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Adverse effects of antimicrobial agents on major organ systems

RAY A. VANOMMEN, M.D.

Department of Internal Medicine,
Section of Infectious Disease

THE problem of adverse antibiotic reactions should be a concern to all physicians. Life-threatening and morbidity-causing factors of antibiotic therapy are largely direct toxic or allergic reactions. Idiosyncratic reactions and individual intolerance to antimicrobial agents may be serious, and awareness of these phenomena may often prove lifesaving. The possibility of adverse effects of antimicrobial agents must be considered at the time of initiating administration. Physicians must now be concerned not only with the infections they are treating but also with the diseases that may be created by treatment.

It is not within the scope of this paper to consider all the adverse reactions to antibiotic therapy. Rather than the usual approach to the subject of antibiotic complications whereby the antimicrobial agents are itemized with their numerous individual toxic effects, specific major organ systems were selected and the significant untoward reactions related to them (*Table 1*) are discussed.

Neurotoxicity

Vestibular ototoxicity. Vestibular dysfunction of the eighth cranial nerve may be produced by *streptomycin* and *gentamicin*. This toxic effect manifests itself on the sensory cells of the vestibular organ. Vertigo and its accompanying signs and symptoms occur in the acute stage that is followed by a chronic phase with ataxia as the most prominent feature. Fortunately, adaptation to the dysequilibrium is accomplished by the use of visual cues and deep proprioceptive sensation for determining movement and position. Recovery may be delayed for many months and in some patients there may be permanent residual damage. To avoid this complication, both total daily dosage and duration of therapy must be carefully considered. With gentamicin therapy this complication appears to be related to excessive concentrations of the drug in plasma, rather than to the duration of therapy or to the total quantity of drug administered.[1, 2] Existing renal impairment predisposes to elevated concentrations in plasma of both streptomycin and gentamicin, and great care must be observed in using these antibiotics in uremic patients.

Auditory ototoxicity. Deafness is a potentially catastrophic complication

Table 1.—Adverse effects of antimicrobial agents

Agents (alphabetic order)	Neurotoxicity				Hematotoxicity					
	Eighth cranial nerve	Optic neuritis	Neuropathy	Neuromuscular blockade	Aplastic anemia	Agranulocytosis	Thrombocytopenia	Hemolytic anemia	Hepatotoxicity	Nephrotoxicity
Amphotericin B	—	—	x	x	—	—	—	—	x	x
Chloramphenicol	—	x	x	—	x	x	x	—	—	—
Erythromycin estolate	—	—	—	—	—	—	—	—	x	—
Gentamicin	x	—	—	—	—	—	—	—	—	x
Kanamycin	x	—	x	x	—	—	—	—	—	x
Neomycin	x	—	x	x	—	—	—	—	—	x
Nitrofurantoin	—	—	x	—	—	—	—	x	—	—
Novobiocin	—	—	—	—	—	—	—	—	x	—
Penicillins	—	—	—	—	—	—	—	x	—	x
Polymyxins	—	—	x	x	—	—	—	—	—	x
Streptomycin	x	x	x	x	—	—	—	—	—	—
Sulfonamides	—	—	—	—	—	x	x	x	x	x
Tetracyclines	—	—	—	—	—	—	—	—	x	—
Triacetyloleandomycin	—	—	—	—	—	—	—	—	x	—
Vancomycin	x	—	—	—	—	—	—	—	—	x

from a significant number of antibiotics. *Dihydrostreptomycin* was one of the early agents noted to have this effect. Since deafness is a more calamitous complication than vestibular dysfunction, dihydrostreptomycin has largely been abandoned for streptomycin when there is clinical indication for their use.[3]

Neomycin when parenterally administered causes irreversible auditory dysfunction. Intramuscular use of neomycin has declined since the advent of more appropriate agents. It must also be appreciated that ototoxicity is a possibility with the use of neomycin as an aerosal, irrigating agent, and topical application to absorptive surfaces such as cutaneous burns. It should not be administered orally in doses of more than 4 g, especially in patients with ulcerative bowel disease or renal disease, since concentrations in the serum may reach sufficiently high levels to cause toxic effects.

Kanamycin also has the capacity to cause irreversible deafness which may be delayed in onset. Even with normal renal function the recommended dosage of 12 to 15 mg per kilogram of body weight per 24 hours may prove to be ototoxic when the duration of therapy and total dosage of the drug are excessive. One should be reluctant to use this agent for more than two weeks or in doses of more than 500 mg at 12-hour intervals. Patients with impaired renal function accumulate higher concentrations in the serum and consequently have a much higher risk of ototoxicity. Great care must be taken in the administration of this agent to patients with renal dysfunction, and the recommended guidelines for therapy should be carefully observed.[4]

Vancomycin is a highly effective agent for treating severe staphylococcal infections, but currently is infrequently used since the advent of penicillinase-resistant penicillins and cephalothin. Vancomycin also can cause total and permanent deafness, and renal function must be carefully monitored during therapy with this agent.

