ADVERSE EFFECTS OF ANTIMICROBIAL DRUGS

Noppamars Wongwitdecha

Department of Pharmacology, Faculty of Science,
Mahidol University, Bangkok 10400.

SUMMARY

All antimicrobial drugs may produce adverse and allergic reaction. These reactions are usually minor, but occasionally, they can be serious and even life-threatening. However, they can often be prevented or minimized by an understanding of how they arise. Antimicrobial drugs may adversely affect the host directly or indirectly. Direct adverse effects are related to the dose and duration of drug therapy, and can often be correlated to their degree of selective toxicity. Organ specific toxicity of drugs recognized as one of serious drug problems. This type of toxicity is known to affect the ear, eye, liver, heart, blood, bone marrow, and so on. Antimicrobial drugs are one of the most common drug groups that cause hypersensitivity reactions. The penicillins are most often responsible for these reactions with sulfonamides rank the second. Penicillin allergy is important which can be anaphylaxis in highly sensitive patients. It is necessary for the physicians to be aware of the adverse reactions which may occur following antimicrobial chemotherapy, and must known how to manage them.

Adverse drug reactions can be conveniently categorised as dose-related, genetically-determined (idiosyncratic) and allergic. In addition, drugs can exert carcinogenic and dysmorphogenic effects, while tolerance and dependence can also be regarded as adverse effects(1).

Adverse reactions to antimicrobial drugs are best considered in relation to the various compounds prescribed. All antimicrobial drugs may produce adverse and allergic reactions. These reactions can often be prevented or minimized by an understanding of how they arise:
this may be related to the particular agent, to increase patient susceptibility or to interactions with other drugs (2,3). The potentially life-threatening reactions which should be familiar to clinicians are shown in Table 1.

Table 1. Potentially life-threatening adverse reactions with antimicrobial drugs.

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Antimicrobial drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic reactions</td>
<td>Penicillins, Cephalosporins</td>
</tr>
<tr>
<td>Blood dyscrasias</td>
<td>Chloramphenicol, Co-trimoxazole</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Clindamycin, Lincomycin, Cephalosporins, Ampicillin, Amoxycillin</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Cephaloridine (high doses)</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines (except doxycycline)</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides (dose-related)</td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Penicillins (high doses)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Tetracycline, Oxacillin, Isoniazid</td>
</tr>
</tbody>
</table>

Antimicrobial agents may adversely affect the host either directly or indirectly (4,6). Direct adverse effects are related to the dose and duration of the drug therapy. The direct toxic effects of antimicrobial agents can often be correlated to their degree of selective toxicity. Indirect toxicity may result from

a) induction of an allergic or hypersensitivity reaction in which components of the immune system (antibody, activated cells complement) mediate damage to host tissues,

b) alteration of the ecological balance of the normal microbial flora which facilitates superinfection or impairs epithelial physiology or nutrition (5,6).
DIRECT ADVERSE EFFECTS

Organ specific toxicity of drugs is recognized to be a serious problem. This type of toxicity is known to affect the eye, liver, kidney, heart, blood, and bone marrow, as well as the ear.

1. Ototoxicity

There are many different classes of drugs reported to produce ototoxicity, and the effect ranges from production of permanent deafness to temporary tinnitus (7,8). The drugs that are most well-known in this regard are the aminoglycosides, quinine and related antimalarials (Table 2).

Table 2. Antimicrobial drugs reported to produce tinnitus.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Kanamycin</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Viomycin</td>
</tr>
</tbody>
</table>

All aminoglycosides are ototoxic: some principally affect auditory function while others damage the vestibular apparatus (Table 3) (13). Ototoxicity occurs in approximately 2% of treated patients and results from rather selective destruction of the sensory hair cells of the organ of Corti (7). The most sensitive cells are those in the basal turn of the cochlea because high frequency sounds are processed in this region. The initial hearing loss involves high frequency sound. The hair cells are incapable of regeneration so that the ototoxicity is permanent. In general the magnitude of the ototoxicity is related to
Table 3. Toxic effects of some aminoglycosides upon the vestibular and auditory components of the eighth cranial nerve.

