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CLINICALLY DESIRABLE DRUG INTERACTIONS

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INTRODUCTION

Drug interactions are usually thought of as undesirable, as detrimental exaggerations or diminutions of the action of one drug upon another. Because of the frequency and the clinical importance of adverse drug interactions, numerous journal articles, reviews, book chapters, and entire books have been devoted to the subject (1, 2). But drugs are also used concurrently to enhance or improve their clinical effect. Much less attention has been given to these beneficial or clinically desirable drug interactions.

A desirable drug interaction is defined as either a beneficial drug effect that is enhanced or a detrimental drug effect that is mitigated by the concomitant use of another drug. For the purposes of this review, this definition excludes antidotes for poisonings and drugs used to block or reverse the adverse side effects of another drug, such as protamine to reverse the anticoagulant effect of heparin.

The following categorization of pharmacologic and physiologic mechanisms producing desirable drug interactions provides a conceptual framework for classifying these interactions.

1. Additive: the resultant pharmacologic effect is equivalent to the combined effect of each drug used alone. An example of an additive interaction is the use of dopaminergic and anticholinergic drugs in the treatment of parkinsonism.

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2. Synergistic: the effect produced is greater than the sum of the effects of each drug used alone. The antimicrobial combination of sulfamethoxazole and trimethoprim to block two sites in the folic acid metabolic pathway in microorganisms exemplifies this type of interaction. Some consider synergism in fact only additive.
3. Augmentative: one drug induces and prolongs an increase in concentration of another drug in a body fluid. Probenecid has this effect on penicillin, and carbidopa produces the same result with levadopa.
4. Facilitative/needful: both drugs are needed for the effect to occur, or one drug makes it possible for the other to produce its desirable action. This type of interaction is exemplified by the combined use of penicillin and an aminoglycoside to treat enterococcal infections.
5. Reparative: in such drug combinations one drug counteracts the undesirable effects of another. Combining laxating magnesium hydroxide with constipating aluminum hydroxide produces an acid-neutralizing effect while sometimes avoiding adverse consequences on the gut.
6. Complementary: drugs are combined that act through different physiologic mechanisms to produce a common beneficial clinical effect. The treatment of congestive heart failure with both digitalis glycosides and diuretics illustrates this mechanism.

In addition to the mechanisms listed, a special category of beneficial drug combination is exemplified by the antidiarrheal drug Lomotil®, a mixture of diphenoxylate and atropine. Diphenoxylate is a meperidine congener that decreases intestinal motility but also has the potential for abuse. Atropine is added in a subtherapeutic amount to discourage deliberate overuse by producing noxious effects.

Interactive mechanisms may overlap. The effect of antihypertensive drugs may be both additive and complementary. The net effect is reduction of blood pressure. Another benefit of complementary drug effects may be the use of smaller doses of each drug, which can lessen the occurrence and severity of undesirable side effects.

Multiple drug therapy for a disease blurs with desirable drug interactions. Drugs, acting through different mechanisms, combine effects to produce the desired therapeutic result. Examples of diseases in which combined drug therapy is a standard approach are listed in Table 1. Treatment of these disorders demonstrates clinical ingenuity in approaching a problem from more than one pharmacologic angle.

Many beneficial interactions are ill defined, vague, or hard to corroborate because their clinical effect is inconsistent or variable. The effectiveness of certain analgesic combinations is illustrative. Pain is a subjective sensation modulated by numerous psychological and physiological factors. It is hard to quantify, hard to reproduce, and difficult to assess precisely. Evaluating single

Table 1 Clinical states often treated with multiple concurrent drugs

Clinical state	Clinical state
infections	rheumatological disorders (e.g., rheumatoid arthritis, gout, degenerative joint disease)
neoplastic diseases	allergic disorders (e.g. allergic rhinitis, asthma)
organ transplantation	immunologic disorders (e.g. systemic lupus erythematosus, Wegener's granulomatosis)
cardiovascular disorders hypertension congestive heart failure angina pectoris acute myocardial infarction arrhythmias hypotension/shock	neurological disorders tension headache migraine headache seizure disorders Parkinson's disease
respiratory disorders bronchospasm (e.g., asthma, chronic bronchitis) cough	psychiatric problems
gastrointestinal diseases reflux esophagitis peptic ulcer disease inflammatory bowel disease (e.g., regional enteritis, ulcerative colitis) chronic active hepatitis constipation diarrhea (e.g., Lomotil)	ophthalmologic disease (e.g. glaucoma)
renal disorders nephrotic syndrome chronic renal insufficiency diuresis	contraception (birth control pills)
	analgesia
	antipyresis (e.g. sequential alternating of aspirin and acetaminophen to maintain continuous antipyresis and avoid excess use of either drug)

and combined drug effects on pain is often elusive. Additionally, individual drugs with beneficial actions may be combined but the effectiveness of the combination may never be fully tested (e.g. mixtures used as cold remedies, cough mixtures, and laxatives).

It is not possible to examine all desirable drug interactions in this review. For example, drug combinations used to treat malignancies encompass a vast field in their own right. We have selected examples of beneficial drug-drug combinations that illustrate the mechanisms of desirable interactions and that affect a broad range of clinical problems. These include antimicrobial drug interactions in treating infections, combined drug use in parkinsonism, combined use of diuretics, and antacid mixtures. The mechanism of the interaction will be examined together with its clinical significance. Any drug use, in combination

or not, can have adverse effects, but these will only be emphasized as they relate to circumstances under discussion.

ANTIMICROBIAL AGENTS

Since their introduction, antimicrobial drug combinations have been used in an effort to produce enhanced clinical benefits. The rationale for their concurrent use can be divided into four general categories (3): (*a*) to broaden the spectrum of antimicrobial coverage, (*b*) to decrease toxicity by use of lower drug concentrations, (*c*) to prevent emergence of resistant organisms, and (*d*) to produce antimicrobial synergism.

Employing multiple antibiotics to insure broad spectrum coverage is appropriate when there is high suspicion of a serious or grave infection not immediately attributable to a particular microorganism, and when delay in beginning treatment might have an adverse outcome (3). The clinical suspicion of gram-negative bacteremia meets these criteria. Over the years various antibiotic combinations have been recommended for suspected gram-negative bacteremia that depend on the most likely putative organism under given clinical circumstances. This approach is successful if the agents chosen are not antagonistic and are active against the infecting organism. The disadvantages of multiple drug therapy are increased cost, increased risk of adverse drug reactions, and heightened chances of superinfection (4).

The use of multiple antimicrobial agents as a means of reducing the dosage of each to prevent toxicity has little current application, although this was commonplace when sulfonamides were first introduced (3). The limited solubility of early sulfonamides caused renal damage from their crystallization in urine. The solubility of one sulfonamide in solution is essentially independent of the concentration of others. The aggregate therapeutic effect of the mixture is about equal to the sum of individual effects. Because of this, sulfonamide combinations were employed as a way of retaining clinical efficacy while reducing the risk of nephrotoxicity. The most popular sulfonamide combination was the so-called triple sulfa, sulfathiazole, sulfacetamide, and sulfabenzamide. The newer, more soluble sulfonamides have made these mixtures obsolete.

Another erstwhile combination was that of streptomycin and dihydrostreptomycin, each at half strength. Streptomycin causes vestibular damage and dihydrostreptomycin produces cochlea damage. The goal was to reduce toxicity, but the mixture was abandoned when it was found to produce severe hearing loss.