It is recommended that these ototoxic drugs should not be used concurrently or sequentially if avoidable, because of possible potentiating effects.

Optic neuritis. Impairment of vision secondary to optic neuritis has been reported after the use of *streptomycin* and also *chloramphenicol.* Walker[5] reviewed the literature concerning this complication associated with these two antibiotics. The visual complaints ranged from blurred vision to complete loss of sight. Fortunately the significant complication was largely reversible in most patients but there was some residual impairment in a small number of patients.

Neuropathy. *Chloramphenicol,* after prolonged administration of large doses, may cause peripheral neurotoxicity manifested by paresthesias and hyperesthesias.[6] Polyneuropathy is a rare manifestation of *nitrofurantoin* toxicity, which appears to be related to high dosage and prolonged therapy, particularly in patients with impaired renal function.[7, 8]

Peripheral neuritis has also been attributed to the use of *streptomycin, neomycin, kanamycin, polymyxin B, colistin,* and *amphotericin B.* Pares-

thesias usually affecting the cicumoral and acral regions may be an adverse effect of these drugs. This reaction is a reversible and not serious complication but is of considerable annoyance to the patient.

Neuromuscular blockade. Neuromuscular blockade is a significant and potentially life-threatening complication when it progresses to respiratory paralysis. This was initially observed after the intraperitoneal administration of *neomycin* during surgery, and was the result of absorbed neomycin and not of the intraperitoneal route of administration.[9] *Streptomycin* as well as neomycin potentiates the effects of other neuromuscular blockading agents such as ether and d-tubocurare and these effects are antagonized by neostigmine.

The neuromuscular blockade produced by *kanamycin* differs in that it is similar to that produced by succinylcholine and therefore neostigmine may worsen the blockade. *Polymyxin B* and *colistin* also produce a noncompetitive blockade which is neostigmine-resistant. Polymyxin B[10] and colistin[11] cause respiratory arrest after as little as a single dose or after prolonged treatment. It is often preceded by dyspnea and restlessness and other central nervous system symptoms. Intravenous injections of calcium have been reported to be effective in the treatment of respiratory paralysis associated with these two antibiotics, but the primary treatment is controlled ventilation until the effect subsides.

All the antibiotics capable of causing neuromuscular blockade should be avoided in anesthetized patients, and care used in the concomitant administration of sedatives and narcotics; they are contraindicated for patients with myasthenia gravis.

Miscellaneous neurotoxic reactions. *Tetracycline* may be a cause of increased intracranial pressure as manifested by bulging of the fontanel in infants.[12] This benign but alarming reaction disappears promptly on cessation of therapy with the drug. Knowledge of this possible complication with tetracycline therapy is important since the differential diagnosis of this condition often involves life-threatening diseases.

Cerebral toxicity may be associated with massive intravenous injections of *penicillin*.[13] It is well known that penicillin is epileptogenic when injected directly into the central nervous system, and this has restricted its subarachnoid and intraventricular administration. Intravenous doses of penicillin in excess of 25 million units daily, particularly in the elderly and in those with renal impairment, may produce a syndrome of decreased consciousness, myoclonic jerking, and grand mal seizures.[14, 15] When penicillin therapy is discontinued or the dosage reduced, improvement usually occurs during the subsequent 24 hours.

Amphotericin B has been reported to cause a neurotoxic syndrome that consists of tremor, incontinence, mental clouding, flaccid paralysis of arms and legs, and weakness of respiratory muscles.[16]

Hematotoxicity

Among the blood dyscrasias that may be associated with the use of antibiotics are aplastic anemia, agranulocytosis and leukopenia, thrombocytopenia, and hemolytic anemia. The most serious of these are aplastic anemia and agranulocytosis because of their frequency of occurrence and their high fatality rate.

