

Ochsner Clinic Number

The Medical Clinics of North America

Unusual Clinical And Laboratory Manifestations Of Disease

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Volume 51 - Number 4

July, 1967.

Unusual Antimicrobial Toxic Reactions

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Antimicrobial agents are presently available for the treatment of infectious diseases caused by bacteria, fungi, *Mycoplasma pneumoniae*, rickettsia, protozoa, metazoa, *Miyagawanella* (lymphogranuloma venereum and psittacosis agents), and *Chlamydozoon* (trachoma and inclusion conjunctivitis agent). Though often lifesaving, these drugs have introduced some problems for the individual as well as for society in general. These include "new" diseases as a result of toxicity (staining of fetal teeth by tetracycline) and sensitization of persons who have never received a certain antimicrobial agent as therapy but have been unknowingly exposed (contamination of milk by penicillin when used to treat mastitis in cattle, etc). The total population increase, as well as the increase in life expectancy in the USA, has been due largely to antimicrobial therapy, because of reduced infant and maternal mortality rates, and treatment of bacterial pneumonia in the elderly. Few persons alive today have escaped receiving an antimicrobial agent at some time. It is estimated that more than two billion dollars is spent on antimicrobials yearly in the USA, representing around 50 per cent of all prescriptions written. The physician has more than 35 different antimicrobials in more than 400 dosage forms from which to choose.

Minor and major toxic effects of some of the antimicrobial agents used *systemically* will be discussed, with special emphasis on the less common toxic reactions. The agents and the respective toxicities will be presented individually. It should be pointed out that little is known of the toxicity of combinations of two or more of these agents administered at the same time. Unfortunately, patients receiving these combinations are usually difficult to evaluate because of the nature of the primary disease and other medications the patient may be receiving at the same time. The antituberculous agents are probably the best studied combination, but there are surprisingly few data even for this group.

Certain persons are more prone to toxic manifestations as a result of antimicrobial therapy. They include the very young with immature enzyme (detoxifying) systems and those with hepatic or renal disease. Older persons may have considerable renal disease and still maintain a normal blood urea nitrogen level and, therefore, antimicrobials excreted by the kidneys may accumulate rapidly in these patients. Probably the biggest single obstacle to good antimicrobial management is the difficulty of determining the level of the antimicrobial agent in the body fluids. The sulfonamides are notable exception to this.

A careful history regarding allergy, especially to antimicrobials and other drugs, remains the best way to prevent hypersensitivity reactions in patients. Even with a negative history, an anaphylactic reaction may occur, especially after parenteral administration of an agent such as penicillin G. The physician administering antimicrobial agents parenterally in the home should remain with the patient for at least 30 minutes and have aqueous epinephrine, adrenocortical steroids for parenteral use, diphenhydramine, a vasopressor such as metaraminol, and a tracheal trocar in his bag. The same principles should be observed when antimicrobials are administered parenterally in the physician's office or hospital emergency room. The tragedy of a death due to anaphylaxis from antimicrobial therapy would be extremely rare if these simple precautions were uniformly observed. Fortunately, anaphylactic reactions after orally administered antimicrobials are far less common, although

some believe that the same precautions should be observed for the penicillins administered in this fashion.

The antimicrobial agents will be considered according to the type of microorganisms against which they are principally active. Comments regarding dosage refer to adults only.

Antifungal Agents

Amphotericin B

This fungistatic antibiotic is the most effective agent available for the treatment of *systemic* candidiasis, mucormycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, and aspergillosis. It is also the preferred treatment for North American blastomycosis. It is given intravenously and can cause chemical phlebitis, which usually responds satisfactorily to administration of 100 mg of phenylbutazone, three times a day for five days, and application of heat. Addition of 20 to 40 mg of heparin to the infusion plus use of a pediatric scalp vein needle help prevent phlebitis due to this and most other antimicrobials administered intravenously.

Unfortunately, many toxic effects of amphotericin B occur in all patients treated with this agent. These include fever (up to 105°F), true rigors, headaches, nausea, vomiting, anxiety, and abdominal pain during or immediately after completion of the usual daily six-hour infusion of 500 mL of 5 per cent solution of dextrose in water with amphotericin B. These toxic effects are more common with the first ten treatments and may be lessened or prevented by intramuscular administration of 50 mg of chlorpromazine and diphenhydramine, 30 minutes before the beginning the infusion, and 100 mg of hydrocortisone intravenously when the infusion is started. After the first ten treatments, tolerance to amphotericin B usually permits discontinuance of one or more of these drugs.