More recently, both beneficial and detrimental effects have been observed from the joint use of amphotericin B and flucytosine in the treatment of patients with cryptococcal meningitis (5). The combination is synergistic and allows for smaller doses of amphotericin B to be used. Although the nephrotoxicity of

amphotericin B is reduced, bone marrow toxicity induced by flucytosine has increased. It has been postulated that renal function is impaired even with the use of smaller than usual doses of amphotericin B, which leads to elevated flucytosine blood levels and increased bone marrow toxicity. Amphotericin B combined with flucytosine is recommended as the regimen of choice in the treatment of cryptococcal meningitis (5), but there must be careful monitoring for the adverse effects to both agents.

The use of multiple drugs to prevent the emergence of resistent strains of microorganisms is important in the treatment of tuberculosis and in the clinical use of rifampin (3, 4). There is a theoretical basis for considering that antimicrobial combinations retard or prevent the appearance of resistant organisms. Even when a microorganism develops resistance to one drug in a multiple drug regimen, it should be killed by one of the other drugs. This principle is the basis for using antimicrobial drug combinations to treat mycobacterial infections, since emergence of resistance to streptomycin, isoniazid, or rifampin is rapid when these drugs are used alone. Combination therapy appreciably prevents the emergence of resistant strains.

The use of rifampin is often accompanied by the rapid development of microbial resistance to this drug. In treating methicillin-resistant staphylococcal infections with rifampin, concomitant use of gentamicin or vancomycin averts the appearance of rifampin-resistant organisms. In gram-negative bacterial infections, rifampin has been combined with nalidixic acid and trimethoprim.

Clinically, antibacterial synergism has been the most successful form of combined antimicrobial drug therapy (3, 4). The three major examples of synergism are (*a*) agents that act on sequential steps in bacterial synthetic pathways, (*b*) joint use of a drug that impedes bacterial cell-wall synthesis with an aminoglycoside, and (*c*) a β-lactamase inhibitor combined with a β-lactam antibiotic. The first two types of synergism are exemplified respectively by the combination of trimethoprim and sulfamethoxazole, which blocks two separate sites in the folic acid metabolic pathway of many bacteria, and by the combination of penicillin and streptomycin to treat enterococcal infections. These combinations will be discussed more fully in following sections.

The third type of synergistic interaction, the combination of a β-lactamase inhibitor and a β-lactam antibiotic for treatment of infections due to β–lactamase producing bacteria, may prove to have appreciable clinical significance. This synergism is based on the probability that the administration of a β-lactamase inhibitor will block the action of bacterial β-lactamase, thus enhancing the antibacterial activity of a β-lactam antibiotic. The synergistic effect of these two agents has been shown in vitro against gram-negative bacilli (6). Dicloxacillin was found to inhibit the β-lactamase activity of a strain of *Citrobacter freundii* producing this enzyme. Ampicillin, a β-lactam antibiotic,

was then able to exert its antibacterial effect on the cytoplasmic membrane (7). An oxacillin-ampicillin combination was effective in vitro against β–lactamase producing *Escherichia coli* strains with low-level β-lactam resistance but not against strains with high-level resistance (8). Clavulanic acid is a β-lactamase inhibitor, and in vitro and in vivo synergy has been demonstrated when it is combined with a β-lactam antibiotic (9, 10). In combination with amoxicillin, clavulanic acid proved safe and 70% effective in the treatment of urinary-tract infections caused by β-lactamase producing amoxicillin-resistant bacteria (10).

Combinations of agents inducing bacteria to produce β-lactamase and β-lactam antibiotics have been noted to be antagonistic. Cefoxitin can antagonize β-lactam antibiotics in vitro by inducing β-lactamase, which inactivates the β-lactam or serves as a barrier to access to target proteins (11). In experimental infections in mice, cefoxitin has been found to reversibly induce β-lactamases that antagonize carbenicillin and a cefamandole-carbenicillin combination (12). Clinically, the resistance of *Enterobacter* to cefamandole was associated with inducible β-lactamase, which produced cross-resistance to other β-lactam antibiotics given concurrently (13). In vitro and in vivo antagonism also has been demonstrated between cefoxitin and carbenicillin (11).

In vitro data on synergism or antagonism between antibiotics are not always applicable to conditions in vivo, and it is difficult to design studies that will clearly establish the clinical efficacy of some antimicrobial combinations. A group of highly useful antimicrobial combinations will be reviewed (trimethoprim-sulfamethoxazole, penicillin-aminoglycoside for enterococcal infection, penicillin-probenecid for gonorrhea, antibiotic-urease inhibitor for *Proteus* urinary tract infection). Additionally, antibiotic combinations used to treat *Pseudomonas* bacteremia, *Staphylococcus aureus* endocarditis, and *Klebsiella* infections will be examined.

Trimethoprim-Sulfamethoxazole

The development of trimethoprim and sulfamethoxazole in combination was based on the recognized differences between man and bacteria in the metabolism of folic acid (14, 15). The concept of using two drugs, each to inhibit separate steps in an essential bacterial biosynthetic pathway, was first proposed by Hitchings (16). Theoretically, this sequential blockade would produce a synergistic effect.

The concurrent use of a sulfonamide and trimethoprim produces a two-pronged block in the bacterial pathway that leads to the synthesis of tetrahydrofolic acid from its precursors. Sulfonamides are structural analogs of para-aminobenzoic acid (PABA), which is essential for tetrahydrofolate synthesis. Sulfonamides competitively inhibit bacterial utilization of PABA to form dihydropteroic acid, the immediate precursor of pteroylglutamic acid (PGA). Because bacteria are unable to utilize preformed folates, this inhibition results

in bacteriostasis (17). Bacteria that are not dependent on folic acid or use preformed folates are not sulfonamide sensitive. Mammals require preformed PGA, and therefore are not adversely affected by sulfonamides.

Trimethoprim is a diaminopyrimidine that strongly inhibits the bacterial enzyme dihydrofolate reductase, which reduces dihydrofolate to tetrahydrofolate (18). Tetrahydrofolate is essential for one-carbon fragment transfer reactions needed for the synthesis of purines, pyrimidines, and some amino acids.

The therapeutic application of trimethoprim was recognized when the inhibition of dihydrofolate reductase by trimethoprim was noted to vary widely according to the species from which the enzyme was derived (19). Trimethoprim has a particularly high affinity for bacterial dihydrofolate reductase, but binds much less tightly to the same enzyme from mammals. There is a high degree of heterogeneity in dihydrofolate reductase from various species. This selective action of trimethoprim on dihydrofolate reductase is based on structural differences in the enzyme isolated from different species and probably is caused by changes in certain amino acids of the enzyme (20).

The use of trimethoprim with sulfamethoxazole produces a much greater antibacterial effect in vitro than the use of either drug alone (17, 21). The folate pathway is probably cyclic rather than linear (22). In microorganisms, tetrahydrofolate is synthesized from PABA. Tetrahydrofolate is reoxidized to dihydrofolate in the synthesis of thymidylate. Dihydrofolate reductase is essential to the maintenance of the tetrahydrofolate pool. Trimethoprim selectively inhibits dihydrofolate reductase, and its effectiveness is markedly enhanced when the synthesis of dihydrofolate is simultaneously blocked by sulfamethoxazole (15). Maximal synergy occurs when bacteria are sensitive to both trimethoprim and sulfamethoxazole, but a synergistic effect still can occur in bacteria resistant to sulfamethoxazole only or resistant to sulfamethoxazole and only moderately sensitive to trimethoprim (17).