<table>
<thead>
<tr>
<th>Aminoglycoside</th>
<th>Vestibular toxicity</th>
<th>Auditory toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td>++</td>
<td>+++++</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Neomycin</td>
<td>+</td>
<td>+++++</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Amikacin</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

+ Mildly toxic
+++++ Highly toxic

both the daily dosage and the duration of therapy. Impaired renal function is the most important determinant of ototoxicity (8,10,12,14,15).

Aminoglycoside ototoxicity is common in the very young, the elderly, those with pre-existing renal insufficiency or hearing loss, and in those who have previously received multiple courses of aminoglycosides. It may also be potentiated by simultaneous therapy with diuretics furosemide and ethacrynic acid, these drugs should be avoided whenever possible in patients receiving aminoglycosides (10,12,16).

Ototoxicity is also occasionally associated with erythromycin and ampicillin in very high dosage. Minocycline has been reported to produce temporary unsteadiness. Quinidine and other antimalarial drugs such as chloroquine and hydroxychloroquine can produce hearing loss and tinnitus. Other drugs such as nitrogen mustard, 6-aminonicotinamide, viomycin and vancomycin have been reported to produce permanent ototoxicity(7).
2. Nephrotoxicity

Nephrotoxicity is a serious clinical problem and its incidence is probably increasing. Many antimicrobial drugs may impair kidney function or may damage renal tissues, or both (Table 4). Examples include the sulfonamides, aminoglycosides, amphotericin B, polymyxins, tetracyclines, cephalosporins, and penicillins. Nephrotoxicity of cephaloridine, the polymyxins, and the aminoglycosides has received the greatest attention recently.

Table 4 Antimicrobial drugs reported to impair kidney function.

<table>
<thead>
<tr>
<th>Aminoglycosides</th>
<th>Polymyxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Sulphonamides</td>
</tr>
<tr>
<td>Cephaloridine</td>
<td>Tetracyclines (outdated)</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Penicillins (high doses)</td>
<td></td>
</tr>
</tbody>
</table>

Sulphonamides were the first antimicrobial agents incriminated as the cause of nephrotoxicity. Precipitation of crystals of sulphonamides with low water solubility produced haematuria and sometimes renal failure (17).

Cephaloridine and cephalothin are both nephrotoxic; cephaloridine is about six times more toxic than cephalothin. Cephaloridine produces renal tubular cell damage with subsequent necrosis; the nephrotoxicity is dose-related and is likely to occur when more than 6 g/day of the antibiotic is given to the patients with normal renal function. However, in patients with renal failure smaller doses may be nephrotoxic (14,15,17). Administration of probenecid to animals appears to protect against the nephrotoxicity of cephaloridine (18). Potent diuretics such as furosemide and ethacrynic acid, and the amino-
glycosides have potentiated the nephrotoxicity of these drugs. Other cephalosporins such as cefuroxime, cephamandole and cefoxitin seem to be free of nephrotoxic effects in man (4,17).

The aminoglycosides, including streptomycin, kanamycin, neomycin, gentamicin, tobramycin, and amikacin, are potentially nephrotoxic, and this may occur in up to 20% of patients treated (2). The nephrotoxicity of the aminoglycosides is generally dose-related and reversible, and rarely fatal (3,4). The proximal tubular cells appear to be the primary site of the damage. The drug enters the cells by active reabsorption and is concentrated in the lysosomes 10 to 20 times more than in the serum. The drugs affect several functions, including glomerular filtration, proximal tubular reabsorption and concentrating ability, as well as causing tubular proteinuria, enzymuria, and electrolyte disturbances. The concentration of the aminoglycoside in renal tissue appears to correlate with the severity of kidney damage (12).

