terfenadine (Honig et al 1993) A specific P-450 enzyme converts terfenadine to an active metabolite Increased concentrations of the parent drug may exert a quinidine-like action, leading to torsade de pointes (Woolsey et al 1993, Novotný 1996, Novotný 1997) Erythromycine and ketoconazole interfere with this enzyme and lead to increased terfenadine plasma levels (Nightingale 1992) Other risk factor for this cardiotoxicity include overdose and serious hepatic dysfunction More work is needed to document the potential interaction between erythromycin or ketoconazole and astemizole

Elimination

Most interactions involving elimination or excretion occur in the kidneys A change in glomerular filtration rate, tubular secretion, or urine pH can alter the excretion of some drugs (Table 5) A potentially dangerous interaction in this category is that between diuretics and aminoglycosides (Table 5)

Pharmacodynamic interactions

Pharmacodynamic interactions generally fall into four categories on the basis of the effects produced antagonistic, synergistic therapeutic, synergistic adverse, and indirect effect

Table 5. Routes of elimination of antimicrobial agents and dose-related toxicities

Drugs	Primary Route of Elimination	Degree of Accumulation[a]	Dose-Related Toxic Effect(s)
Penicillins			
Ampicillin	Renal	Significant	CNS (seizures, etc)
Carbenicillin	Renal	Significant	Platelet dysfunction, CNS toxicity, sodium overload
Methicillin	Renal	Moderate	?Nephritis
Mezlocillin	Renal/Hepatic[b]	Moderate	?Platelet dysfunction
Nafcillin	Renal/Hepatic[b]	Insignificant	?Neutropenia
Oxacillin	Renal/Hepatic[b]	Insignificant	?Neutropenia
Penicillin G	Renal	Significant	CNS toxicity, hyperkalemia (with K^+ salt)
Piperacillin	Renal/Hepatic[b]	Moderate	?Platelet dysfunction
Ticarcillin	Renal	Significant	CNS toxicity, platelet dysfunction
Cephalosporins			
Cefamandole	Renal	Significant	Hypoprothrombinemia
Cefepime	Renal	Significant	None
Cefazolin	Renal	Significant	CNS toxicity
Cefmetazole	Renal	Significant	Hypoprothrombinemia
Cefonicid	Renal	Significant	None
Cefoperazone	Renal/Hepatic[b]	Moderate	Hypoprothrombinemia
Cefotaxim	Renal/Hepatic[b]	Moderate	None
Cefotetan	Renal	Significant	Hypoprothrombinemia
Cefoxitin	Renal	Significant	None
Ceftazidime	Renal	Significant	None
Cefizoxime	Renal	Significant	None
Ceftriaxone	Renal/Hepatic[b]	Insignificant	None
Cefuroxime	Renal	Significant	None
Aminoglycosides	Renal	Significant	Nephrotoxicity, ototoxicity
Tetracyclines	Renal (except doxycycline)	Significant	Exacerbation of azotemia, possible hepatotoxicity
Miscellaneous			
Aztreonam	Renal	Moderate	None
Chloramphenicol	Hepatic	Moderate	Gray baby syndrome,marrow suppression
Ciprofloxacin	Renal/hepatic	Moderate	CNS toxicity
Clindamycin	Hepatic	Moderate	None
Erythromycin	Hepatic	Insignificant	Ototoxicity
Fleroxacin	Renal	Moderate	CNS toxicity
Imipenem	Renal	Significant	CNS toxicity
Lomefloxacin	Renal	Moderate	CNS toxicity
Metronidazole	Hepatic/renal	Moderate	Encephalopathy, neuropathy
Ofloxacin	Renal	Significant	CNS toxicity
Polymyxins	Renal	Significant	Nephrotoxicity, neuropathy, neuromuscular blocade
Sulfonamides	Renal/Hepatic[b]	Moderate	Kernicterus
Trimethoprim	Renal	Moderate	Megaloblasic anemia
Antifungal Agents			
Amphotericin B	Unknown	Insignificant	Most adverse effects increase in frequency with cumulative dose, no individual dosage size
Fluconazole	Renal	Significant	?Hepatotoxicity
Flucytosine	Renal	Significant	Marrow suppression, ?hepatotoxicity

