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General principles of investigating and managing drug allergy

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Adverse reactions to medication are common. Some are predictable side-effects of the drug, others involve individual sensitivity to the drug. Allergic reactions are an important subset of these, but other specific sensitivities are caused by variations in the metabolism or mode of action of the drug. Patients who have experienced adverse reactions to medication will often refer to themselves as being allergic to the drug, regardless of the actual mechanism that caused the reaction. Consequently, anyone taking a history of 'drug allergy' needs to keep an open mind about the mechanism that may have been involved. Fortunately, most idiosyncratic reactions are minor, but some are severe, or even life-threatening. In most situations, there are satisfactory alternatives for the drug in question, but sometimes it is necessary to investigate and get an accurate diagnosis. The over-riding priority is to distinguish anaphylactic, potentially life-threatening reactions from other types of drug reaction, which are generally more protracted, less dangerous and usually managed by simple avoidance. While all doctors need to understand the underlying principles, drug challenges should only be undertaken by clinicians experienced in this area.

Introduction

Adverse reactions to medication are common. Some are predictable side-effects of the drug, others involve individual sensitivity to the drug. Allergic reactions are an important subset of these, but other specific sensitivities are caused by variations in the metabolism or mode of action of the drug. Patients who have experienced adverse reactions to medication will often refer to themselves as being allergic to the drug, regardless of the actual mechanism that caused the reaction. Consequently, anyone taking a history of 'drug allergy' needs to keep an open mind about the mechanism that may have been involved. Fortunately, most idiosyncratic reactions are minor, but some are severe, or even life-threatening. In most situations, there are satisfactory alternatives for the drug in question, but sometimes it is necessary to investigate and get an accurate diagnosis. The over-riding priority is to distinguish anaphylactic, potentially life-threatening reactions from other types of drug reaction, which are generally more protracted, less dangerous and usually managed by simple avoidance. While all doctors need to understand the underlying principles, drug challenges should only be undertaken by clinicians experienced in this area.

Clinical presentations

There are three distinct scenarios which need to be discussed. First, it is essential to consider the possibility of drug allergy in any patient presenting with a skin rash or other unexpected clinical event which could conceivably be an adverse drug reaction. Second, a strategy is needed for dealing with patients who give a history of reactions to previous medication, in whom there is no immediate need to treat with that class of drug. Third, it is sometimes necessary to reach a quick decision in a patient with history of adverse drug reaction in whom there is an urgent need to treat with the suspect drug or a related compound. While there are some recurring themes, the strategy for each of these scenarios differs substantially.

Patient presenting with a rash or other plausible adverse event

It goes without saying that a complete drug history is an essential part of any clinical history, but in patients with an emerging or evolving illness, the possibility of an adverse drug reaction always needs to be addressed in the differential diagnosis, if only to dismiss it. Particular care is needed in patients with unusual skin rashes, neurological or muscular illnesses, but the list of known and suspected

conditions caused by medication is very long [1], and nobody can expect to remember them all. While a balance needs to be struck between ignoring the possibility and extreme paranoia about drug reactions, it remains true to say that only by considering the possibility will the correct diagnosis be reached.

As well as capturing the current medication list, it is useful to record when drugs were started, whether doses have been changed and whether any side-effects have been noted or suspected by the patient or their medical advisers. In addition, it is appropriate to ask specifically about previous medications, especially drugs which have recently been discontinued. Occasionally there can be delayed adverse reactions, but more often withdrawal of a drug may alter the metabolism or handling of other current drugs, thereby potentiating a drug that continues to be taken, or increasing the likelihood of an adverse immune reaction.