Trimethoprim-sulfamethoxazole in vitro has antibacterial activity against numerous gram-positive and gram-negative bacteria (Table 2) (14). Some strains of *Campylobacter fetus* and *Chlamydia* are sensitive but the two drugs together are not synergistic. Although some *Pseudomonas* species are sensitive to trimethoprim-sulfamethoxazole, *Pseudomonas aeruginosa* is not. The drug is also effective in *Pneumocystis carinii* pneumonia. However, trimethoprim-sulfamethoxazole is inactive against *Mycoplasma, Mycobacterium tuberculosis,* and *Treponema pallidum*.

The ratio of trimethoprim to sulfamethoxazole in pharmaceutical preparations is 1:5. This produces a plasma concentration between 1:15 and 1:22, the range in which antibacterial activity is potentiated (14, 23).

Trimethoprim-sulfamethoxazole (co-trimoxazole, Bactrim®, Septra®, and others) is available as tablets formulated with 80 mg trimethoprim and 400 mg sulfamethoxazole or 160 mg and 800 mg of each drug respectively. Suspen-

Table 2 Bacteria sensitive to trimethoprim-sulfamethoxazole

Gram-positive	Gram-negative
Streptococcus pyogenes	*Escherichia coli*
Streptococcus viridans	*Klebsiella-Enterobacter*
Streptococcus pneumoniae	*Proteus* species
Staphylococcus aureus	*Salmonella* species
	Shigella species
	Haemophilus influenzae
	Bordatella pertussis
	Neisseria gonorrhoeae
	Neisseria meningitidis
	Vibrio cholera
	Pseudomonas (but not *P. aeruginosa*)
	Serratia species
	Yersinia species
	Nocardia species

sions, intramuscular, and intravenous preparations also are available. Trimethoprim alone is marketed as Proloprim®, and sulfamethoxazole has been sold as Gantanol®.

Penicillins and Aminoglycosides for Enterococcal Infections

Enterococcal *(Streptococcus faecalis)* endocarditis is best treated with a combination of penicillin and an aminoglycoside, which produces both facilitative and synergistic actions against this microorganism. Although occasional patients with enterococcal endocarditis could be cured with large doses of penicillin alone (24), the cure rate was never greater than 10–20% (4). In vitro and in vivo synergy between penicillin and streptomycin against the enterococcus was noted soon after the introduction of streptomycin.

Early in vitro experiments showed that penicillin alone was bacteriostatic against enterococci and streptomycin alone occasionally delayed growth, but a combination of penicillin and streptomycin was synergistic (i.e. less penicillin was needed) and was bactericidal (25, 26). Similar results have been found in experimental enterococcal endocarditis in the dog (27). Penicillin alone depressed the level of bacteremia, but streptomycin alone had no effect on the level of bacteremia. When penicillin and streptomycin were combined, a more rapid and more sustained decrease in bacteremia occurred.

The intact cell wall of enterococci is relatively impermiable to streptomycin and other aminoglycosides. Penicillins and other inhibitors of cell-wall synthesis enhance the uptake of aminoglycosides by inhibiting cell-wall synthesis and reducing the permeability barrier (28). A similar mechanism accounts for penicillin-streptomycin synergy against *E. coli* (3). Cephalothin alone or in

combination with an aminoglycoside, however, is not effective therapy for experimental enterococcal endocarditis (29).

A lack of penicillin-streptomycin synergy occurs in up to 30% of enterococcal strains. Nearly all such strains, however, show in vitro synergy to a penicillin-gentamicin combination. Enterococcal strains not inhibited by the penicillin-streptomycin combination and resistant to streptomycin concentrations of 50,000–150,000 μg/ml were sensitive to a combination of penicillin-gentamicin (30, 31). It has been recommended that penicillin-gentamicin replace penicillin-streptomycin in the treatment of enterococcal infections. In experimental enterococcal endocarditis in rabbits, little difference was found when enterococci sensitive to streptomycin were treated with penicillin and streptomycin and penicillin and gentamicin (32). Clinical cures of enterococcal endocarditis and meningitis have been produced with penicillin and gentamicin, corroborating its in vitro and experimental effectiveness (33). A penicillin-gentamicin combination now often is used routinely to treat enterococcal infections. Ampicillin is more active than penicillin against enterococci in vitro. However, there is no strong evidence that it is any more useful clinically than penicillin. The successful therapy of enterococcal endocarditis requires prolonged administration of synergistic antibiotic combinations (31, 35, 36). Patients with symptoms for more than three months or with mitral valve endocarditis should receive six weeks of therapy to avoid a high recurrence rate (34). Those with a shorter duration of symptoms and aortic valve disease can be treated for four weeks. In patients allergic to penicillin, vancomycin can be substituted. Vancomycin is synergistic with streptomycin and gentamicin (37). These combinations are potentially ototoxic and patients must be carefully observed for hearing loss.

In summary, no single antibiotic combination is completely effective therapy for enterococcal infections (33). A combination of penicillin and an aminoglycoside has proved effective in vitro, in experimental animals, and in clinical studies (35). In most cases of enterococcal endocarditis, combined therapy with penicillin and streptomycin remains effective (35). If the minimal inhibitory concentration of streptomycin for the enterococcus is 2000 μg/ml or greater, gentamicin can be substituted for streptomycin. Determining in vitro bactericidal titers and monitoring serum drug levels are important in guiding therapy. For penicillin-allergic patients, vancomycin is substituted.

Other Antimicrobial Combinations

As corollaries of the synergy between drugs inhibiting cell-wall synthesis and aminoglycosides in the treatment of enterococcal infections, there are three other infections in which this combination may prove useful: *Staphylococcus aureua* endocarditis, *Klebsiella pneumoniae* infections, and *Pseudomonas aeruginosa* bacteremia.

The in vitro combination of a semisynthetic penicillinase-resistant penicillin such as oxacillin or nafcillin with gentamicin is synergistic against most strains of *Staphylococcus aureus*. In patients with penicillin-sensitive *S. aureus* endocarditis, however, those treated with penicillin and gentamicin had the same survival as those treated with penicillin alone (38). When nafcillin alone was compared with nafcillin and gentamicin in treating *S. aureus* endocarditis, the combination produced a more rapid clinical response manifested by defervescence and normalization of the leukocyte count and a reduced duration of bacteremia, but morbidity and mortality were the same in both treatment groups (39). Further studies are needed to accurately assess the efficacy of a penicillin-aminoglycoside combination in treating staphylococcal endocarditis.

The combination of an active antibiotic inhibiting cell-wall synthesis and an aminoglycoside has also been used to treat *Klebsiella pneumoniae* infections. A synergistic effect has been demonstrated in urinary tract infections (40). Similarly, the response to *Klebsiella* causing bacteremia was 92% effective if synergistic antibiotic combinations were used, compared to 61% when nonsynergistic combinations were employed. These results did not reach statistical significance (41), however. *Klebsiella* infections also respond to a combination of cefazolin and amikacin (42). In neutropenic rats septicemia due to amikacin-sensitive *K. pneumoniae* responded better to a combination of cefazolin and amikacin than to either antibiotic alone (43).