Table 5. (continued)

Drugs	Primary Route of Elimination	Degree of Accumulation[a]	Dose-Related Toxic Effect(s)
Itraconazole	Hepatic	Insignificant	?None
Miconazole	Hepatic	Insignificant	?Hepatotoxicity
Ketoconazole	Hepatic	Insignificant	None
Antiviral Agents			
Acyclovir	Renal	Significant	CNS toxicity, nephrotoxicity
Foscamet	Renal	Significant	Nephrotoxicity, CNS toxicity
Ganciclovir	Renal	Significant	Marrow suppression
Vidarabine	Hepatic/renal[b]	Insignificant	?CSN toxicity
Ribavirin	Hepatic	Insignificant	?
Antitubercular Agents			
Isoniazid	Hepatic	Insignificant	Neuropathy
Ethambutol	Renal	Moderate	Optic neuritis
Pyrazinamide	Hepatic	Moderate	?None
Rifampin	Hepatic	Insignificant	?None

[a] Accumulation of parent compound and/or active/toxic metabolites in patients with decreased capacity of primary route of elimination [b] Accumulation is probably significant in combined hepatic and renal failure, but data are sparse

Antagonistic effects

Antagonistic interactions occur when two drugs with opposing pharmacologic effects are given together For example, a nonspecific β-adrenergic blocking agent such as propranolol may induce bronchoconstriction because of its effect on the β receptors in the bronchi of a patient taking theophylline for bronchodilation This interaction may also be beneficial, for instance, when the opiate antagonist naloxone is given to reverse the effects of opiate analgetics

Synergistic or additive therapeutic effects

Two drugs with similar therapeutic effects may interact For example, coadministration of two central nervous system depressants, such as diazepam for anxiety and chloral hydrate for insomnia, may result in oversedation

Administration of a drug that inhibits platelet aggregation (such as aspirin) together with warfarin increase the anticoagulant effects, possibly to the point of bleeding

Synergistic or additive side effects

This interaction is similar to the preceding one, exept that it involves the side effects rather than the therapeutic effects of the drug Administration of an antihistamine with a skeletal muscle relaxant such as cyclobenzaprine, both of which cause drowsiness, may result in additive sedation The administration of two drugs with anticholinergic side effects, such as disopyramide and tricyclic antidepressant, may produce intolerable effects Drug interactions involving antiviral agents primarily involve shared toxicities (e g , neutropenia with ganciclovir and zidovudine) (Morris 1994)

Indirect pharmacodynamic effects

In this type of interaction, the pharmacologic effect of one drug indirectly affects another drug's action Diuretics that decrease body potassium concentrations may alter the therapeutic effects of digoxin and some other antiarrhythmics The effect of digoxin is enhanced by potassium depletion, whereas the effects of some antiarrhythmics, such as lidocaine and quinidine, are decreased

Pharmaceutic interactions

Pharmaceutic interactions occur when two drugs are mixed in the same intravenous fluid, resulting in physical or chemical incompatibility (chemical inactivation or precipitation) Incompatibility is common with the use of intravenous phenytoin, because crystallization or precipitation may result if the drug's vehicle is altered or the pH lowered (Sachtles 1973, Burke 1975) Therefore, phenytoin sodium injection should not be mixed in the same intravenous fluid with other drugs

Beneficial interactions

Drug-drug interactions are generally throught of as detrimental, but many are actually clinically desirable Probenecid inhibits secretion of penicillins into the proximal tubule, thus reducing the rate of penicillin excretion, this combination results in a twofold higher and more prolonged blood penicillin concentration (Weiner and Mudge 1985) Trimethoprim and sulfamethoxazole sequentially inhibit two steps in an essential bacterial biosynthetic pathway, resulting in synergistic antibacterial activity