Aplastic anemia. *Chloramphenicol* is now the leading single cause of drug-induced aplastic anemia in man. A distinction, however, should be made between the reversible hematopoietic depression that frequently accompanies chloramphenicol therapy and the aplastic anemia that results from the administration of this drug.[17] Reversible toxicity from chloramphenicol is a pharmacologic action of the drug which can be induced in most if not all patients receiving large doses of the antibiotic, and is characterized by anemia with or without leukopenia or thrombocytopenia, all of which are usually reversible when administration of the drug is discontinued.[18] There may be temporary morphologic changes in the erythrocyte maturation series including intranuclear and cytoplasmic vacuolization. The biochemical mechanism for this effect is not well understood. Monitoring of certain blood tests such as the leukocyte and differential count and the serum concentration of iron may alert the physician to the development of this complication. Depression of the bone marrow may be more prevalent in patients receiving chloramphenicol who have hepatic and renal insufficiency.[19]

Even less understood is the mechanism by which chloramphenicol causes irreversible bone marrow aplasia. This type of toxicity may have a late onset, is not necessarily related to dosage, and is characterized by an aplastic bone marrow, pancytopenia, and often a fatal outcome. Oxymethalone therapy may help to promote a reversal of the aplasia due to chloramphenicol. There is no indication that this disastrous complication of chloramphenicol therapy is related clinically or pathogenetically to the reversible erythropoietic lesion from the drug. Bone marrow aplasia is rare, with no definite relationship to drug dosage, and an individual susceptibility is the more likely basic mechanism involved. Precautionary blood monitoring determinations are of little predictable value. The most important step, therefore, in preventing bone marrow aplasia from chloramphenicol is not the monitoring of its administration but the careful selection of the use of this agent for serious infections for which no other drug is likely to be effective, and repeated courses should be avoided if possible. Chloramphenicol is a highly effective antibiotic, but fortunately there are now a number of available substitutes for this agent. In the rare life-threatening situation for which there is no satisfactory substitute, chloramphenicol must certainly be employed.

Agranulocytosis and leukopenia. The *sulfonamides* cause agranulocytosis by an immune phenomenon, with a direct myelotoxic effect evident in the arrest of bone marrow maturation at the myeloblast stage. The granulocytopenia is not related to dosage or blood content of the drug, and the reaction

may appear suddenly or after a period of progressive neutropenia. Fortunately, most patients recover spontaneously with supportive care, but the return of granulocytes to normal levels may be considerably delayed after withdrawal of drug administration.

Chloramphenicol may at times cause this selective bone marrow depressive reaction without effect on the other marrow elements.

Bone marrow depression with significant neutropenia has been reported secondary to *methicillin* administration.[20, 21] This toxic effect was reversible in all patients after cessation of therapy.

Thrombocytopenia. The *sulfonamides* and *chloramphenicol* have been noted to cause thrombocytopenia, which is infrequent and usually a minor adverse hematologic drug reaction. The exact mechanism is not always understood, but in many instances is caused by an immune reaction. The presenting signs usually are petechiae, easy bruising or bleeding. Bleeding from drug-related thrombocytopenia seldom is severe, and recovery is usually rapid after use of the drug has been discontinued.

Hemolytic anemia. *Sulfonamides* and *nitrofurans* are the notable antibiotics causing hemolytic anemia. These agents are among a long list of hemolytic oxidant drugs that activate this process in patients whose erythrocytes are deficient in the enzyme glucose-6-phosphate dehydrogenase. Patients with this genetic deficiency in the erythrocytes are unable to generate triphosphopyridine nucleotide in its reduced form, and as a result are unable to produce reduced glutathione, and these metabolites are necessary to reverse the oxidation of hemoglobin. The erythrocytes are unable to tolerate the concentration of the drugs produced by ordinary therapeutic doses. Hemoglobin is oxidized and, by mechanisms not entirely understood, the erythrocyte is hemolyzed.[22] Hemolysis by these drugs is not entirely limited to patients with this enzyme deficiency and can occasionally occur in other patients when the concentration of the drug is sufficiently high.[23] High concentrations of the drug in the blood may be related to excessive dosage or to delayed excretion due to renal insufficiency. In addition to causing hemolysis, nitrofurantoin may occasionally cause an associated megaloblastic erythropoiesis.[24]

Penicillin-induced immunohemolytic anemia with the administration of large doses of *penicillin* has been reported.[25, 26] This anemia is accompanied by reticulocytosis, hyperbilirubinemia, a decrease in the erythrocyte life span, and a strongly positive direct Coombs' test. The serum of these patients is found to have a circulating antipenicillin antibody that is capable of mediating a hemolytic anemia.

Cephalothin has been noted to cause a positive direct Coomb's test in many patients and particularly in those with poor renal function.[27] The significance of this reaction as a cause of hemolytic anemia is not clear at this time.