A combination of cephalothin and gentamicin was found to act synergistically in vitro against more than 80% of *Klebsiella* isolates. Induced intraperitoneal *Klebsiella* infections in rats, however, were not affected differently when treated with gentamicin alone, cephalothin and gentamicin, and gentamicin and chloramphenicol (44).

The in vitro synergy of carbenicillin and an aminoglycoside against most strains of *Pseudomonas aeruginosa* is well documented (45, 46). In addition, the value of carbenicillin-gentamicin against *Pseudomonas* infection has been shown in animal models (47). The combination is most useful in patients with impaired defense mechanisms against infection (42). Whether the combination has value in the uncompromised host is not clear. Cancer patients being treated with antineoplastic drugs often become neutropenic and febrile and may develop *Pseudomonas* bacteremia. The outcome in these patients is better when they are treated with carbenicillin-gentamicin (six of seven patients improved) then with cephalothin-gentamicin (none of five improved) (48). A cephalothin-gentamicin combination is of minimal value against *P. aeruginosa* and in addition is nephrotoxic, especially in the elderly (49).

Current recommendations are that in patients with neutropenia who are suspected of having bacteremia antimicrobial therapy for possible *Pseudomo-*

nas aeruginosa infection should be started promptly. Best results are obtained when at least one antibacterial agent is bactericidal in vitro (49). Presently, a combination of either carbenicillin or ticaricillin with either gentamicin or tobramycin is recommended (48, 49).

Ampicillin/Amoxicillin/Penicillin and Probenecid

Gonococci have become increasingly resistant to penicillin, and larger doses of the antibiotic are now recommended for treatment of gonococcal infections. Even though resistant strains of penicillinase-producing gonococci occur, penicillin therapy remains the intial treatment of choice. The combined use of probenecid plus ampicillin, amoxicillin, or procaine penicillin G on one occasion has made it possible to treat infected patients by using the augmentative effect of probenecid on blood levels of penicillins (50).

Probenecid reduces the rapid renal loss of penicillin and was especially valuable when penicillin was scarce during the 1940s. Probenecid influences proximal renal tubular transport mechanisms for organic molecules and thus affects the excretion and resorption of many compounds. Although mainly used clinically for its uricosuric effect, probenecid also inhibits secretion of penicillins in the proximal tubule and reduces their excretion. Thus, the combined use of probenecid and a penicillin leads to a twofold or higher and more prolonged blood penicillin concentration (51). This allows prophylaxis and treatment of uncomplicated gonorrhea in one session (52, 53). Oral penicillin and intramuscular benzathine penicillin G are not adequate therapy since they do not produce therapeutic blood concentrations. Concurrent administration of probenecid also leads to higher and more prolonged blood levels of ampicillin and amoxicillin. The only difference between ampicillin and amoxicillin is that the latter is more rapidly and more completely absorbed after oral administration, producing higher mean peak serum concentration and a greater area under the curve (54, 55). Tetracycline is used in penicillin-allergic persons, but a week of therapy is required. There is no single-dose tetracycline regimen.

These drug regimens are ineffective against anorectal and pharyngeal gonorrhea and against chlamydial infections, and other treatment regimens are recommended for disseminated and penicillin-resistant gonococcal infections (50).

Chlamydia coexist with gonococci in 27–63% of women with endocervical gonorrhea and 4–32% of men with urethral gonorrhea (56). The best treatment for coexistant gonococcal and chlamydial infection is not clear (50). One of the single-dose amoxicillin or ampicillin regimens, plus probenecid coupled with tetracycline or doxycycline treatment for a week, may be appropriate for combined infection. However, no data on the efficacy of such a regimen is presently available. This type of mixed venereal infection may require the use of additional antibiotic combinations for treatment.

Acetohydroxamic Acid and an Antibiotic

Urinary tract infections due to urea-splitting bacteria can produce struvite and carbonate apatite stones, usually staghorn renal calculi or bladder stones. Nearly all species of *Proteus* and some strains of *Pseudomonas, E. coli,* and *Staphylococcus* produce urease (57). Bacterial urease hydrolyzes urea to ammonia and carbon dioxide, the latter forming carbonate and bicarbonate ions. Increased urinary concentrations of carbonate and bicarbonate and the alkalinity produced by ammonia lead to a urine supersaturated with magnesium ammonium phosphate and calcium phosphate. As a result, there is crystallization of struvite ($MgNH_4PO_4.6H_2O$) and carbonate apatite ($Ca_{10}[PO_4]_6CO_3$) (58).

Acetohydroxamic acid is structurally similar to urea, inhibits urease action, and is relatively nontoxic (59). It inhibits alkalinization of urine, reducing supersaturation and subsequent crystallization of struvite and calcium apatite (60). After oral administration, acetohydroxamic acid is rapidly absorbed and is excreted in the urine (58). With single doses of 1.0 g per day, a reduction of urinary ammonia and pH is regularly achieved (58). Reduction in the size of stones or their dissolution may follow the use of acetohydroxamic acid.

The effectiveness of antimicrobial drugs in treating urinary tract infection in patients forming stones has been increased when acetohydroxamic acid is added to the therapeutic regimen (58). After surgical removal of stones, antibiotics plus urease inhibitors (hydroxyurea or acetohydroxamic acid) eliminates urinary infection more frequently than antibiotics alone (61).

The *Proteus* causing urinary tract infections are active producers of urease (62, 63). In the mouse, however, a urease-negative mutant of *Proteus mirabilis* is just as infectious but produces less renal damage (63). Urease is nephrotoxic and may contribute to the pathogenesis of pyelonephritis. It damages tubular epithelial cells and allows intracellular infection (62). The invasive properties of *Proteus* in the urinary tract appear largely dependent on alkalinization of urine by urease, which results in damage to the renal epithelium (64). In experimental animals, pyelonephritic changes from *Proteus* infection can be prevented by administering a urease inhibitor (57, 64, 65). In vitro, acetohydroxamic acid potentiates the effect of certain antimicrobial agents against several bacterial species (66–68). Although the cause of this synergy is unknown, diverse mechanisms have been suggested. In vitro studies with urease-producing organisms have shown that kanamycin increases cell permeability, allowing urease inhibitors to enter the cell and interact with pyridoxal phosphate, ultimately leading to cell damage (66). Synergy occurred in 17% of instances when twelve antimicrobial agents and acetohydroxamic acid were tested against gram-negative bacteria *(Proteus, Pseudomonas, E. coli, Klebsillas, Enterobacter,* and *Providencia)* (68). In 5%, however, antagonism was noted. Synergy has been observed between methenamine and acetohydroxamic

acid against strains of *Proteus*. Reducing alkalinization of the urine may allow formaldehyde to be produced from methenamine, the former being the effective antibacterial substance (67).

Acetohydroxamic acid has only recently been available for clinical use. It may prove a useful adjunct to the treatment of urinary tract infections with urea-splitting organisms. There is evidence that inactivation of urease can make the organism both less virulent and more susceptible to concurrent antimicrobial therapy.