The nephrotoxicity of the aminoglycosides is most likely to become clinically important in the presence of hypovolaemia, increasing age, underlying renal functional impairment, and exposure to other nephrotoxic substances, e.g., other aminoglycosides, cephalothin, and frusemide (10,12,17).

The polymyxins B and E (colistin) caused a dose-related impairment of renal function, proximal tubular damage, and acute tubular necrosis (4,19). Tetracyclines, apart from doxycycline and minocycline, may exacerbate uraemia and should be avoided in patients with renal impairment. There is the rare reversible Fanconi-like proximal tubule syndrome attributed to a degradation product of tetracycline, anhydro-4-epitetracycline. Acute renal failure in association with liver failure has been reported in pregnant or postpartum women given large doses of tetracycline intravenously (17). Nephrotoxic effects are related to the dose and severity of pre-existing renal dysfunction, and are probably due to the antianabolic effects of tetracyclines. Doxycycline is
probably the only tetracycline which may be administered to elderly or dehydrated patients since it is reported not to accumulate in patients with renal insufficiency (2).

Very occasionally interstitial nephritis with proteinuria, haematuria, pyrexia and eosinophilia occurs during treatment with high doses of the penicillins and renal tubular damage may complicate therapy with rifampicin (2).

3. Neuromuscular blockade

Four major groups of antibiotics are capable of inducing neuromuscular blockade in humans. These include (a) the aminoglycosides-streptomycin, neomycin, kanamycin, gentamicin and tobramycin; (b) the polymyxins-colistin and polymyxin B, (c) the tetracyclines-oxytetracycline.

Table 5 General features of antimicrobial-induced neuromuscular blockade.

<table>
<thead>
<tr>
<th>Aminoglycosides</th>
<th>Polymyxins</th>
<th>Tetracyclines</th>
<th>Lincomamides</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presynaptic effect</td>
<td>+</td>
<td>possible</td>
<td>-</td>
</tr>
<tr>
<td>2. Postsynaptic effect</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>3. Effect on neuromuscular blocking activity of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competitive drugs</td>
<td>potentiate</td>
<td>potentiate</td>
<td>potentiate</td>
</tr>
<tr>
<td>Depolarizing drugs</td>
<td>potentiate</td>
<td>potentiate</td>
<td>-</td>
</tr>
<tr>
<td>4. Reversibility of antimicrobial-induced blockade by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>complete</td>
<td>inconsistent</td>
<td>inconsistent</td>
</tr>
<tr>
<td>Anticholinesterase</td>
<td>inconsistent</td>
<td>inconsistent</td>
<td>inconsistent</td>
</tr>
<tr>
<td>(may augment)</td>
<td>(may augment)</td>
<td>(may augment)</td>
<td></td>
</tr>
</tbody>
</table>
Adverse effects of Antimicrobial Drugs

Adverse effects of Antimicrobial Drugs

Table 5 summarizes the general features of the neuromuscular blockade induced by the four groups of antibiotics. These episodes of antibiotic-induced blockade almost always have been associated with concomitant use of other neuromuscular depressants or local instillation of the antibiotics or both. They have also tended to occur more frequently in patients with preexisting neuromuscular disease or serum electrolyte imbalance. All four drug groups appear to potentiate the effects of competitive neuromuscular blocking agents (4).

The aminoglycosides can produce paralysis from neuromuscular block and may lead to respiratory paralysis. In "competitive hypothesis", Brazil and Prado - Franceschi states that aminoglycosides, like magnesium, compete with calcium ions and thus inhibit the prejunctional release of acetylcholine (ACh). They also decrease the sensitivity of the motor end plate to the depolarizing action of ACh, and have a depressant effect on denervated muscle which, unlike the presynaptic effect, is enhanced by calcium (20,21).