Later toxic effects include normocytic normochromic anemia, which is reversible, but is treated with blood transfusion while therapy is continued, if the hemoglobin is less than 10 gm/100 mL. Complete blood counts are performed weekly. In two patients treated recently, reversible granulocytopenia developed in the peripheral blood. Treatment was not altered, and no apparent ill effects have occurred.

The metabolic fate of amphotericin B is unknown, but only a small portion is excreted in an active form in the urine. Nephropathy with increased blood urea nitrogen and creatinine levels; decreased renal concentrating ability; decreased phenolsulfonphthalein excretion; decreased clearance of urea, creatinine, and inulin levels; and decreased clearance of para-aminohippurate occurs, and usually some irreversible renal damage results if a total of 2.5 gm of amphotericin B is given. The pH of the urine is frequently alkaline in addition to containing cellular elements and casts. Proteinuria is uncommon. Maintenance of acid pH urine with ascorbic acid has not prevented rise in blood urea nitrogen or creatinine levels. If daily administration of amphotericin B results in a rise in blood urea nitrogen or creatinine, the drug may be given on alternate days. The goal is to keep the blood urea nitrogen level less than 40 mg/100 mL or the creatinine less than 2 mg/100 mL. One of these determinations should be obtained weekly, and if values exceed the levels quoted, treatment should be discontinued until acceptable levels are obtained.

Hypokalemia with increased urinary excretion of potassium usually occurs, and severe muscle weakness and paralysis have been reported. I routinely prescribe a solution of potassium salts in a dosage of 15 mEq or more four times a day to maintain normal serum potassium concentration.

Idiosyncratic reactions, including anaphylactoid shock, thrombocytopenia, acute hepatic failure, flushing, vertigo, generalized pain, grand mal convulsions, cardiac arrest, peripheral neuropathy, and ventricular fibrillation, rarely occur. I obtain weekly serum for glutamic pyruvic transaminase determinations and have occasionally noted slight rises.

Griseofulvin

This fungistatic antibiotic is used in the treatment of cutaneous infections caused by microsporum, epidermophyton, and trichophyton (usually 0.5 to 1 gm every day for six to 24 weeks). Griseofulvin is mainly fixed and carried with keratin in the body, the remainder being detoxified in the liver. Most patients tolerate it well.

An occasional patient will have an oral or gastrointestinal disturbance, such as dry, painful, or black tongue; angular stomatitis; anorexia; epigastric pain; nausea; vomiting or reactivation of chronic colitis with bloody diarrhea. *Rarely*, dermatologic lesions occur, including urticaria (sometimes angioneurotic edema), petechiae, erythemas, lichen planus-like eruptions, pruritus, and photosensitivity (including a lupus erythematosus-like syndrome). Candidiasis of the skin and mucous membranes may occur during treatment with griseofulvin.

Rarely, neurologic reactions occur, including blurred vision, disorientation, nightmares, vertigo, and potentiation effects of alcoholic beverages. Lack of coordination and lapses of attention and memory were noted in two pilots during prolonged treatment with griseofulvin. Headache during the first few days of treatment is rather common but subsides even though use of the drug is continued. Granulocytopenia that is reversible and probably of no clinical significance occasionally occurs.

Miscellaneous (and nonspecific) reactions include thirst, fatigue, generalized malaise, engorgement of the breast, and fainting. Griseofulvin affects porphyrin metabolism experimentally, and it has precipitated attacks in patients with acute intermittent porphyria during remission. This fungistatic antibiotic has been reported to decrease the severity of pain in patients with angina pectoris and result in improvement in some patients with shoulder-hand syndromes. The chemical structure of griseofulvin is somewhat similar to colchicine and apparently potentiates its action in the treatment of acute gouty arthritis. Sodium variation antagonism may occur.

Agents Principally Active Against Gram-Positive Bacteria

Cephalothin

This bactericidal antibiotic is excreted mainly by the renal tubules, as is penicillin G; however, when given alone, it does not accumulate or produce toxicity in patients with poor renal function. This is presumably because of rapid inactivation by deacetylation in the liver.

It should be administered only parenterally, being extremely painful when given intramuscularly.

