

The Management of Adverse Drug Reactions

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Introduction

In this article, we limit our discussion to the management of two major types of adverse drug reactions; those of an allergic nature, with or without a proven IgE mechanism, and those that affect mainly the skin. We do not discuss the diagnosis of these commonly occurring clinical problems, as this aspect is presented in the preceding article (*see Vervloet et al., this issue*) and, especially as concerns the skin, in a recent publication by Roujeau and Stern (1).

Cutaneous eruptions are the most frequent manifestations of drug hypersensitivity. Among patients seen in hospitals with a cutaneous drug reaction, one-third tend to have a fixed drug eruption, one-third an exanthematous reaction, and one-fifth an urticarial or angioedematous reaction. The prevalence of adverse reactions to drugs varies from 6–15% in the general population. It varies, of course, with the number of drugs taken and with the route of administration (oral, iv, etc.). Among hospitalized patients, 20–40% have been reported to have had an adverse drug reaction (1–3). Patients with human immunodeficiency virus (HIV) infection or the acquired immunodeficiency syndrome (AIDS) have an even greater risk of having one or another type of drug reaction, a frequency of from 24–50% having been reported (4). Patients with Sjögren's syndrome are also at risk.

The approach to the treatment of an established presumed drug reaction depends obviously on the type and the severity of the reaction. In all cases, the first thing to do is to identify the drug and to discontinue its administration. We proceed from there.

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Treatment of Immediate Hypersensitivity-Type Drug-Induced Reactions

Treatment of the classical immediate hypersensitivity reactions—urticaria, angioedema, asthma, and anaphylaxis—whether owing to a drug or to some other agent is generally well known to allergists. Here, we give the approach that we use at the Rothschild Hospital in Paris.

Urticaria

Urticaria, both acute or chronic, is in most cases a relatively mild immediate hypersensitivity reaction that is sometimes drug induced. It can often be controlled with an oral H1 antihistamine alone: hydroxyzine, 25–50 mg/d in adults, 1 mg/kg body weight in children; dexchlorpheniramine, 5–10 mg/d in adults, 0.5–4 mg/d in children; or cetirizine, 10 mg/d. These drugs may be continued for 6–8 d. Corticosteroids may also be used, starting with an initial dose of 30–40 mg of prednisone orally in adults or 1–2 mg/kg body weight in children. Because corticosteroids are slower to act than antihistamines, we do not prescribe them in most cases (1,5,6).

Angioedema

An antihistamine alone is often sufficient for the treatment of angioedema (5,6,7). When a patient with angioedema is first seen, we usually administer hydroxyzine, 50 mg iv every 8 h in an adult or 1 mg/kg body weight in a child, or dexchlorpheniramine, 5 mg iv every 8 h in an adult or 5 mg iv every 12 h in a child over 30 mo of age. Treatment may be required for up to 24–48 h in severe cases. We then usually prescribe a nonsedating oral antihistamine (e.g., cetirizine, terfenadine, or loratidine) to be taken once daily until the symptoms disappear completely. In patients who present with dyspnea, an injection of aqueous epinephrine should also be given. In the more severe cases, a corticosteroid may also be given for several days to prevent recurrence of the episode.

Asthma

Asthma may occur as a result of the inhalation, ingestion, or parenteral administration of a drug. Aspirin and the nonsteroidal anti-inflammatory drugs are probably the major cause of drug-induced asthma (Table 1) (1,8). Treatment of drug-induced asthma is not specific. Except for strict avoidance of the drug in any form, such reactions are treated as any other type of asthma.

Anaphylaxis

Whenever possible, the patient with an anaphylactic reaction, whatever the cause, should be treated in a hospital emergency unit

Table 1
Drugs that Have Induced Asthma

Acetylsalicylic acid
Nonsteroidal anti-inflammatory drugs
Sulfites
β -adrenergic blockers
Pilocarpine
Angiotensin-converting enzyme inhibitors