Drug-food interactions

Administration of drugs with food may result in an interaction that modifies the activity of the drug or the nutritional effect of the food (decreased drug response, increased drug response, or impairment of nutritional status) The most frequently observed type of drug-food interaction affects drug absorption Drugs whose absorption may be delayed or reduced by food include most penicillins, tetracycline, digoxin, acetaminophen, levodopa, and aspirin Absorption of some drugs – for example, spironolactone (Melander et al 1977) and griseofulvin (Crounse 1961) is increased when the drug are taken with certain foods

Pregnancy

Pregnant patients or nursing mothers pose important problems when it comes to the use of antimicrobial agents, because most of these drugs cross the placenta to some degree One must consider the potential teratogenic and toxic effects of these drugs on the fetus (Table 6) Certain agents such as metronidazole are teratogenic in lower animals and therefore may have this effects in humans Other agents such as rifampin and trimetoprim may have a teratogenic potential and should be used only when alternative agents are unavailable

Use of tetracyclines in pregnancy should be avoided because they alter fetal dentition and bone growth Tetracyclines have also been associated with hepatic, pancreatic, and renal damage in pregnant women Streptomycin has been associated with auditory toxicity in children of mothers treated for tuberculosis Sulfonamides should not be used during the third trimester of pregnancy because they may displace bilirubin from albumin-binding sites and cause CNS toxicity in the fetus

Many antibiotics are excreted in breast milk and cause the newborn's microflora to be distorted, or act as a sensitising agent to cause future allergy

Age

Closely related to the pharmacokinetic principles is the patient-related factor of age How a patient handles drugs varies greatly from birth to old age Hydrophilic and lipophilic drugs may be affected by the patient's lean body mass or the amount of adipose tissue The ability of the liver to metabolize certain drugs may be reduced in the very young and the very old Renal function tends to decrease with the increasing age A drug's volume of distribution varies greatly between infant, child, adult, and elderly patients Dosage guidelines based on age must be closely adhered to so as to prevent adverse reactions

Table 6. Antimicrobial agents to be avoided during pregnancy

Agent	Potential Toxicity
Antibacterial	
Aminoglycosides	Nerve VIII damage
Chloramphenicol	Gray baby syndrome
Erythromycin estolate	Cholestatic hepatitis
Metronidazole	Possible teratogenicity
Nitrofurantoin	Hemolytic anemia
Sulfonamides	Hemolysis in the newborn with glucose-6-phosphate dehydro genase deficiency, increased risk of kernicterus
Tetracyclines	Limb abnormalities, dental staining, inhibition of bone growth
Trimethoprim	Altered folate metabolism
Quinolones	Abnormalities of cartilage
Vancomycin	Possible auditory toxicity
Antifungal	
Griseofulvin	Teratogenic in animals
Ketoconazole	Teratogenic in animals
Antitubercular	
Isoniazid	Use with caution
Rifampin	Use with caution
Antiviral	
Amantadine	Teratogenic

Genetics

Idiosyncratic reactions to drug result from an abnormal susceptibility of the patient to the drug These reactions occur in genetically abnormal subjects and are dose related One of the best known examples is drug-induced hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency This genetic enzyme deficiency in erythrocytes causes weaknesses in the cell membrane Certain drugs are capable of affecting the integrity of the cell membrane and causing it to hemolyze These drugs include doxorubicin, furazolidone, methylene blue, nalidixic acid, nitrofurantoin, phenazopyridine, primaquine, and sulfamethoxazole Blacks, persons of Jewish descent, and other dark-hued Caucasian groups (such as persons of Greek or Iranian descent) tend to have a greater incidence of this deficiency (Kirkman 1968)