In most cases, adverse drug reactions occur soon after the introduction of the drug, but there are some important exceptions. ACE inhibitors are the commonest cause of drug-related angioedema, which can begin several years after the ACE inhibitor was first given. The underlying mechanism is inhibition of bradykinin breakdown (a predictable action of all ACE inhibitors). Angioedema occurs when bradykinin is generated and then cannot be inactivated. Consequently the risk of the reaction is present continuously but the circumstances that will trigger episodes only occur sporadically. Other drugs may only cause reactions above a certain threshold. For example, patients who are sensitive to aspirin and other NSAIDs may tolerate long-term dosage with low dose aspirin, and then experience adverse reactions when larger doses are taken. So although someone who takes low dose aspirin for heart disease has no side-effects, they may nevertheless react when given an NSAID for gout or arthritis. It follows that one should not discount NSAID sensitivity as a cause of reactions in someone who apparently tolerates low dose aspirin or occasional doses of ibuprofen. Similarly, patients who have documented allergies to penicillin are more likely to tolerate penicillin or its derivatives given orally, than the same drug given intravenously. It follows that a history of recently tolerating oral amoxicillin does not automatically invalidate a vague history of penicillin allergy in childhood.

Some types of drug reaction occur well after the drug is started, e.g. acute generalized exanthematous pustulosis (AGEP), serum sickness and drug reactions with eosinophilia and systemic symptoms (DRESS). AGEP usually starts within 7–10 days of commencing on the responsible drug, and can develop after the drug has been discontinued. It is believed to be T-cell mediated and forms part of a spectrum of maculopapular and pustular drug reactions. Although these delayed onset reactions are known to involve T cells, the mechanism of T-cell is not fully understood [2]. Some drugs can react directly with T-cell receptors, triggering a T-cell mediated reaction, but without involving true antigen recognition. This has been termed the p-i concept (p-i standing for pharmacologic interactions with immune receptors) [3]. Carbamazepine, lamotrigine, lignocaine, ciprofloxacin and sulphamethoxazole have all been implicated.

Serum sickness reactions have been reported with a variety of drugs including penicillins, sulphonamides, phenytoin and thiouracils. These present with fever, arthralgia, lymphadenopathy, urticaria and other rashes. They may appear 1–3 weeks after starting on the offending agent and continue for several weeks despite treatment with corticosteroids and antihistamines.

DRESS is relatively rare, but usually comes on 2–8 weeks after starting the responsible drug. As such, the attending clinician needs to have a higher degree of suspicion and be sure to obtain a full drug history, including drugs that are not currently being taken. DRESS develops gradually over several days, with facial oedema, fevers and blood eosinophilia as its cardinal features. Lymphadenopathy is present in about 75% of cases and hepatitis in 50%. Lung, kidney, thyroid and myocardial inflammation are also recognized. Symptoms may worsen after stopping the drug, and may continue for weeks or even months despite drug withdrawal. DRESS occurs most often with anticonvulsants or sulphonamides, but has also been reported with minocycline and allopurinol [4, 5]. Very severe drug reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) involve epidermal detachment, the chief distinction between SJS and TEN being the extent of epidermal damage. Both start with purpuric macules which become confluent with skin shedding, mucosal lesions and involvement of eyes, liver, kidneys and lungs. These conditions are usually easy to recognize, and most often occur with sulphonamides, anticonvulsants, cephalosporins, allopurinol and NSAIDs. Certain patient groups are at increased risk of SJS/TEN, including those with HIV, SLE and bone marrow transplants.

With the advent of new biological agents (cytokines, monoclonal antibodies, etc.) new syndromes of drug reaction have become recognized. Some of these reactions are predictable effects of the immunological activity of the agent (e.g. flu-like symptoms with interferons and anti-TNF agents). The cytokine release syndrome comprises fever, rash, wheeze, capillary leakage, aseptic meningitis and GI symptoms. It has been described particularly with rituximab (anti-CD20) and muronamab (anti-CD23), and needs to be recognized as distinct from anaphylactic or serum sickness reactions to monoclonal antibodies.

Thus, when faced with a patient with an unexpected rash or emergent illness, the general principle is to obtain a full history of all drugs taken during and immediately before the present illness, and then to check whether the symptoms of the present illness are compatible with the documented adverse reactions to these drugs. Unfortunately, data sheets describe drug-related adverse reactions

which are common as well as a long list of adverse events which were reported in clinical trials, but were not necessarily due to the drug.

If the clinical scenario fits with the known side-effects of a currently taken drug, it is usually sensible to stop the drug. The main caution is to set in place an appropriate management plan or alternative drug to address whatever the suspect drug was being used to treat. Where there is no obvious link between the new symptoms and any currently taken drugs, a careful review of medication should be undertaken. This may allow some or all of the current medication to be withdrawn on a temporary or permanent basis.