The relative pre-and postjunctional effects of the aminoglycosides vary with the drug employed, the concentrations of the drugs and ionized calcium, and the type of the muscle preparation studied. A low concentration of ionized calcium has been shown to potentiate the presynaptic block without affecting the postsynaptic block. In contrast, high concentrations of ionized calcium decrease the presynaptic component, but enhance or not affect the postsynaptic component (21-24).

Both the pre-and postsynaptic components of aminoglycoside-induces blockade appear to depend upon a drug-membrane interaction which affects the passage of positive ions through the membrane. The aminoglycosides, acting at a superficial site, decrease total calcium uptake and increase calcium efflux. These effects appear to result from decreased binding of free calcium coupled with displacement of bound calcium (21,25-28).
Polymyxins are the most potent neuromuscular blockers among the antibiotics. The primary effect of the polymyxins is to decrease the motor end plate sensitivity to ACh. They also produce a local anesthetic effect equivalent to lidocaine on desheathed nerves, and depress the response of muscle to direct stimulation (21,29).

Tetracyclines decrease the response of the motor end plate to ACh without affecting either presynaptic release of ACh or muscle response to direct stimulation. Chelation of calcium had been proposed as a possible mechanism for tetracycline-induced blockade (21,29-32).

The predominant effect of lincosamides on neuromuscular functions appears to vary with the concentration employed. The two lincosamide, lincomycin and clindamycin, vary in their abilities to produce certain effects. Lincomycin at low concentrations had a nerve terminal stimulatory effect as reflected by an increase in miniature end plate potential frequency (33). At moderate concentrations, lincomycin had depressant pre-and postsynaptic effects as shown by decreased ACh release, depressed miniature end plate potential amplitude, and decreased end plate sensitivity to directly applied ACh (33). At high concentration, lincomycin depressed muscle response to direct stimulation (34). Similar concentration-dependent effects were seen with clindamycin. It also produced a local anesthetic effect on desheathed nerve that was not observed with lincomycin (34).

4. Neurological toxicity

A. CNS toxicity

Neurotoxicity has been observed following the use of almost any penicillins; Most of the toxicity has been manifested as seizure disorder. Toxicity almost invariably has been associated with the very high serum levels following "massive" doses of the drug or continued administration of usual doses to patients with renal failure (6,35).

Isoniazid may produce a variety of dose-related effects on the peripheral and central nervous systems (36,37). Occasionally,
patients develop symptoms of excitability, which may range from mild euphoria, irritability to generalized seizure activity in patients with overdosage of isoniazid (36-38).

Cycloserine may also produce toxicity on the CNS similar to that of isoniazid (37,39); these include dizziness, headache, slurred speech, tremor, insomnia, and also potentially serious episodes of depression, anxiety and psychosis. These symptoms usually disappear rapidly when the drug is stopped. It should not be given to patients with a history of epilepsy or psychiatric disease. Cycloserine-induced seizures may also be prevented or ameliorated by administration of large doses of pyridoxine (37,39).

B. Encephalopathy

When penicillin, polymyxin, or amphotericin B is injected intrathecally toxic side effects are observed (2). Penicillin may cause arachnoiditis and encephalopathy. Amphotericin B may induce vision, impairment, paresthesias, and nerve palsy (foot drop). Polymyxin B can give rise to meningeal irritation (2).

C. Optic neuritis

The major toxicity of ethambutol is optic neuritis, first manifested by loss of ability to perceive green color followed by diminution of visual acuity. All patients should have regular (monthly) tests of visual acuity and green color vision (6,37).

Chloramphenicol may induce optic neuritis, especially in children with mucoviscidosis who have been treated for prolonged periods. Retinal ganglion cells are lost symmetrically and optic nerve fibers may degenerate. Administration of large doses of B-complex vitamins may reverse the neuritis despite continuation of chloramphenicol (6).

D. Peripheral neuritis

Peripheral neuropathies are generally associated with high
dose and/or long term therapy of some drugs to patients with renal impairment. The effects are usually reversible. Isoniazid occasionally causes a peripheral neuropathy or pellagra-like syndrome. The isoniazid-induced peripheral neuritis may be prevented or reversed by administration of pyridoxine (37).