Another well-recognized example is the recessive autosomal trait affecting an individual's ability to acetylate isoniazid Slow acetylators develop high serum concentrations of isoniazid when given normal doses and show a much higher incidence of dose-related adverse effects such as peripheral neuropathy Interestingly, the incidence of isoniazid-induced hepatitis is higher in fast acetylators, probably secondary to faster rate of formation of toxic metabolites (Lunde et al 1977) The reactions that appear to be idiosyncratic include nausea and vomiting, renal and hepatic reactions, gastrointestinal reactions, and fever

The uninformed patient

An uninformed patient is a serious-but preventable-patient-related risk factor for the development of adverse drug reactions The patient must be carefully instructed on the proper use of his or her medications

Potential adverse drug reaction should be discussed with the patient Adverse reactions transient in nature should be identified for the patient as well as reactions about which the patient should notify his or her physician or pharmacist immediately

Educating patients about their drug therapy can aid in preventing or minimizing drug interactions The use of nonprescription medications should be discussed with the patient Interactions with these agents are often overlooked

Finally, patients should be encouraged to ask questions about their drug therapy Potential drug-drug and drug-food interactions should be discussed with the patient All instructions for appropriate administration must be fully understood by the patient

Adverse drug reaction monitoring and reporting programs

The clinician must have a thorough understanding of the pharmacology of the drugs he or she administers to patients in the practice setting

A comprehensive adverse drug reaction monitoring and reporting program includes multiple systems for identifying reactions Once the potential reaction is identified, it must be assessed and appropriatelly managed The reactions should be reported in an organized and predefined fashion Methods to prevent future adverse reactions should be established and educational feedback given to prescribers

This entire process constitutes a good adverse drug reaction monitoring and reporting program

Identification, assessment, and management

Several mechanisms are used to detect a potential adverse drug reaction The first step taken is to determine if the effect seen is drug related Published literature on the drug is reviewed to determine if such an effect has been previously described This includes reviewing known reactions to the drug, drug-drug interactions, and drug-disease interactions that might be responsible, and the characteristics of these published effects At the same time, information about the patient is gathered on the details of the reaction A complete review of the patient's medical history is done to determine other drugs or disease states that could be responsible The patient-specific information is compared with the medical literature to determine the likelihood of a drug cause If the reaction is severe enough and there is enough evidence pointing to the drug, the medication is discontinued or changed to an alternative therapy This is called *dechallenge*

Management of drug interactions usually consists of monitoring specific parameters and then taking the appropriate action

Methods for monitoring and detecting

Several methods are available for monitoring and detecting adverse drug reactions Each of the methods has strengths and weaknesses The best system should incorporate multiple methods based on the resources available

Retrospective systems

Patient charts can be reviewed retrospectively by a random or selective process Chart screening can be performed by supportive personnel and may generate more reports than voluntary methods However, retrospective reviews rely solely on the written record Also this method provides no benefit to the patient who experienced the reaction An alternative to random screening is to preselect high-risk drugs or high-risk patients to be monitored retrospectively This allows fairly rapid identification of the types of problems that may be encountered so prospective programs can be developed

Prospective or concurrent monitoring systems

Formalized prospective monitoring offers many benefits because patients can be identified and treated readily The most commonly used method is the voluntary system because it is easy to implement and is inexpensive When enquiries about a potential adverse drug reaction or interaction are received in the pharmacy or drug information center, the pharmacist should determine whether the question is patient specific

Setting up a prospective or concurent surveillance system for drugs and patients with a high risk for the development of an adverse drug reaction or drug interaction is highly desirable Drugs with known serious adverse drug reaction profiles should be targeted for ongoing surveillance Health care personnel should be educated on the potential problems with these drugs As new drugs are marketed, their use should be closely watched until their adverse reaction profile is well defined Patient at high risk for adverse effects should also be the focus of ongoing surveillance

The patients who experience a reaction benefit from these prospective systems because the reaction is recognized earlier and future patients benefit from information learned from past patients Other benefits could include the economic impact of reduced hospitalization, efficient and economical drug use, and minimized organizational liability

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