PARKINSONISM

The biochemical basis of parkinsonism is complex and not completely understood, but the primary defect is a decrease in dopaminergic neurons in the basal ganglia. Although viral encephalitis, carbon monoxide exposure, atherosclerosis, and drugs that impede dopamine action in the basal ganglia (phenothiazines, butyrophenones, thioxanthines, metoclopramide, and reserpine) can cause parkinsonism syndromes, the etiology of the neuronal degeneration in idiopathic Parkinson's disease is unknown. The absolute deficit in excitatory dopaminergic neurons is further opposed by the inhibitory activity of cholinergic neurons, leading to a relative cholinergic excess with a resultant imbalance of these neurotransmitter systems. A balance between dopaminergic and cholinergic activity appears necessary for smooth, integrated voluntary movements. This neurochemical disbalance accounts for the cardinal symptoms of parkinsonism: resting tremor, rigidity, bradykinesia, stooped posture, poor balance, and gait disturbances. Symptomatic improvement can be produced pharmacologically either by enhancing dopaminergic activity or by dampening cholinergic activity. Both approaches are clinically useful (69).

Levodopa and Carbidopa

Since parkinsonism is due to central dopamine deficiency, administering exogenous dopamine would be expected to ameliorate symptoms. However, dopamine does not cross the blood-brain barrier and is therefore therapeutically ineffective. Dopamine's immediate precursor, levodopa, does cross the blood-brain barrier, enters the basal ganglia of the brain, and is converted to dopamine by the enzyme dopa decarboxylase located in the remaining dopaminergic nerve terminals. Even though dopaminergic terminals, and hence dopa decarboxylase activity, are diminished in parkinsonism, enough enzyme remains to convert levodopa to adequate amounts of dopamine to produce a therapeutic effect. This has led to the notable success of levodopa in the treatment of parkinsonism. About three-quarters of patients show improvement when treated with levodopa.

Levodopa is well absorbed after oral administration, but about 95% of the drug is rapidly decarboxylated to dopamine, mainly in the liver, by peripheral dopa decarboxylase (70). Probably less than 1% of an administered dose of levodopa enters the brain. In order to insure that an adequate amount of levodopa will reach and cross the blood-brain barrier, large doses must be administered. Many of levodopa's adverse effects, notably anorexia, nausea, vomiting, and hypotension, are due to the large amount of dopamine produced by peripheral decarboxylation. Adverse effects are particularly common in the elderly and in sufferers of postencephalitic parkinsonism (70). Undesirable side effects can be avoided by starting with a small dose of levodopa and gradually increasing it over weeks until the greatest clinical response has been achieved or until unacceptable side effects appear (71).

Dopa decarboxylase is a pyridoxine-dependent enzyme. Small doses of pyridoxine (Vitamin B_6), such as those found in many multivitamin preparations (5 mg or more), enhance dopa decarboxylase activity and the conversion of levodopa to dopamine (72). Consequently, concomitant use of levodopa and pyridoxine can negate the therapeutic effect of levodopa or, conversely, rapidly diminish toxic effects. There is not enough pyridoxine in the average diet to interfere with the action of levodopa. Furthermore, the use of levodopa does not produce pyridoxine deficiency.

The combination of carbidopa, a peripheral dopa decarboxylase inhibitor that does not enter the central nervous system, with levodopa has greatly improved the clinical management of parkinsonism. When these two drugs are given concurrently, decarboxylation of levodopa to dopamine in peripheral tissues is appreciably diminished. This produces higher levodopa plasma concentrations and a prolonged half-life, which allows more drug to cross the blood-brain barrier and reach the nigrostriatal structures for conversion to dopamine (73). Carbidopa also counteracts the antagonistic effect of pyridoxine on levodopa metabolism (74). As a result of dopa decarboxylase blockade, more levodopa is present to enter the brain, and the optimally effective dose can be reduced by about three-quarters. This combination of levodopa and carbidopa is the most effective method available for treating parkinsonism (74). Consequently, adverse effects such as hypotension and vomiting from dopamine stimulation of the emetic center in the medulla, which is not protected by the blood-brain barrier, are largely eliminated or markedly diminished (70, 74). A maximally effective dose can be reached more quickly, since there is less need to develop tolerance to the peripheral effects of levodopa, which are due to peripherally produced dopamine. Apparently large fluctuations in the concentration of dopamine in the brain are dampened and smoother control of symptoms ensues. In addition, the number of patients who improve is somewhat greater than with levodopa alone. About 90% of patients respond to either levodopa or the carbidopa-levodopa combination (75).

Prolonged treatment with levodopa or carbidopa-levodopa has its limita-

tions. After five years of treatment, deterioration occurs in over half of patients (76). The most common difficulties are loss of drug efficacy, abnormal involuntary movements (dyskinesias), the on-off phenomenon, the wearing-off or end-of-dose reaction, and confusion.

Loss of efficacy cannot always be managed by increasing the dose of levodopa. The addition of other drugs, anticholinergics and amantadine and especially bromocriptine, may be helpful.

Dyskinesias may consist of facial grimacing, rhythmic and jerking movements of the hands, head bobbing, chewing and smacking movements of the mouth and lips, and jerking movements extending to the trunk (70). They are decreased by diminishing the dose of levodopa and worsened by increasing levodopa dosage and by anticholinergics.

The on-off phenomenon may occur in up to half the patients. It is characterized by on periods of mobility and off periods of severe akinesia. The on-off phenomenon may occur up to several times in an hour. It generally does not respond to changes in the dose or time of administration of levodopa. The on-off phenomenon may be due to variable plasma levels of levodopa but also to faulty uptake and subsequent synthesis and release of dopamine from this precursor in the basal ganglia.

The wearing-off reaction is a rapid deterioration of symptoms occurring before the next scheduled dose of levodopa. Akinesia becomes more prominent. It results from a short half-life of levodopa and may respond to smaller, more frequent doses.

Confusion, coupled with agitation and impaired recent memory, may progress to delusions and hallucinations. This state has been ascribed to increased central dopaminergic activity resulting from levodopa. The elderly are more susceptible to nocturnal confusion and hallucinations (70).

Carbidopa is combined with levodopa and marketed as Sinemet®. Sinemet 10/100 contains 10 mg of carbidopa and 100 mg of levodopa, while Sinemet 25/250 has 25 mg and 250 mg of these compounds respectively. Sinemet 25/100 provides more carbidopa to block dopa decarboxylase activity and is useful in patients most sensitive to the peripheral toxic effects of dopamine, such as nausea and vomiting (77). This increased ratio of carbidopa to levodopa also produces more rapid symptomatic response than the 1:10 combinations (78).

Treatment with levodopa does not affect the progressive loss of dopaminergic neurons in the basal ganglia. As the process continues, levodopa becomes therapeutically less effective. Other drugs may be helpful at this point, early in the disease, or to ameliorate adverse effects.

Other Drugs

Additional drugs are available to assist in the treatment of parkinsonism (Table 3). They can be used in concert with levodopa to improve the clinical symptoms

Table 3 Drugs used to treat Parkinson's disease

Dopaminergic	Anticholinergics	Antihistamines
levodopa (Larodopa® and others)	benztropine myselate (Cogentin®)	chlorphenoxamine hydrochloride (Phenoxene®)
carbidopa-levodopa (Sinemet®)	biperiden hydrochloride (Akeniton®)	diphenhydramine hydrochloride (Benadryl®)
amantadine hydrochloride (Symmetrel®)	cycrimine hydrochloride (Pagitanc®)	orphenadrine hydrochloride (Disipal®)
bromocriptine mesylate (Parlodel®)	ethopropazine hydrochloride (Parsidol®)	
	procyclidine hydrochloride (Kemadrin®)	
	trihexyphenidyl hydrochloride (Artane®)	

of parkinsonism. They fall into three categories: centrally acting dopaminergic drugs, centrally acting anticholinergics, and monoamine oxidase inhibitors.