5. **Hepatotoxicity**

Many antimicrobial drugs can cause hepatitis. In general, hepatotoxicity is most frequently encountered among those drugs that are metabolized or excreted by the liver. Examples include isoniazid, rifampin, erythromycin estolate, tetracycline, novobiocin, nitrofurantoin and sulphonamides.

Jaundice has been reported during treatment with rifampicin, sulphonamides and nitrofurantoin; if it develops the drug should be stopped immediately (2).

Isoniazid has been shown to cause liver function abnormalities (10% to 20% of patients) and hepatitis (40,41). The risk of hepatitis is age related; the risk is eight times greater for patients over 65 years of age than for those under 25 (0.3% vs 2.3%). (40,42). Clinically, isoniazid-induced hepatitis resembles viral hepatitis; the onset usually begins during the first 3 months isoniazid administration. The mortality of overt isoniazid-associated hepatitis is relatively high (12.3%), (38).

Erythromycin estolate and nitrofurantoin can produce hepatic cholestasis with pyrexia and eosinophilia (43,45). With erythromycin this syndrome seems to occur only when the course of treatment exceeds 10-14 days (2).

Tetracyclines may be injurious to the liver when administered in large doses orally or parenterally, especially when given intravenously. Care should be taken with the uses of tetracyclines in patients with liver disease as acute liver failure has reported with this group
of antibiotics principally in association with intravenous administration during pregnancy or renal failure (3).

6. Gastrointestinal toxicity

Almost all antimicrobial agents have been implicated as cause of annoying but seldom life-threatening reactions such as nausea, vomiting, diarrhea and intestinal cramping. These reactions are usually dose-related and occur more frequently when a drug is administered orally (46).

A. Malabsorption

Malabsorption has been reported following oral administration of a variety of broad-spectrum antimicrobial agents, usually in high doses or for prolonged periods, or both (46,47). When given by mouth, the aminoglycosides, especially neomycin and paromomycin, can interfere with intestinal function and produce malabsorption of fat, protein, carbohydrate, cholesterol, carotene, glucose, lactose, sodium, calcium, iron, and cyanocobalamin (47).

B. Pseudomembranous colitis

Pseudomembranous colitis is characterized by watery diarrhea, abdominal pain, and fever. Stools contain mucus and leukocytes. Colonoscopy shows colonic and small-bowel mucosal inflammation, usually without ulceration. Pseudomembranous colitis may be a severe and potentially life-threatening complication of antimicrobial therapy (48). Clindamycin, lincomycin, ampicillin, tetracyclines, and chloramphenicol have been implicated in this toxicity (4). Antibiotic-associated pseudomembranous colitis is now known to result from colonization of the gut by a toxin-producing anaerobe, Clostridium difficile, but the mechanism by which antibiotic therapy induces overgrowth and toxin production by this organism is uncertain (49-51).

Pseudomembranous colitis may occur up to several weeks after chemotherapy and its incidence after clindamycin treatment is about 3 to 30% of patients (52). Oral therapy, increased age, and severe
underlying disease may promote the development of clindamycin-associated colitis. Treatment consists of discontinuation of clindamycin therapy and administration of fluids intravenously. Clindamycin-associated colitis occur frequently enough-and is so serious that use of the drug should be restricted to patients with serious anaerobic infections outside the CNS and to patients with severe gram-positive infections who are allergic to penicillin and cephalosporin (52).

7. **Cutaneous toxicity**

A variety of cutaneous reactions have been associated with the use of antimicrobial agents. Most of these have been linked convincingly to host-mediated hypersensitivity to the drug administered. Three groups of reactions may be mediated by other mechanisms: phototoxicity, flushing, and many of the rashes resulting from the use of ampicillin.