Cephalothin is effective against most bacteria which are penicillin-sensitive. Fortunately, cross-sensitivity between the penicillins and cephalothin does not occur; therefore, cephalothin can be administered safely to penicillin-allergic patients. Hypersensitive reactions to cephalothin, itself, can occur, the most common of which are eosinophilia alone or rashes. Other toxic manifestations are infrequent, but reversible neutropenia and elevation of the serum glutamic oxalacetic transaminase (SGOT) level may occur. Reversible renal failure has occurred in three patients with severe systemic disease who were receiving cephalothin (12 to 18 gm daily intravenously) plus other drugs, including other antibiotics, such as colistimethate and rolitetracycline. Patient with renal dysfunction should probably not receive more than 6 gm of cephalothin a day. On the other hand, a penicillin-G-allergic patient was given 18 gm of cephalothin intravenously every day for 30 days for alpha hemolytic streptococcal bacterial endocarditis without difficulty. A positive reaction to the direct Coombs' test may occur in cephalothin-treated patients with azotemia.

Erythromycin

This bacteriostatic macrolide antibiotic is effective treatment for *Mycoplasma pneumoniae* infections and can be used as an alternative drug for the penicillins in the treatment of non-life-threatening infectious diseases. Since it is excreted primarily in the bile, the usual dose (250 to 500 mg every six hours) does not need to be altered for patients with renal disease.

Erythromycin has caused no serious toxic effects. Minor toxic effects (primarily gastrointestinal) are common, however. These include stomatitis, black tongue, nausea, abdominal pain, vomiting, loose stools occasionally with proctitis, and alcoholic intolerance. These reactions rarely necessitate discontinuance of administration of erythromycin. Headaches, dizziness, rashes, and superinfection with *Candida* are uncommon. Discoloration of teeth and enamel hypoplasia due to erythromycin in one child have been reported.

I do not prescribe erythromycin estolate or the similar triacetyloleandomycin because they can produce hepatic disease, and they have no advantage over plain erythromycin. Erythromycin for parenteral administration is available, but as a rule, if the patient is ill enough to require administration by this route, another antibiotic should be used, such as one of the penicillins, cephalothin, or vancomycin.

Lincomycin

This antibiotic is excreted primarily in the bile with up to 30 per cent in the urine. It has not been used extensively enough to evaluate its proper place in therapy of infections caused by gram-positive cocci, although it shows some promise in the treatment of staphylococcal osteomyelitis in the penicillin-allergic patient. When administered parenterally, it is well tolerated. Diarrhea, which is apparently the most frequent toxic effect of oral administration, has necessitated discontinuance of use of the drug on some occasions. With more extensive use of this antibiotic other toxic effects may become apparent.

Novobiocin

I do not prescribe this bacteriostatic antibiotic because of its high incidence of toxicity (jaundice, rashes, blood dyscrasias, fever, and other signs of hypersensitivity) and because of the availability of more effective and less toxic agents. Use of fixed combinations of antibiotics, such as tetracycline and novobiocin, is not recommended.

The Penicillins

Penicillin G (Benzyl Penicillin). This bactericidal agent is excreted by the renal tubules with some inactivation in the liver. With the exceptions of fever and hypersensitivity reactions (contact dermatitis, urticaria and delayed serum sickness, and immediate anaphylaxis), toxic manifestations of penicillin G and alpha phenoxymethyl penicillin are unusual. Direct Coombs-positive hemolytic anemia rarely occurs. Penicillin G has been implicated as an activator of systemic lupus erythematosus (SLE). Acute psychotic reactions may develop after injections of aqueous procaine penicillin. Such reactions are probably due to intravascular leakage of procaine.

When large amounts of penicillin G are given, the potassium or sodium content may be significant, especially if renal failure is present (each million units contains approximately 1.7 mEq of potassium *or* sodium plus 0.3 to 0.4 mEq sodium in the sodium citrate buffer). Irritation of the central nervous system manifested by seizures occasionally develops in patients given large doses of penicillin G (20 to 80 million units daily), but usually such patients have underlying cerebral disease. Intrathecal administration is contraindicated because of neural irritant properties. Nephritis (presumably hypersensitivity type) associated with penicillin G and methicillin therapy has been reported. The urine contains cellular elements (especially red blood cells and red blood cell casts), and proteinemia may be striking.