DOPAMINERGIC DRUGS Amantadine, originally introduced as a prophylactic drug against influenza A, was found by chance to have antiparkinsonism activity. It is believed to act by causing indirect dopamine release, with some additional direct stimulation of dopamine receptors (79). Amantadine can enhance and smooth out the effects of levodopa. The drugs have an additive effect. However, patients receiving essentially maximal benefit from levodopa receive little additional improvement from amantadine.

The antiparkinsonism effect of amantadine is less than that of levodopa but somewhat more than that of anticholinergics (80). When used together, amantadine and anticholinergic drugs are additive in producing control of parkinsonian symptoms, but confusion is a frequent adverse effect.

Efficacy varies widely from patient to patient. Amantadine exerts its maximal pharmacologic effect after a few days of use, but it is not sustained. Its efficacy diminishes after six to eight weeks of continuous treatment (80, 81). Either increasing the dose or temporarily discontinuing the drug for a few weeks can result in a return of efficacy.

Bromocriptine, an ergot derivative originally used as a prolactin secretion inhibitor, was found to be a striatal dopaminergic agonist as well (82). Bromocriptine and levodopa have an additive effect. Bromocriptine is most useful when given concurrently with levodopa. Treatment with levodopa that is less than optimal may be improved with the addition of small doses of bromocriptine (83). Patients who experience excessive on-off phenomena or wearing-off reactions may be helped by taking bromocriptine. Optimal clinical results may be achieved by levodopa and supplemental doses of bromocriptine, but if

bromocriptine is added the use of levodopa should be reduced to prevent more adverse effects. Using bromocriptine results in a reduced dose of levodopa, improved responsiveness, and a decrease in side effects (69, 82–84). Bromocriptine's main disadvantage is the high incidence of untoward mental symptoms, particularly nightmares, hallucinations, and paranoid delusions (85).

Bromocriptine has been used in previously untreated patients with Parkinson's disease in the hope of extending the duration of a favorable therapeutic response in the disease (86). The response rate was less to bromocriptine (56%) than to levodopa (74%), and the pattern of deterioration or diminished responsiveness to bromocriptine was similar to previous experiences with levodopa therapy. Thus, giving bromocriptine before levodopa does not extend the duration of effective drug therapy.

ANTICHOLINERGIC DRUGS The reduction of dopamine in the basal ganglia in parkinsonism makes the excitatory effects of acetylcholine more prominent. In fact, centrally acting cholinesterase inhibitors such as physostigmine intensify parkinsonism tremor, while centrally acting anticholinergics decrease tremor (87). Anticholinergics were the first drugs used to treat parkinsonism. Centrally acting anticholinergic drugs work well in early or mild parkinsonism and as adjuncts to dopaminergic therapy. In the opinion of some clinicians, they are the preferred drugs for initial treatment. Anticholinergic drugs may be used alone, or when added to levodopa they can further improve symptoms in parkinsonism, especially tremor and rigidity, in about half of patients. Antihistamines have mild anticholinergic effects and are often better tolerated by the elderly.

Large doses of anticholinergic drugs, however, can delay gastric emptying sufficiently to retard small bowel absorption of levodopa. This effect can appreciably diminish the therapeutic effect of levodopa (88). The adverse effects of anticholinergics, particularly confusion and urinary retention, limit their usefulness in the elderly. They may also precipitate or worsen glaucoma, cause dry mouth, constipation, memory defects, and hallucinations. In addition, tricyclic antidepressants are used to treat depression, a frequently encountered problem in patients with parkinsonism. These drugs have notable anticholinergic effects that may at times benefit symptoms of parkinsonism, but they also can produce undesirable anticholinergic side effects as well as sedation and postural hypotension.

MONOAMINE OXIDASE INHIBITORS Attempts to use monoamine oxidase (MAO) inhibitors with levodopa as a means of enhancing the anti-akinetic properties of levodopa were unsuccessful because hypertensive crises were produced. Later, two types of MAO were discovered: MAO-type A occurs peripherally and MAO-type B occurs predominately in the brain (89). Tyramine and dopamine are substrates for both MAO-type A and MAO-type B, but

in the human brain dopamine is metabolized preferentially by MAO-type B. Most MAO inhibitors inhibit both types of MAO indiscriminately, but deprenyl (an experimental drug) preferentially inhibits MAO-type B (90). This has led to clinical trials using deprenyl in patients with Parkinson's disease. By inhibiting the breakdown of dopamine in the brain, deprenyl prolongs and enhances the duration of action of levodopa. Deprenyl's lack of effect on peripheral MAO-type A reduces the chance of producing adverse effects with centrally active amines and with tyramine-containing foods that cause hypertensive crises. Clinical studies have shown favorable results (91). Deprenyl not only increases the duration of levodopa's action but also improves mobility in wearing-off reactions (92). It appears to be a good adjuvant when used with levodopa. At this writing, deprenyl is not available for clinical use.

In summary, in parkinsonism drugs and drug combinations appreciably improve symptoms but do not retard the progress of the underlying disease. The most effective drug is a combination of carbidopa and levodopa, which greatly improves mobility. Other drugs are adjunctive. Drug reactions are not insignificant and occur more frequently in the elderly.

DIURETICS

Diuretic combinations can produce two beneficial effects: prevention of diuretic-induced hypokalemia and enhanced diuresis. The use of a potassium-wasting and a potassium-sparing diuretic combination to prevent hypokalemia is additive and reparative. Enhanced diuresis is synergistic.

Prevention of Hypokalemia

Thiazide diuretics and the structurally different but functionally equivalent chlorthalidone, quinethazone, and metolazone increase urinary excretion of sodium, chloride, and water by inhibiting sodium reabsorption in the early distal tubule. This is accompanied by an appreciable augmentation of potassium excretion, which can lead to hypokalemia. Serum potassium concentrations frequently decrease during long-term diuretic treatment and may be associated with a mild degree of hypochloremic alkalosis. Patients receiving digitalis and those with cirrhosis may be at greater risk from hypokalemia, which can induce digitalis intoxication and hepatic encephalopathy respectively.

Loop diuretics (furosemide, ethacrynic acid, and bumetanide) act on the ascending limb of the loop of Henle. They are potent diuretics with a rapid onset and a short duration of action. Their diuretic effect is much greater than that of the thiazides. An equivalent diuretic effect is produced by 40 mg of furosemide, 50 mg of ethacrynic acid, and 1 mg of bumetanide. Potassium

excretion in the distal segment, as with thiazide diuretics, is related to the increased flow rate through this segment of the tubule.

Three potassium-sparing diuretics are available: spironolactone, triamterene, and amiloride. Although mechanisms of action differ, they produce the same final effect, potassium conservation.

Spironolactone is a competitive inhibitor of aldosterone. Aldosterone increases the distal resorption of sodium and chloride while increasing the excretion of potassium. Spironolactone blocks this effect and enhances diuresis while conserving potassium. When spironolactone is used alone, it has a weak diuretic effect.