(9,10). Epinephrine is the single most important agent in the treatment of anaphylaxis. The initial treatment consists of an injection of aqueous epinephrine, 0.01 mg/kg body weight, either subcutaneously or intramuscularly. This dose may be repeated every 10 min if the symptoms and signs of the reaction continue. Aggressive iv fluid administration is necessary if the systolic blood pressure is 90 mm Hg or less. If the blood pressure remains below this threshold, then the administration of dopamine 400 mg iv is indicated to maintain the systolic pressure at 90–100 mmHg. If the reaction includes severe bronchospasm, then oxygen must be administered at a rate of 4–6 L/min by nasal canula, and salbutamol by aerosol inhalation should also be given. If severe laryngeal edema occurs, tracheostomy may be necessary. Parenteral or oral corticosteroids are used to prevent or control a late-phase reaction. We give either 200 mg of hydrocortisone iv or 60 mg of prednisone orally initially and repeat this dose in 6 h if the reaction has not completely subsided. Most patients can be discharged once their blood pressure has remained normal without further epinephrine administration, usually within 6–12 h after the onset of the reaction. *A special note of caution:* Because anaphylaxis can be potentiated by β -adrenergic blocking drugs (in tablets or in eye drops), it is important to ask if the patient is taking any drug of this type and, if so, then it should be discontinued immediately and its use avoided thereafter (11,12).

Treatment of Serum Sickness

The symptoms and signs of serum sickness include fever, urticaria, angioedema, lymphadenopathy, arthralgias, and swelling of the extremities (2,3,6,8). These manifestations occur from between 5 d and up to 2 wk after the first dose of the causative drug. Table 2 lists the numerous drugs that can cause a serum sickness reaction. For most patients, symptomatic treatment with antihistamines and/or analgesics (e.g., acetaminophen, paracetamol, or dextropropoxyfen) are all that is needed. Severe manifestations may require treatment with an oral corticosteroid in decreasing doses over a period of 1 wk.

Table 2
Drugs that Have Induced Serum Sickness

Acetylsalicylic acid	Thiouracils
Penicillin	Cefaclor
Streptomycin	Propanolol
Sulfonamides	Hydantoins
Phenylbutazone	Gammaglobulin preparations
Metronidazole	Heterologous sera

Table 3
Drugs that Have Induced
Toxic Epidermal Necrolysis^a

Frequently	Occasionally
Allopurinol	Cephalosporins
Amithiozone	Diclofenac
Aminopenicillin	Ethambutol
Barbiturates	Fenbufen
Benoxaprofen	Flouroquinolones
Carbamazepine	Ibuprofen
Chlormezanone	Ketoprofen
Hydantoin	Naproxen
Isoxicam	Rifampicin
Phenylbutazone	Sulindac
Piroxicam	Tenoxicam
Sulfadoxine	Thiabendazole
Sulfadiazine	Tiaprofenic acid
Sulfasalazine	Vancomycin
Trimethoprim-sulfa- methoxazole (Bactrim)	

Treatment of Cutaneous Drug Reactions

Toxic Epidermal Necrolysis (TEN)

Because TEN has such a high mortality rate (30%), it is extremely important to recognize it as early as possible after the first symptoms and signs appear. Any drug that has been introduced within the preceding month should be suspect. A partial list of drugs that have been reported to cause TEN is given in Table 3. It should be noted that the type and dose of drug causing the reaction apparently does not affect the prognosis. Increased age, severe epidermal detachment, visceral involvement, and an increased blood urea nitrogen concentration are poor prognostic signs. Patients with widespread skin involvement should be treated either in an intensive care unit or in a specialized

burn unit (3,13,14). Sepsis is the principal cause of death in affected patients.

The principles of therapy are the same as for thermal burns. The patient may be placed on an air-fluidized bed. Pain should be controlled with appropriate doses of analgesics. Nutrition, fluid, and blood electrolyte levels must be carefully monitored through the course of the reaction.

Infection control requires frequent culture of mucocutaneous erosions, iv lines, and the blood. Topical antiseptic preparations containing chlorohexadine and silver nitrate solution must be used to prevent cutaneous infections. In cases with eye involvement, antiseptic and/or antibiotic eye drops must also be used, and synechiae should be disrupted with a blunt instrument. The routine use of antibiotics is still controversial as this may lead to the emergence of resistant bacterial strains. On the other hand, initiation of antibiotics after the blood culture has become positive may be too late to prevent fatal septic shock. For that reason, we tend to use a broad spectrum antibiotic prophylactically in severe cases of TEN.