The mechanism of development of hypersensitivity to the penicillin is poorly understood. In some patients this hypersensitivity apparently disappears spontaneously. We do not have any completely reliable laboratory or clinical tests to enable us to predict whether an anaphylactic reaction will follow penicillin therapy. There is no justification for administration of any of the penicillins (including penicillin O) to a patient known to be allergic to penicillin, because other antibiotics, such as cephalothin and vancomycin, are effective. When penicillin therapy is initiated parenterally, the precautions mentioned previously should be observed. If anaphylaxis occurs (hypotension, wheezing, angioneurotic edema), I administer aqueous epinephrine (1:1000, 0.5 to 1.0 mL), methylprednisolone (40 to 125 mg) or hydrocortisone (200 to 500 mg), and diphenhydramine (50 mg) in that order, all intravenously through the tubing of a 5 per cent dextrose infusion. Penicillinase is not used. Oxygen by mask is given and an open airway is maintained (with tracheostomy if necessary). Patients usually respond to such treatment rapidly, and further use of epinephrine is rarely required. If hypotension persists, vasopressors, such as metaraminol or levarterenol, are given. Administration of adrenocortical steroids and diphenhydramine is continued until the body has had time to excrete or inactivate the particular penicillin given. Benzathine penicillin remains in the body for at least three weeks, but prednisone in a dosage of 10 mg every eight hours and diphenhydramine (25 mg every six hours) usually prevent hypersensitivity symptoms after control of the initial episode of hypotension.

Methicillin. This antibiotic is used only to treat severely ill patients with infections caused by *Staphylococcus aureus*. It is administered intravenously (usually 6 to 12 gm a day with physiologic saline solution) and can cause fever and hypersensitivity reactions similar to penicillin G. Rarely, reversible bone marrow depression (especially erythroid aplasia) has been noted. Associated with this depression is elevated serum iron concentration and saturated total iron-binding capacity. To my knowledge there have been no reports of aplastic anemia associated with methicillin therapy. On the rare occasion when clinical and laboratory signs of renal and hepatic disease have been noted during methicillin therapy, a direct cause and effect were not established.

Cloxacillin. This semisynthetic penicillin is active against penicillinase-producing *Staphylococcus aureus* strains and is well absorbed orally. It is preferable to the similar oxacillin, especially in children. Cloxacillin, oxacillin and nafcillin differ from the other penicillins in being excreted primarily in the bile. Anaphylactic reactions do not appear to occur as frequently to cloxacillin as to penicillin G or methicillin, possibly because no parenteral form is available, as well as the fact that it has been less extensively used. Cross-sensitivity between the various types of penicillins may or may not occur.

Rashes and fever occur, as well as minor gastrointestinal complaints, such as bitter eructations and nausea, the latter rarely necessitating discontinuance of administration. I have seen no patients with over hepatic or renal disease associated with cloxacillin therapy. Slight elevations of SGOT have occurred during therapy.

Ampicillin. This bactericidal antibiotic is rapidly excreted in the urine and is effective against some gram-negative bacilli (*E. coli*, *Shigella*, *Salmonella*, *Hemophilus*, and *Proteus mirabilis*) as well as gram-positive cocci with exception of penicillinase-producing staphylococci. Because of the greater variety of antimicrobial action, superinfections with *Candida* species would be expected to be more common than with the other penicillins.

Recently, I studied 45 consecutive patients treated with ampicillin. In three (6.7 per cent) a rash thought to be due to the drug developed, two early and one late in course of treatment. In two others clinical candidiasis developed and five complained of loose stools or diarrhea. Quantitative fecal cultures for *Candida* species on treatment days 1, 5, and 10, respectively, were performed on 32 patients given 500 mg every six hours primarily for genitourinary infections. Approximately one-half showed a great increase in *Candida* species in the stool at the end of treatment with a similar number showing no change throughout treatment. There was no correlation between the loose stools or diarrhea and the number of colonies of *Candida* species in the stool.

It is my impression that rashes (possibly not all on a hypersensitivity basis) occur more frequently with ampicillin therapy than with the other penicillins. Rises in SGOT have been reported, but no clinical hepatic or renal disease has been attributed to ampicillin.

Nafcillin. I do not prescribe this agent because it has no advantage over the previously discussed penicillins and it is not absorbed from the gastrointestinal tract as well as cloxacillin.

Vancomycin

This bactericidal antibiotic is not absorbed when given orally, but may be administered in this fashion for treatment of staphylococcal pseudomembranous enterocolitis (0.5 gm every six hours). It is given intravenously for severe infectious disease due to penicillin G or methicillin-sensitive microorganisms in a penicillin- *and* cephalothin-allergic patient. Unfortunately, phlebitis with thrombosis occurs in most patients in spite of all precautions.