Triamterene acts directly on the distal segment of the tubule independent of the effect of aldosterone. The rate of potassium secretion is reduced as the result of a primary reduction in sodium resorption. When used alone, triamterene produces only a paltry diuresis.

Amiloride, too, is not an aldosterone antagonist. Amiloride produces natriuresis with either only a slight increase or sometimes an absolute decrease in potassium excretion. This effect is enhanced when a thiazide diuretic is given concurrently. The combination is additive with respect to sodium and chloride excretion but antagnostic with respect to potassium loss.

Kaliuresis is most marked with brisk diuresis and may be negligible during chronic diuretic administration with little diuresis. Potassium deficiency is particularly likely to occur when there is secondary hyperaldosteronism, as in cirrhosis and accelerated hypertension, but also occurs with less marked elevations of aldosterone (congestive heart failure, nephrosis). Diuresis in the face of mineralocorticoid excess can produce marked hypokalemia. Potassium depletion can lead to alkalosis, reduced carbohydrate tolerance (and worsening of diabetes), impaired neuromuscular function (from weakness to paralysis and ileus), abnormal myocardial function, and a renal concentrating deficit with polyuria.

Diuretic-induced potassium deficiency can be prevented or treated with supplemental potassium administration. Oral preparations have drawbacks, however. Liquids taste bad and can cause gastric upset. Tablets can cause ulceration, bleeding, and resultant stricture in the gut. The combination of a thiazide or loop diuretic and a potassium-sparing diuretic obviates the use of oral potassium supplements. In fact, oral potassium supplements can cause severe or fatal hyperkalemia, especially in the elderly, when given in addition to a potassium-sparing diuretic in combination with other diuretics (93). Thiazides are prescribed in combination with potassium-sparing diuretics as a means of obtaining an additive diuretic effect and conserving potassium. This enhanced diuretic effect and the amelioration of potassium loss are both marked in hyperaldosterone states.

Table 4 Fixed-dose thiazide and potassium-sparing diuretic combinations

Name	Ingredients	Dosage
Aldactazide®	spironolactone	25 mg/50 mg
	hydrochlorothiazide	25 mg/50 mg
Dyazide®	triamterene	50 mg
	hydrochlorothiazide	25 mg
Moduretic®	amiloride	5 mg
	hydrochlorothiazide	50 mg

Varying combinations and doses of thiazide and loop diuretics can be used with the potassium-sparing diuretics to achieve maximal clinical benefit in both diuresis and maintenance of potassium balance (94). Fixed-dose combinations of thiazide and potassium-sparing diuretics are available and can be employed to advantage once the ratio of diuretics has been established (Table 4).

These combinations are popular for treating hypertension because they (*a*) effectively lower blood pressure, (*b*) avoid the use of potassium supplements, which often are not taken because of their unpleasant taste and their propensity to induce nausea, and (*c*) can be administered as a single tablet once or twice a day. Regardless of theoretical objections to fixed-dose drug combinations, these preparations have probably done much to enhance compliance to antihypertensive regimens and produce the desired effect of lowering blood pressure. In addition, although excess sodium intake has long been regarded as playing an etiologic role in the pathogenesis of hypertension (95), evidence is mounting that increasing body potassium may have a beneficial effect in reducing the level of elevated blood pressure (96). These drug combinations may thus provide triple benefit: loss of sodium, retention of potassium, and lowering of blood pressure.

There is evidence that combinations of potassium-sparing and potassium-losing diuretics provide a useful interaction leading to improved potassium balance. Long-term treatment with triamterene alone, chlorothiazide alone, and both drugs together showed that the drug combination produced the highest incidence of normal plasma potassium values (97). In a study of 1,156 elderly subjects using thiazide diuretics or chlorthalidone, serum potassium concentrations were 3.74 and 3.47 meq per liter respectively. Conversely, in those using a combination of hydrochlorothiazide-triamterene or hydrochlorothiazide-spironolactone, serum potassium concentrations were 3.99 and 4.04 meq per liter respectively (98). An extensive literature review of diuretic-induced hypokalemia showed the use of potassium-sparing diuretics to be more effective than potassium supplements (94). A study of elderly veterans using digoxin and various diuretics and diuretic combinations concluded that a potassium-sparing diuretic may be used safely to reduce potassium excretion and the risk of

digitalis intoxication and arrhythmias (99). Thus, combining potassium-losing and potassium-sparing diuretics is a practical and effective way of reducing diuretic-induced hypokalemia.

Enhanced Diuresis

No convincing data exist to indicate that combining two thiazide or thiazide-like diuretics will produce any greater diuretic effect than that induced by using maximal dosages of any single agent. However, the efficacy of thiazide and related diuretics can be increased by concomitant use of a potassium-sparing agent or loop diuretic. The beneficial effects of these regimens appear to result from combined actions at different sites in the nephron and differing mechanisms of action.

Thiazide diuretics produce their effects by inhibiting sodium and chloride reabsorption in the cortical diluting segments of the ascending limb of the loop of Henle and distal convoluted tubule, whereas loop diuretics (furosemide, ethacrynic acid, and bumetanide) act on the medullary portion of the ascending limb of the loop of Henle.

Unresponsiveness to the action of loop diuretics can occur from a marked reduction in glomerular filtration rate or the use of sodium-retaining drugs. The combination of a thiazide-type diuretic and a loop diuretic has been found useful in the management of refractory edema (100). Although the addition of a relatively small dose of a thiazide diuretic to a large dose of a loop diuretic in the face of refractory edema would not be expected to produce a vigorous diuresis, it may in fact do so (101). This synergistic effect has been successfully used to treat severe sodium retention in congestive heart failure, renal failure, the nephrotic syndrome, hypertension, and cirrhosis. Effective diuretic combinations have included thiazides, quinethazone, and metolazone used with furosemide, ethacrynic acid, bumetanide, and piretanide (101). It is postulated that the thiazide-type diuretic impedes the increased distal tubular sodium resorption that limits the effect of the loop diuretic (102).

Massive diuresis may produce marked fluid and electrolyte losses (particularly potassium), worsening azotemia, and circulatory collapse and death (101). A potassium-sparing diuretic or supplemental potassium should be used because of large potassium losses (102). Although a high incidence of adverse effects has been noted with this diuretic combination, employing two diuretics can be clinically very useful. It is recommended that the dose of a loop diuretic be reduced and that small amounts of thiazide-type diuretics be used initially to avert excessive fluid and electrolyte losses.

ANTACIDS

Antacids hasten the healing of peptic ulcers, are beneficial for reflux esophagitis, and are used for a number of unrelated gastrointestinal symptoms by both

physicians and the public. Large doses of antacids produce healing of duodenal ulcers at a rate superior to that of a placebo (103). Antacids and cimetidine produce similar rates of symptom relief and healing of duodenal ulcers (104). Healed ulcers tend to recur promptly when treatment with antacids or cimetidine is discontinued, with half of patients having a recurrence in six months (105). Cimetidine and ranitidine are comparable in their ability to heal duodenal ulcers (106).

Antacids vary in their ingredients, their acid-neutralizing ability, and probably their clinical effects (107). Antacids generally contain aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate, or some combination of these ingredients (108). Each ingredient has advantages and disadvantages. Sodium bicarbonate and calcium carbonate are excellent antacids but both are absorbable and can cause systemic alkalosis. Sodium bicarbonate can cause sodium overload and alkalinization of the urine, which can lead to nephrolithiasis. Calcium carbonate can produce hypercalcemia.