Miscellaneous hematotoxic reactions. In most patients receiving *ampho-*

tericin B therapy a severe anemia develops. The anemia appears to be related to therapy and not to the underlying fungal infection, since it develops despite clinical improvement and remits when use of the drug is stopped. Anemia also precedes the azotemia that may occur during treatment. It has been postulated that this anemia is a consequence of defective reutilization of iron.[28]

The *tetracyclines* have been shown to be able to interfere with blood coagulation, particularly in patients who have other intrinsic tendencies to bleed. These agents apparently alter the physicochemical characteristics of the blood lipoproteins and thereby affect lipid factors essential for the normal blood-clotting process.[29] Antimicrobial agents that have been associated with a slight increase in the prothrombin time include the penicillins, novobiocin, and sulfonamides.

Hepatotoxicity

Numerous agents including several antibiotics used in the treatment of infectious diseases may produce hepatic dysfunction with or without jaundice. It has been observed that the *tetracyclines* may injure the liver, and that in patients receiving large doses orally or intravenously clinical evidence of hepatic dysfunction developed, and that microscopic study of the liver revealed fine vacuoles, cytoplasmic changes, and an increase in fat.[30] Most reactions of this type develop in patients receiving 2 g or more of the drug per day parenterally; however, this effect may also occur when large quantities are administered orally or with a combination of the two modes of administration.

Six obstetric patients treated with large intravenous injections of tetracycline all died after the development of nausea, vomiting, fever, jaundice, acidosis, azotemia, and terminal hypotension.[31] Necropsy revealed fine-droplet fatty metamorphosis of all portions of the liver lobule, but no evidence of inflammation or biliary obstruction.

Azotemia may considerably increase the content in serum of the tetracyclines, and therefore great care must be taken in their administration in patients with renal insufficiency, so as to protect against the possibility of hepatotoxicity. Patients with preexisting hepatic disease who received tetracycline were found on biopsy to have an increase in fat in the liver.[32] The chances of hepatotoxicity from tetracycline administration appear to be related to daily dosage, duration of therapy, pregnancy, underlying hepatic disease, conjoint use of other hepatotoxic drugs, and impaired renal function.

Erythromycin estolate, which is the lauryl sulfate salt of erythromycin proprionate, may produce hepatic dysfunction which generally has occurred after one or two weeks of continuous therapy or after several courses of the drug.[33] The absence of reports of jaundice with other forms of erythromycin suggests that the hepatotoxicity is specific for this ester. Jaundice, abnormal

results of liver function tests, and eosinophilia may occur which usually subside rapidly when use of the drug is discontinued. The effect seems to be one of intrahepatic cholestasis resulting from a form of sensitization. That hypersensitivity is responsible for this syndrome is suggested by its rarity, that it usually does not appear with first exposure to the drug unless it is continued for 10 or more days, and because it is not related to dosage.

Triacetyloleandomycin has been found to impair hepatic function in a rather large number of patients receiving this drug for two weeks or longer, although the development of jaundice is infrequent.[34] The dosage of medication in these patients was not above the amount usually recommended. The abnormalities were demonstrated by impaired sulfobromophthalein excretion, abnormal cephalin flocculation test, and elevated serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase concentrations. In patients without jaundice, these liver function tests rapidly return to normal within a week after withdrawal of use of the drug, although the cephalin flocculation test may remain abnormal in some patients for a few additional weeks. Laboratory tests and biopsy studies indicate that the type of hepatic abnormality and the jaundice have hepatocellular as well as cholestatic features.

Novobiocin in a small percentage of patients may cause a yellow discoloration of the skin, sclera, and serum, with this effect being ascribed to the presence of a yellow pigment produced by the metabolism of novobiocin.[35] In infants, though, there appears to be some possibility of neonatal hyperbilirubinemia during novobiocin administration, suggestive of interference of the drug with bilirubin metabolism.[36]

Sulfonamides and *amphotericin B* may occasionally provoke hepatic injury and failure, and the available data suggest that the hepatic lesion is characterized by hepatocellular damage with toxic degeneration.[37, 38]

Elevation of the serum glutamic pyruvic transaminase concentration has been reported with the use of a considerable number of antibiotics, including *ampicillin, oxacillin, cloxacillin, lincomycin, colistin, cephalothin,* and *nalidixic acid,* but the exact significance is not clear.

Nephrotoxicity

A large number of antibiotics currently in clinical use have a potentially nephrotoxic effect. These antimicrobial agents are of great value in treating patients with serious sepsis. It is fortunate that the nephrotoxicity of these drugs appears to be largely reversible, providing their administration is discontinued soon enough. It is essential that when these agents are administered that renal function be regularly monitored. Patients having preexisting renal disease appear to be particularly sensitive to many of these agents, but even uremic patients should not be denied the lifesaving effects of these drugs when they are indicated, and they can be given under these circumstances providing the principles of modified dosage schedule are closely

followed. The concomitant use of renal toxic agents should be avoided or should be undertaken with great caution.