Vancomycin is excreted primarily by glomerular filtration, and very high serum levels can occur in patients with renal disease given ordinary doses (0.5 to 1.0 gm every six hours). The most serious complication of vancomycin therapy has been decrease in hearing or total deafness, but this is rare in patients with normal renal function. Reversible nephropathy may occur but has not been a problem with recent lots of the drug. Drug fever, urticarial and macular rashes, and generalized tingling (during vancomycin infusion) may occur. Allergic reactions and peripheral neuropathy are rarely associated with this agent.

Agents Principally Active Against Gram-Negative Bacilli

Chloramphenicol

I use this antibiotic only in the rare tetracycline-allergic patient with rickettsial or *Miyagawanella* infection. Chloramphenicol is the leading cause of drug-induced aplastic anemia in the USA. In addition, it can produce acute and fatal circulatory collapse in patients deficient in hepatic-conjugating enzymes as well as cause serious visual disturbances (amblyopia, decreased visual acuity, and scotomata). Agranulocytosis, thrombocytopenia, and hemolytic anemia in glucose-6 phosphate dehydrogenase (G6PD) deficient persons may also occur.

Colistimethate and Polymyxin B

For practical purposes, these two bactericidal preparations may be considered identical. Both are administered parenterally for systemic infection caused by *Pseudomonas*, *Klebsiella*-*Aerobacter* group, and some other gram-negative bacilli. Colistimethate (polymyxin E) is preferred for intramuscular injection (usually 100 mg every eight hours or 2.5 to 5 mg/kg body weight/day) because it is combined with dibucaine and is less painful. Polymyxin B may be administered intramuscularly or intrathecally. The usual intravenous or intramuscular dose is 50 mg every eight hours (1.5 to 2.5 mg/kg body weight/day).

The most distressing toxic effects involve the nervous system. These include paresthesia (especially circumoral), nystagmus, ataxia, and dysarthria. Fortunately, these effects may be minimized or eliminated by a decrease in the dose, and apparently there is no permanent damage. Respiratory arrest (apnea) due to neuromuscular blockade during use of these agents has been reported. This complication is not common and appears to be associated with high blood levels. The latter is most likely to occur in patients with renal disease, as the compounds are excreted by the kidneys. Increased susceptibility to this complication would be expected in anesthetized patients and those with myasthenia gravis. It is not known whether neostigmine (Prostigmine) or calcium ion (calcium chloride or gluconate IV) is the better antidote.

Dermatitis, drug fever, and nephrotoxicity (rising blood urea nitrogen level with or without formed elements in the urine) all may occur, but nephrotoxicity has not been a problem if recommended doses are not exceeded. Obviously, in the presence of renal disease the dosage must be adjusted. If the creatinine is 1.5 to 5 mg/100 mL, an initial loading dose of 2.5 mg/kg body weight of colistimethate (1 mg/kg if polymyxin B is used) is given during the first 24 hours, and every two to three *days* afterward. If the creatinine level is higher than 5 mg/100 mL after this initial dose, the same dosage is repeated every six or seven *days*.

Kanamycin

This bactericidal antibiotic is excreted by glomerular filtration and is administered intramuscularly or intravenously in the treatment of serious infectious diseases due to most gram-negative bacilli, including Klebsiella-Aerobacter group, paracolon, Proteus species, and E. coli. The average adult dose is 0.5 mg every eight hours (10 to 15 mg/kg body weight/day). Circumoral and other paresthesias, peripheral neuropathy, restlessness, blood dyscrasias, rashes, headaches, visual complaints, drug fever, and other allergic reactions occur rarely with kanamycin therapy.

Nephrotoxicity with azotemia occurs in patients with previous renal disease unless dosage is adjusted. Neuromuscular blockade (succinylcholine-like effect) with respiratory paralysis and apnea may follow intraperitoneal, intrapleural, or rapid intravenous administration, particularly if associated with ether anesthesia. Kanamycin administered by these routes is contraindicated in ether-anesthetized patients, patients with myasthenia gravis, and those known to be hypersensitive to succinylcholine. Experimental studies suggest that calcium chloride (0.5 to 1.0 gm intravenously) is the preferred antidote. Some believe neostigmine is contraindicated, since it may worsen the neuromuscular blockade.