Phototoxic reaction may occur following the use of nalidixic acid, the sulfonamides and the tetracyclines, especially demethylchlorotetracycline and doxycycline (53,56). The clinical spectrum of the reactions ranges from mild paresthesias and abnormal sunburn to severe bullous eruptions with or without onycholysis and pigmentation of the nails. The reaction is precipitated by light in the ultraviolet spectrum (6).

Occasional patients given the polymyxins (polymyxin B or colistin) develop annoying, but seldom severe, flushing and other subjective side effects suggestive of histamine release (57). Many of these effects appear to have been ameliorated by administration of antihistamines (57).

The rate of development of skin rashes is generally greater for patients given ampicillin than for patients given other penicillins (58). The disparity in rates is even more pronounced for patients with underlying infectious mononucleosis (59-61).
8. **Pulmonary toxicity**

The sulphonamides and nitrofurantoin can be associated with pulmonary eosinophilia. The condition is normally reversible but after repeated courses of nitrofurantoin, pulmonary fibrosis may develop, accompanied in some cases by hepatotoxicity and autoimmune antibody production (2).

9. **Haematological toxicity**

Chloramphenicol is probably better known for these adverse effects than any other antibiotics. It may cause serious and even fatal blood dyscrasias such as aplastic anaemia, thrombocytopenia and agranulocytosis (62). This drug should be used under strict medical supervision, preferably in the hospital as a last resort in the management of infections. Blood dyscrasias reported with co-trimoxazole include a anaemia (aplastic and haemolytic). Thrombocytopenia has been reported most frequently but resulted in very few deaths. Pancytopenia, agranulocytosis and granulocytopenia have occasionally been reported (3).

Aplastic anemia: drug-induces aplastic anemia has a mortality of over 50%. The reaction is not related to total dosage unlike the dose-related and usually reversible neutropenia or thrombocytopenia. It is also unrelated to duration or route of administration, and usually begins weeks or months after treatment (62). Aplastic anaemia following chloramphenicol appears to be more common in patients suffering from viral hepatitis (63). Other antimicrobial drugs which can cause this reaction include co-trimoxazole, the sulphonamides, benzylpenicillin, ampicillin and the tetracyclines (64).

Haemolytic anaemia associated with the administration of sulphonamides, nitrofurantoin, nalidixic acid, chloramphenicol and primaquine, are frequently the result of glucose-6-phosphate dehydrogenase deficiency. Probenecid and trimethoprim can produce a similar condition. Since trimethoprim may not be given during pregnancy, early lactation or in patients with megaloblastic bone marrow (2).
Chloramphenicol, sulfonamides, novobiocin and polymyxins can cause leukopenia. If leukopenia is the result of direct toxicity, recovery will follow either reduction in dose or cessation of administration. However, leukopenia may be a warning sign of agranulocytosis. Because agranulocytosis is apparently an adverse reaction of hypersensitivity and it may be irreversible, the inciting drug must be discontinued (2).

Co-trimoxazole is now the most common cause of neutropenia and penicillins have also implicated in this toxicity. Sulfonamides are commonly responsible for thrombocytopenia. The cephalosporins and also rifampicin may induce platelet antibodies which can lead to thrombocytopenia (2).

10. Miscellaneous: adverse effects on bone and teeth formation
Deposition of tetracycline-Ca$^{++}$ complexes in deciduous and permanent teeth causes discoloration, enamel hypoplasia and reduced mineralisation. Tetracyclines are also deposited in calcifying areas of the nails and bones. Thus administration of tetracyclines should be avoided during pregnancy and the first decade of life (3).

INDIRECT TOXICITY

1. Hypersensitivity or allergic reaction
Antimicrobial drug are one of the most common drug groups that cause hypersensitivity reactions (Table 6). Allergic reaction to antibiotic accounts for a small proportion (6%) of adverse drug reactions in hospitalized (52,65). The penicillins (incuding the semisynthetic beta-lactamase-resistant agents and ampicillin) are most often responsible for allergic reaction and then followed by the sulfonamides (including trimethoprim-sulfamethoxazole) and the cephalosporins. Aminoglycosides and tetracyclines cause allergic reaction much less
Table 6  Example of allergic drug reactions.