Aluminum hydroxide ($Al[OH]_3$) and magnesium hydroxide ($Mg[OH]_2$) are regarded as nonabsorable or nonsystemic antacids; this is because they do not produce systemic alkalosis since the cation forms insoluble basic compounds in the intestine that are nonabsorbable (109). Aluminum hydroxide is constipating and magnesium hydroxide is laxating. They are often combined in the hope that one will cancel out the undesirable effect of the other. In addition, total buffering time is increased by combining fast-acting magnesium hydroxide with slow-acting aluminum hydroxide (109). Although remarkable success is often achieved, great clinical variability occurs from patient to patient, so that a mixture that has no effect on bowel action in one person may lead to constipation in another and more frequent stools in still another. Nonetheless, the combination of aluminum hydroxide and magnesium hydroxide remains a common, useful, and beneficial reparative drug interaction.

The mechanism by which aluminum compounds cause constipation is unknown. Their astringent properties, which are related to reactions with proteins, have been suggested as a mechanism, but the low concentration of the aluminum ion in the intestine makes this an unlikely explanation (109).

Magnesium hydroxide, although a very effective antacid, is better known in its other guise as the cathartic milk of magnesia. Its laxating action is due to the retention of water in the bowel.

Although considered nonabsorbable antacids, small amounts of the metal ions are indeed absorbed. In the presence of renal insufficiency, aluminum can cause encephalopathy. Aluminum antacids bind phosphate in the gut and help ameliorate the hyperphosphatemia of renal failure. This effect can ultimately lead to osteomalacia, however. Greater amounts of magnesium are absorbed than aluminum, and with renal failure hypermagnesemia can occur and, rarely, alkalosis.

An antacid's ability to reduce gastric acidity in vivo is related to its in vitro acid-neutralizing ability (110). Commercially available liquid antacids vary up to seventeenfold in their neutralizing ability per milliliter, but these differences are usually not reflected in the manufacturer's dosage recommendations. Dosage should be determined on milliequivalents of neutralizing capacity rather than by an arbitrary volume or number of tablets.

The composition, neutralizing capacity, and sodium content of commonly used liquid antacids are shown in Table 5 (107, 108, 111). Wide variations exist in the antacid content in 5 ml of liquid antacids. As a result, the acid-neutralizing capacity varies from a low of 1.4 meq/ml for Amphojel® to a high of 4.2 meq/ml for Maalox TC® and Titralac®. These values correlate inversely with the dose in milliliters containing 80 meq of neutralizing capacity. Thus, 61.5 ml of Amphogel but only 15.7 ml of Maalox TC or 20.0 ml of Titralac is needed to neutralize 80 meq of acid.

Even liquid antacids that contain only aluminum hydroxide and magnesium hydroxide show wide variations in amounts and ratios of these ingredients in 5 ml of antacid (Table 5). Simethicone, an antifoaming agent, is present in many antacid mixtures but has no effect on buffering capacity. All currently available antacids are relatively low in sodium content except those that contain sodium bicarbonate (e.g. Bisodol®).

In selecting an antacid, one should aim for the most acid-neutralizing effect with the least degree of gastrointestinal undesirable effects. Individuals may need to test multiple antacids with varying ratios of aluminum hydroxide and magnesium hydroxide to find the one that produces little or no change in intestinal function while requiring a relatively small volume to be effective.

SUMMARY

Controversy has surrounded the use of combinations of different drugs. Most often, this controversy has been about the desirability or appropriateness of combining two or more drugs in the same dosage form, tablet or solution. The administration to a patient of several different drugs at the same time has been common practice, however. Simultaneous administration of different drugs has been used to achieve different therapeutic effects or to achieve beneficial effects from two or more drugs used for the same therapeutic purpose. Some have contended that when two or more drugs are given to enhance a particular therapeutic effect, these drugs should not be combined in the same dosage form but should be given separately. We have not become engaged in this controversy in preparing this paper. We have emphasized, however, that the concurrent administration of two or more drugs in special circumstances can produce beneficial results, and in some instances appears to be quite appropriate.

Table 5 Liquid antacids

Name	Ingredients (5 ml)	Acid-neutralizing capacity (meq/ml)	Dose (ml) containing 80 meq neutralizing capacity	Sodium (mg/5ml)
Aludrox®	aluminum hydroxide, 307 mg magnesium hydroxide, 103 mg	—	29.6	1
Delcid®	aluminum hydroxide, 600 mg magnesium hydroxide, 665	4.1	9.2	1.5
Di-Gel®	aluminum hydroxide, 282 mg magnesium hydroxide, 87 mg simethicone, 20 mg[a]	—	38.1	9
Gelusil®	aluminum hydroxide, 200 mg magnesium hydroxide, 200 mg simethicone, 25 mg[a]	2.2	38.1	0.7
Gelusil-II®	aluminum hydroxide, 400 mg magnesium hydroxide, 400 mg simethicone, 30 mg[a]	3.0	16.7	0.7
Kolantyl®	aluminum hydroxide, 150 mg magnesium hydroxide, 150 mg	—	38.1	< 5
Maalox®	aluminum hydroxide, 225 mg magnesium hydroxide, 200 mg	—	30.8	1
Maalox Plus®	aluminum hydroxide, 225 mg magnesium hydroxide, 200 mg simethicone, 25 mg[a]	2.3		2.5
Maalox T.C.®	aluminum hydroxide, 600 mg magnesium hydroxide, 300 mg	4.2	15.7	< 1–1.2
Mylanta®	aluminum hydroxide, 200 mg magnesium hydroxide, 200 mg simethicone, 20 mg[a]	—	32.0	< 1
Mylanta II®	aluminum hydroxide, 400 mg magnesium hydroxide, 400 mg simethicone, 30 mg[a]	3.6	16.3	1.1
Simeco®	aluminum hydroxide, 365 mg magnesium hydroxide, 300 mg simethicone, 30 mg[a]			7–14
Bisodol®	sodium bicarbonate, 644 mg magnesium carbonate, 475 mg	—	—	196
Camalox®	aluminum hydroxide, 225 mg magnesium hydroxide, 200 mg calcium carbonate, 250 mg	3.2	23.5	2.5–3
Riopan®	magaldrate, 480 mg		36.4	< 1
Titralac®	calcium carbonate, 1000 mg	4.2	20.0	11
AlternaGEL®	aluminum hydroxide, 600 mg	3.4	23.5	2
Amphojel®	aluminum hydroxide, 320 mg	1.4	61.5	7
Basaljel®	aluminum hydroxide, 400 mg	—	—	2
Basaljel Extra Strength®	aluminum hydroxide, 1000 mg	2.0	18.6	23

[a] Not an antacid but an antifoaming agent

Evaluation of the clinical effectiveness of drug combinations for a particular therapeutic effect cannot be determined entirely from in vitro observation. On the other hand, several drug combinations have been developed specifically from an understanding of the pathogenesis of diseases and the application of pharmacologic principles in the design of effective drugs. This has represented one of the most powerful examples of rational drug development.

As we learn more about complex and increasingly common chronic and degenerative diseases, it is likely that single drugs will prove to be less effective than two or more drugs with complementary effects, resulting in beneficial drug interactions. As more and more drugs are administered to a single patient, however, it is important to recognize that this also increases the risk of untoward or adverse drug effects.

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