The most frequent and, unfortunately, a serious toxic effect of kanamycin is damage to the cochlear division of the eighth cranial nerve. Permanent, bilateral, perceptible deafness may occur, but it is unusual in patients treated for no more than two weeks, unless renal disease is present. Daily questioning regarding tinnitus and pressure or fullness in the ears; biweekly creatinine or blood urea nitrogen determinations; and weekly audiography should be performed during kanamycin therapy, and use of the drug discontinued if the infection is controlled and any of these tests reveal abnormalities. Obviously, in a severely ill patient with, for example, Proteus vulgaris pneumonia and septicemia, deafness may have to be accepted as a price for survival. Other potentially ototoxic antibiotics, such as neomycin, streptomycin, vancomycin, and viomycin, should *not* be administered concurrently.

If patients with renal disease require kanamycin treatment, the following is recommended: (1) Creatinine value of 1.5 to 5 mg/100 mL, a single 1 gm dose followed by 0.5 gm every two to three *days*. (2) Creatinine value of more than 5 mg/100 mL, a single 1 gm dose followed by a single 0.5 gm dose in four *days*.

Nalidixic Acid

This synthetic antimicrobial agent is excreted primarily in the urine, and is used for the treatment of genitourinary infections. It has not been used extensively enough for adequate evaluation of toxic effects; however, a few interesting observations have been made.

Rashes, nausea, vomiting, eosinophilia, polyarthritus, and dizziness may occur. Overdosage (usually 0.5 to 1.0 gm four times a day is given) may precipitate convulsions in patients with disease of the central nervous system and cause convulsion, hyperglycemia, and glycosuria suggesting diabetic ketosis. The plasma acetone value is normal in the latter. Visual difficulty, including diplopia, and photosensitivity reactions may occur during therapy with nalidixic acid. The latter reaction probably will eventually be found to be associated with a lupus erythematosus-like syndrome.

An increase in the thymol turbidity reaction and SGOT has occurred. Patients receiving nalidixic acid should have periodic liver function tests and complete blood counts until more is known about the drug. Of practical interest is the fact that a glucuronide conjugate of nalidixic acid, which is excreted in the urine, may give a false-positive glucose reaction with Clinitest or Benedict's solution, but not with Clinistix. Because of the rapid emergence of nalidixic acid resistant bacteria during treatment, this agent will probably be used less frequently in the future.

Neomycin

This antibiotic is similar to kanamycin. It is not used systemically but a small amount may be absorbed from the gastrointestinal tract with oral use for hepatic disease, and if renal disease is also present, enough may accumulate to produce toxic effects similar to kanamycin. Neuromuscular blockade similar to kanamycin may occur if neomycin is used intraperitoneally.

Nitrofurantoin

This synthetic agent is widely used by urologists in the treatment of genitourinary infections and is probably the leading cause of nausea, vomiting, and drug fever in their patients. I do not prescribe this expensive agent, which "sterilizes" the urine but does not cure the infection. In addition to the toxic effects already mentioned, severe peripheral neuropathy, allergic tracheobronchitis, anaphylaxis, rashes, and anemia (both hemolytic in G6PD-deficient individuals and megaloblastic) may occur.

An unusual, but probably more common than generally realized toxic manifestation, is small pulmonary infiltrations with or without eosinophilia which clinically resemble pulmonary emboli. In one patient who had retropubic prostatectomy, fever developed during nitrofurantoin therapy and its administration was discontinued. Correlation of the febrile episode with the drug, however, was not appreciated and administration of nitrofurantoin was restarted. Dyspnea, tachypnea, tachycardia, apprehension, fever, and substernal pain developed, and coarse breath sounds were heard. No abnormalities were detected in roentgenograms of the chest and electrocardiograms. Suppurative pelvic thrombophlebitis with pulmonary emboli was suspected, and the inferior vena cava was ligated. The patient improved, but administration of nitrofurantoin had also been stopped because of the operation. One week later, administration of nitrofurantoin was again started, and fever, thoracic pain, and coarse breath sounds returned. This time the patient had informed his physicians that the medication was making him sick.

Another patient taking nitrofurantoin showed signs and symptoms suggestive of pulmonary embolism. No abnormality was noted in roentgenograms of the chest, but the lung scan supported the diagnosis. The patient rapidly improved when nitrofurantoin was withdrawn, and six days later, a lung scan showed considerably more clearing than would be expected if pulmonary embolism had occurred.