<table>
<thead>
<tr>
<th>Type</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Penicillins &gt; Cephalosporins</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Penicillins, Sulfonamides</td>
</tr>
<tr>
<td>Immune haemolytic anaemia</td>
<td>Penicillin, Sulfonamides, Cephalothin, Rifampicin, Isoniazid, PAS, Quinidine</td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td>Quinidine, Sulfonamides, Rifampicin</td>
</tr>
<tr>
<td>Cutaneous and systemic</td>
<td>Penicillins, Sulfonamides, Tetracyclines, Isoniazid</td>
</tr>
<tr>
<td>vasculitis</td>
<td>Drug fever</td>
</tr>
<tr>
<td>Drug fever</td>
<td>Penicillins, Cephalosporins, Amphotericin B, PAS, Quinidine</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Methicillin &gt; other penicillins</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>PAS, Sulfonamides</td>
</tr>
</tbody>
</table>

frequently (52,66). Penicillin allergy is important; all of the penicillins including ampicillin, can produce anaphyaxis in truly allergic patients.

In 0.05% of the patients treated there is an immediate reaction (IgE mediated) producing anaphylaxis. In other patients there is a delayed reaction (IgG mediated) producing type 3 reactions such as serum sickness or erythema nodosum. Cephalosporins can produce similar reactions and up to 10% of penicillin-allergic patients will also be hypersensitive to the cephalosporins (2).

Persons with history of reaction to certain antibiotic or class of antibiotics are particularly prone to antibiotic allergy. Adults in general are more susceptible than children. There is no difference between males and females in frequency of allergic react-
ions. Oral administration appears to be less sensitizing than is parenteral administration. Topical use is definitely associated with a high frequency of sensitization and should be avoided (52).

Because IgE antibodies fix to skin, the likelihood of an immediate or accelerated reaction can be evaluated by skin testing. Skin testing is most useful in detecting penicillin allergy; its use in detecting sensitivity to other antibiotics is less well standardized. Skin tests for penicillin allergy may be falsely negative if patients are taking antihistamines or sympathomimetic amines or have recently had an anaphylactic reaction.

Antihistamines are of some value in relieving the pruritus of the skin eruptions that result from sensitization (67). They are without effect, however, on most of the other manifestations of hypersensitivity. If these become severe, the use of corticosteroids may be helpful, but the administration of such agents in the presence of active infection may be dangerous and should be avoided. Epinephrine is the drug of choice for acute anaphylactic reactions.

2. Biological and metabolic alterations in the host

This includes alterations in normal microbial flora, superinfections and interference with nutritional state of the host. Several factors have been found to play a role in the pathogenesis of superinfections. These are: 1) age under 3 years, 2) the presence of acute or chronic pulmonary disease other than tuberculosis, and 3) the spectrum of antibacterial activity of single or combined drugs. The more "broad" the effect of an antibiotic on micro-organisms, the greater is the possibility that a single component of the normal microflora will predominate and produce infection. Thus, the incidence of superinfection is lowest with penicillin G and highest with the tetracyclines and chloramphenicol and with mixture of broad-spectrum antibiotics.
The proper management of superinfections involves:
1. immediate discontinuation of the drug being given.
2. culture of the suspected infected area.
3. administration of an antimicrobial agent effective against the new offending organism.

CONCLUSION

Antimicrobial drugs are comparatively safe compounds. However, all of them may produce adverse effects which are usually minor, but occasionally they can be serious and even life-threatening. It is necessary for physicians to be aware of the reactions which may occur, and to know how to manage them. Clinicians must concern themselves not only with selection of appropriate antimicrobials but also with the adverse reactions that can result from their use.

REFERENCES

Adverse effects of Antimicrobial Drugs

Noppamas Wongwitdecha