The efficacy of systemic corticosteroids in the treatment of TEN also remains controversial. Retrospective studies actually demonstrate no benefit and even higher rates of morbidity and mortality in corticosteroid-treated patients.

Plasmapheresis, cyclosporine, cyclophosphamide, and monoclonal anticytokine antibodies have been proposed in anecdotal reports for the treatment of TEN, but their efficacy remains to be demonstrated.

Stevens-Johnson Syndrome (SJS)

SJS can be considered to be a less severe form of TEN. Drugs that have been reported to cause SJS are the same as those that can cause TEN (*see* Table 3). Roujeau and Stern (1) classified cases with detachment of less than 10% of the epidermis as SJS and those with more than 30% as TEN. Cases with epidermal detachment of between 10 and 30% fall within an intermediate zone (1,13,14). Patients with SJS often have mucous membrane involvement, which can lead to serious complications. Ocular manifestations, notably keratitis, uveitis, corneal erosions, and perforation of the globe, are the most frequent serious complications. Involvement of the tracheobronchial tree and/or the esophagus may lead to stricture formation.

The treatment of this condition is largely symptomatic. Because of the possibility of complications, hospitalization is necessary. In addition to treatment of the skin lesions (as described), mouthwashes and eyewashes with antiseptics are essential. Pain should be controlled with analgesics and local infections with antibiotics. As in TEN, the use of systemic corticosteroids remains controversial.

Table 4
Drugs that Have Induced
Exfoliative Dermatitis and Erythroderma

Allopurinol	Griseofulvin
Ampicillin	Hydantoin
Aminosalicylic acid	Isoniazid
Barbiturates	Lithium
Captopril	Nitrofurantoin
Carbamazepine	Penicillin
Cefoxitin	Phenybutazone
Chloroquine	Quinidine
Chlorpromazine	Streptomycin
Cimetidine	Sulfonamides
Diltiazem	Sulfonylureas
D-penicillamine	Thiacetazone
Gold	

Erythroderma-Exfoliative Dermatitis

A widespread, confluent erythema (erythroderma) that is often associated with desquamation (exfoliative dermatitis) is one of the most dangerous patterns of adverse cutaneous drug reactions (15,16). It may follow exanthematous eruptions or it may develop as erythema and exudation that generalizes rapidly. Table 4 lists some of the drugs that are known to cause this type of reaction.

Other Types of Cutaneous Drug Reactions

Exanthematous reactions (e.g., macular or papular rashes), fixed drug eruptions, or erythema multiforma eruptions, are the principal other types of cutaneous drug reactions. Their etiology (Tables 5 and 6), clinical aspect, and histology are different, but their treatment is quite similar (6). Antihistamines and topical applications of antiseptics (e.g., chlorohexadine or hexamidine) and/or emollients (e.g., cold cream) are all that is needed. These treatments should be used continuously until there is complete healing of the lesions. If the rash is severe or progressive, then administration of an oral corticosteroid should be considered.

Prevention and Prophylaxis

The best ways to reduce the incidence of allergic drug reactions is to prescribe only those medications that are clinically appropriate and to avoid prescribing the drugs that are most likely to cause such reactions. Of course, with the increasing number of over-the-counter drugs that are available, we might predict an increase in the incidence of adverse drug reactions. It is therefore important that we be aware of

Table 5
Drugs that Have Induced
Exanthematous Eruptions

Frequently	Occasionally
Ampicillin	Atropine
Carbamazepin	Barbiturates
Gentamycin	Cephalosporins
Gold	Isoniazid
Penicillin	Meprobamates
Phenybutazone	Naproxen
Other pyrazolones	Phenothiazines
Phenytoin	Quinidine
Sulfonamides	Thiazides

Table 6
Drugs that Have Induced Fixed Drug Eruptions

Acetylsalicylic acid
Anticonvulsants
Barbiturates
Betalactamins
Nonsteroidal anti-inflammatory drugs
Acetaminophen/paracetamol
Sulfonamides
Tetracycline

which drugs our patients have been taking, whatever their presenting condition may be.