Chills and fever developed in a physician while receiving nitrofurantoin for prostatitis. Changes suggestive of pulmonary emboli were demonstrated in roentgenograms of the chest. Fortunately, eosinophilia of 24 per cent was demonstrated, and a diagnosis of nitrofurantoin toxicity was made. Symptoms subsided upon discontinuance of administration of the drug. These three cases are presented to focus attention on a toxic manifestation of nitrofurantoin that can resemble a life-threatening disease (pulmonary embolism) which, if present, would demand drastic therapeutic measures (possibly inferior vena cava ligation).

Streptomycin

This bactericidal antibiotic has been used extensively in the treatment of mycobacterial and *Pasteurella* infections, but always in combination with other antimicrobials, as otherwise bacterial resistance develops rapidly. Hypersensitivity reactions to streptomycin occasionally occur, including dermatitis, fever, eosinophilia, and rarely, angioneurotic edema. Much less common complications include bone marrow depression, peripheral neuropathy, and nephrotoxicity.

The more common manifestations of injury to the nervous system are vestibular nerve dysfunction and neuromuscular blockade. Vertigo and ataxia usually do not appear until at least a total dose of 0.5 gm/kg body weight has been given, although these symptoms may start after the first injection. Use of the drug should be stopped and bed rest with regular doses of prochlorperazine (10 mg every four hours while awake) should be administered until the symptoms can be tolerated or disappear. Intraperitoneal, intrapleural, or rapid intravenous administration may result in curare-like neuromuscular blockage with respiratory paralysis and apnea. Streptomycin should not be used in anesthetized patients or those with myasthenia gravis. Neostigmine, 0.5 mg or more intramuscularly, is the antidote of choice.

Sulfonamides

There are many different types and combinations of these synthetic antimicrobials. I prescribe *sulfadiazine* (nocardiosis and certain intestinal inflammations), *sulfisoxazole* and *sulfamethoxazole* (some genitourinary infections) and *trisulfapyrimidines* (toxoplasmosis) systemically. Precipitation of sulfonamide crystals in the renal tubules and pelvis has been no problem with these preparations if adequate hydration and an alkaline urine pH is maintained (with sodium bicarbonate if necessary).

Other toxic effects which may occur and require discontinuance of sulfonamide therapy include nausea, vomiting, dizziness, agranulocytosis, hepatitis, anemia (both hemolytic, in patients with G6PD deficiency, and aplastic), thrombocytopenic purpura, cyanosis (met- or sulfhemoglobinemia), photosensitivity, kernicterus in newborn infants by competing with bilirubin protein-binding, fever, hypoprothrombinemia, polyarteritis nodosa,

Stevens-Johnson syndrome (especially with the nonrecommended long-acting preparations), dermatitis, and anaphylaxis.

The Tetracyclines

Because of their wide range of bacteriostatic antimicrobial activity and unusual toxic manifestations, the tetracyclines will be discussed separately.

Tetracycline, Oxytetracycline and Rolitetracycline. There is no added advantage to using chlortetracycline or demethylchlortetracycline in the treatment of any infectious disease. The former is less stable and the latter more toxic (photosensitization, anaphylactoid reactions, and nephrogenic diabetes insipidus) than the parent compound, tetracycline, or oxytetracycline. The following comments regarding tetracycline apply equally well to oxytetracycline, and there is no evidence that either one has any advantage in the treatment of infectious diseases or in the production of toxic effects in the adult.

Oral administration of tetracycline can cause the following minor toxic effects: nausea, vomiting, anorexia, epigastric distress, diarrhea, flatulence, and increase in stool bulk. Stomatitis, glossitis, vaginitis, and proctitis as a result of candidiasis may occur and are more common than with the use of antimicrobial agents of more limited application. Rashes and other manifestations of hypersensitivity rarely occur.

It is estimated that 50 per cent or less of the oral dose of tetracycline is absorbed, the rest remaining in the intestines. Because the bacterial population in the intestines may be so altered that vitamin K is not synthesized in adequate amounts, it is probably preferable that 5 mg of vitamin K be administered orally each day while the patient is receiving one of the tetracyclines for longer than one week. Riboflavin deficiency is also a possibility and, with prolonged therapy, a multivitamin preparation should be given daily.