Kanamycin and *neomycin* are closely related both chemically and in antimicrobial action. Since neomycin has a higher degree of toxicity in general, kanamycin has virtually replaced neomycin for parenteral use. The renal lesion produced by these antibiotics primarily involves the proximal convoluted tubules, and clinically is evidenced by a decrease in glomerular filtration rate, in paraaminohippuric acid clearance, and in maximal tubular concentration.

Polymyxin B and *colistin,* chemically closely related antibiotics, may be considered together. Both are potentially nephrotoxic, and the main differences are in structure and dosage. These drugs also produce proximal tubular necrosis, although they are fairly well tolerated in patients without preexisting renal impairment. In azotemic patients receiving these drugs an alarming increase in serum creatinine and blood urea nitrogen may develop, with only a slow return to normal values after therapy has been discontinued or reduced.[39, 40]

Gentamicin was observed to cause renal tubular necrosis in dogs during acute toxicity studies.[41] Adverse renal reactions have also been observed in a small percentage of patients receiving this antibiotic.[42] Monitoring of renal function should be carried out when administering this antibiotic, and considerable caution exercised in its use when there is preexisting renal impairment.

Cephaloridine is capable of producing adverse effects on the kidneys; however, such effects are infrequent when the recommended dosages of 4 g or less daily are administered to patients without preexisting renal impairment.[43] Renal function should be followed during therapy and use of the drug discontinued should impairment develop. Cephaloridine should be used cautiously in patients with azotemia.

Bacitracin has notable nephrotoxic properties destructive both of the proximal and of the distal convoluted tubules. Formerly it was frequently used parenterally in the treatment of penicillin-resistant staphylococcal infections, however, with the current availability of more effective and less toxic agents the therapeutic role of bacitracin for parenteral therapy has largely been supplanted.

Amphotericin B is the only available drug effective in preventing death from a number of serious systemic fungal infections and therefore continues to be widely used despite numerous toxic properties. The accepted nephrotoxicity of amphotericin B is underlined by the fact that the daily dosage of the drug is usually governed by the degree of azotemia present rather than by the therapeutic response of the patient. The clinician's decision to use this drug must be made with the full understanding that impaired renal function and damaged renal structure occur in most patients. Amphotericin B produces renal vasoconstriction and reduction in renal blood flow, which

may be an important factor in the glomerular and tubular damage and calcium deposition noted in patients after they have received this agent.[44] Renal function may improve after cessation of therapy, but there often are various degrees of permanent residual damage.

The ingestion of deteriorated outdated *tetracycline* has been observed to cause a syndrome of nausea, vomiting, proteinuria, acidosis, glycosuria, and amino-aciduria in patients.[45, 46] Renal biopsy in such cases[47] reveals severe tubular changes. The glomeruli are also affected, and this explains the massive proteinuria. This pathologic process resembling the Fanconi syndrome appears to be entirely reversible in from four to six weeks after withdrawal of use of the antibiotic. The possibility of this potentially serious renal toxic effect dictates that the physician not prescribe tetracycline in an amount to exceed that needed for a single illness, and that the patient be instructed to discard leftover medication.

Nephropathy associated with *penicillin* and its homologues, particularly *methicillin*, has been reported in recent years.[48, 49] This adverse change is believed to be on the basis of a hypersensitivity reaction. The syndrome is often ushered in by spiking fever, malaise, anorexia, abdominal aching, and may be associated with eosinophilia and skin rash. The renal manifestations most frequently include hematuria, pyuria, albuminuria, and oliguria. Fortunately the patients recover fairly rapidly when this complication is recognized and therapy discontinued.

Certain *sulfonamides* may cause severe renal damage by deposition of crystalline aggregates leading to development of irritation and obstruction. Two other mechanisms, toxic nephrosis and hypersensitivity reaction, rarely are factors in the production of tubular necrosis or necrotizing angiitis of the kidneys.

Summary and conclusion

The adverse antimicrobial reactions on major organ systems have been reviewed to alert the physician again to the significant and often life-threatening effects of these widely used and effective therapeutic agents. Potentially harmful effects in the use of antibiotics must never discourage a physician from their administration for any condition in which they are clearly indicated, since the use of any potent therapeutic agent is accompanied by a calculated risk. To be concerned only with their potential danger is no less unrealistic and unwise than to accept them as invariably applicable, completely beneficial, and entirely harmless.

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