When there is a choice, the oral route of administration is preferable to parenteral administration since it is less apt to sensitize the patient and, if an allergic reaction does occur, it is likely to be less severe. Prolonged administration of a drug increases the likelihood of an allergic reaction. Therefore, patients should be instructed to limit the duration of treatment to the period prescribed.

Patients who develop an allergic drug reaction should be informed fully of the cause and be advised to carefully avoid future exposure to the same and related drugs. Patients should also be advised to carry a card or wear a bracelet signaling this allergy. The physician should report details of the case to the local drug reaction control center as well as to the manufacturer of the drug.

It is now well known that patients who are sensitive to aspirin are also likely to be sensitive to cyclo-oxygenase-inhibiting nonsteroidal anti-inflammatory drugs, including piroxicam, ibuprofen, pheybutazone, naproxen, mefenamic acid, ketoprofen, diclofenac, and so on,

and drugs of this type must be avoided by aspirin-sensitive patients. On the other hand, acetaminophen (paracetamol), salicylanamide, and sodium salicylate are usually well tolerated by aspirin-sensitive patients.

Patients with sulfite-induced asthma should avoid drugs containing sulfites (as preservative), for example, isoproterenol, metaproterenol, iv dexamethasone, and sc procaine or lidocaine with epinephrine, the latter often being associated with sulfite. Nevertheless, even though epinephrine solutions contain sulfite, epinephrine can be used to treat anaphylaxis in patients who are sensitive to sulfites.

In some cases, it may be necessary to administer a drug to a patient who has reacted to it in the past. For example, the risk of inducing an anaphylactic-like reaction on readministration of a radiologic contrast medium (RCM) is from 20–35%. Some patients may be able to tolerate the same or a related RCM with no adverse effects if they are premeditated (1,17,18). Premedication with an antihistamine (e.g., 50 mg of hydroxyzine given orally 1 h before the procedure) and a corticosteroid (50 mg of prednisone given 13, 7, and 1 h before the procedure) can reduce the likelihood and the severity of such a reaction in patients who are at risk. A single dose of ephedrine (25 mg orally) given 1 h before the procedure is also said to reduce the risk of a repeat reaction.

In case an allergic drug reaction occurs during a course of treatment and there are no acceptable or available alternatives, then the use of reaction-suppressing drugs may allow continued use of the drug responsible for the reaction (19,20). For example, corticosteroids have been used to suppress drug-induced fever and rash during antituberculosis therapy. Likewise, oral corticosteroids and antihistamines can be used to allow patients with human immunodeficiency virus infection who have had a reaction to trimetoprim-sulfamethoxazole to tolerate cotrimoxazole (21).

In general, however, the concomitant use of antihistamines and/or corticosteroids should be reserved for those patients who have experienced only a mild reaction. This approach should never be used in patients with TEN, SJS, toxic hepatitis, or agranulocytosis. If the patient must be given the causative drug for imperative reasons and no acceptable substitute is available, then a course of desensitization may be proposed.

The aim of desensitization is to abolish the allergic reaction to a specific drug. This approach is particularly indicated when the reaction is known to be IgE mediated, as the mechanism of desensitization is probably through a reduction in the level of drug-specific IgE antibodies. Desensitization is carried out by administering gradually increasing doses of the offending drug, beginning with a subthreshold dose and then giving doubling doses every 15–30 min until a therapeutic dose is reached without a clinically evident adverse reaction. Table 7

Table 7
Oral Desensitization to Penicillin^a

Dose no.	Dose, mg	Cumulative dose, mg
1	1	1
2	2	3
3	4	7
4	8	15
5	16	31
6	32	63
7	64	127
8	100	227
9	200	427
10	300	727
11	500	1227

^aDoses given at 15-min intervals.

shows the schedule that we usually follow in desensitizing patients to penicillin. Other drugs for which desensitization has been used successfully include antibiotics (sulfonamides, vancomycin, isoniazid, rifampicin, and pyrazinamide), analgesics, antimitotic agents (cisplatin and cytarabine), D-penicillamine, sulfasalazine, and allopurinol. Desensitization has been used successfully in HIV-infected patients who have reacted to trimethoprim-sulfamethoxazole (although the mechanism of this reaction is unknown) by giving increasing doses of the drug orally at 30 min intervals (4,20).

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