Tetracyclines can cross the placenta and affect the calcification of the deciduous teeth, a process which begins during the fourth month of gestation. A permanent disfiguring brown or yellow pigmentation may result, and it is recommended that tetracyclines not be given to pregnant women during the last two trimesters, or to children younger than 6 years of age. There is some evidence that oxytetracycline is less likely to produce these dental effects. An unusual toxic effect in the mouth is glossitis with atrophy of the filiform and enlargement of the fungiform papillae on the tongue.

Amino-aciduria, hypokalemia, and other features of the Fanconi syndrome have been produced by degraded tetracycline as well as stimulated systemic lupus erythematosus. This degradation is more likely to occur when the capsules have been improperly stored under conditions of extreme heat and humidity. Other rare toxic manifestations include benign intracranial hypertension causing bulging fontanelles in infants (reversible), transient myopia, and acute hemolytic anemia with thrombocytopenic purpura (oxytetracycline).

When administered to some patients with renal disease, tetracycline will produce an increase in blood urea nitrogen without a change in the creatinine level. It has been known that tetracyclines have a mild antianabolic effect in the patient with no renal disease, but this has not been a problem. The dose of tetracycline should be altered for the rare patient with

renal disease who requires this drug. It is recommended that after an initial loading dose of 0.5 gm orally, 250 mg should be given every six to eight hours if renal function is 75 per cent or more of normal, as estimated by creatinine clearance. If the creatinine clearance is 10 to 30 mL/min, a maintenance dose of 250 mg should be given only once every two days.

Rolitetracycline, the preferred parenteral form of tetracycline, is usually administered in 350 mg doses every 12 hours. Undesirable effects, which usually disappear within five to ten minutes after intravenous injection, include pruritus, flushing of the face, headache, dizziness, nausea, epigastric pain, and bitter taste, with or without an ethereal odor. The most serious toxic effect of parenteral use of tetracyclines is hepatic and pancreatic disease (occasionally fatal), which may occur if the recommended dose is exceeded or not adjusted when renal disease is present.

Despite the foregoing comments regarding toxicity of tetracycline, these complications occur rarely when the drug is administered properly, and tetracycline remains an outstanding antimicrobial agent. Death as a direct result of administration of tetracycline has been extremely rare.

Conclusions

Introduction of antimicrobial agents represents the greatest medical advance during the past hundred years, but unfortunately none of these agents is a panacea for the cure of infection, and all are potentially toxic to man. It behooves the physician to be aware of the toxic effects of antimicrobial agents he uses, especially the life-threatening ones. Frequently, these effects are reversible if recognized promptly and therapy is altered accordingly.

Generic And Trade Names Of Drugs

Alpha phenoxymethyl penicillin - penicillin V
Ampicillin - Omnipen, Penbritin, Polycillin
Benzathine penicillin - Bicillin, Permapen
Cephalothin - Keflin
Chloramphenicol - Chloromycetin
Chlorpromazine - Thorazine
Chlortetracycline - Aureomycin
Cloxacillin - Tegopen
Colistimethate - Coly-Mycin
Demethylchlortetracycline - Declomycin
Diphenhydramine - Benadryl
Erythromycin - Erythrocin, Ilotycin
Erythromycin estolate - Ilosone
Fungizone - Amphotericin B
Griseofulvin - Fulvicin-U/F, Grifulvin-V, Grisactin
Kanamycin - Kantrex
Levarterenol - Levophed
Lincomycin - Lincocin
Metaraminol - Aramine
Methicillin - Dimocillin-R/T, Staphcillin
Nafcillin - Unipen
Nalidixic acid - NegGram
Neomycin - Mycifradin, Neobiotic
Neostigmine - Prostigmin
Nitrofurantoin - Furadantin
Novobiocin - Albamycin, Cathomycin
Oxacillin - Prostaphlin, Resistopen
Oxytetracycline - Terramycin
Penicillin G - Benzyl penicillin
Penicillin O - Cer-O-Cillin
Penicillinase - Neutrapen
Polymyxin B - Aerosporin
Prochlorperazine - Compazine
Rolitetracycline - Syntetrin
Sulfamethoxazole - Gantanol
Sulfisoxazole - Gantrisin
Tetracycline - many trade names
Triacetyloleandomycin - Cyclamycin, TAO
Trisulfapyrimidines - Terfonyl, Trisureid
Warfarin - Coumadin, Panwarfin, Prothromadin
Vancomycin - Vancocin.