If the symptoms then resolve, but the clinical need for the drug remains valid, it may be appropriate to reintroduce some or all of the medication. Where several drugs have been stopped, this would usually be done one drug at a time, starting with the drug thought most important for the patient's clinical care (as opposed to the one thought most likely to have caused the reaction). Allow 48–72 h before restarting the next drug. However, the decision to restart drugs will be influenced by the severity of the symptoms, the availability of alternative options and the likelihood that any specific drug caused the problem.

Patient with history of reaction to previous medication, but no immediate need to treat

This scenario arises most commonly in relation to antibiotics. Many people believe that they are allergic to penicillin. Often they have no direct recollection of the index event, for example they may have been told by their parents that they reacted to antibiotics in infancy or early childhood. We know that antibiotics are often given to children with non-specific febrile illnesses, and also that viral illnesses are by far the commonest cause of urticaria in childhood. It is therefore inevitable that some children who have a viral illness that can cause urticaria, will be given antibiotics and will go on to get urticaria, not because of drug allergy, but because of the underlying infection. Similarly, rubelliform macular and maculopapular rashes can be due to antibiotics but also occur with a range of childhood viral illnesses. Testing for penicillin allergy can help to determine the risk of allergic reactions if beta-lactam drugs are used (or need to be used) in future (see below).

Another relatively common scenario is a patient who has had an adverse event associated with general anaesthesia. Hypotension and wheeze can arise for many reasons during an operation, but adverse reactions to neuromuscular blocking agents, colloid, antibiotics, latex and other anaesthetic drugs should always be considered. Once the immediate event is over, it is appropriate to refer these patients for assessment so that the true cause of the reaction may be confirmed, and safe alternatives identified for use in any future anaesthetics (see below).

For many other drugs which patients may report as having caused problems, there are no reliable skin or blood tests. In all cases, the most important thing to do is to obtain as accurate a history as possible, ideally by reference to the original clinical notes or by interrogating those who were there at the time. Clearly this may not be possible when the patient had a vague episode in childhood and has no direct memory of the event. In some cases, it will be clear that the reaction described was not in fact allergic in origin. For example, most cases of diarrhoea or sickness associated with medication will not be due to allergy. The most difficult symptom to disentangle is a skin rash, and here the timing of onset is usually the only thing in the history that will help differentiate intercurrent illness from drug allergy.

For drugs where there is a wide choice of alternatives, there is a judgment to be made based on (i) the likelihood that the drug might have caused the reported reaction and (ii) the risk of denying the patient the use of the suspect drug. In most cases, clinicians are likely to decide to play safe and avoid an adverse reaction by not using the suspect drug. This approach is fine when only one drug is involved, but less satisfactory when patients report a long list of drugs that they have been told they cannot take, without ever having a clear diagnosis or any analysis of the likelihood that the drugs actually caused a problem. Occasionally it may be appropriate to challenge patients with medication to determine whether they are indeed sensitive. However, if the index episode was severe (e.g. Stevens-Johnson syndrome) or if the drug is unlikely to be needed and there are several good alternatives, the risk of triggering an adverse event will normally outweigh the desirability of pinning down the diagnosis.

Patient with history of reaction to previous medication, with an immediate need to treat

Occasionally, patients present with an acute illness which is best treated with a particular drug to which they give a history of adverse reactions. The most extreme examples are patients with bacterial endocarditis or syphilis, where penicillin-based drugs may be both desirable and effective. If the next best alternative drug is unavailable or judged to be much less effective, clinicians may want to use the suspect drug. In an ideal world the issue of drug sensitivity would have been sorted out in cold blood, but if there is no room for delay, there are really only three choices: try the best drug and hope it is tolerated, use an alternative in the knowledge that it may be ineffective or test rapidly and hope that the tests are reliable. If the nature of the index reaction was not severe, and the patient is under direct supervision, in most cases it is reasonable to try the suspect drug, after informing the patient what is being done, and why this is the best option. Most patients will accept a degree of risk in this situation provided that they are involved in the decision-making process. In contrast, patients (and lawyers) find it difficult to accept the development of an adverse reaction if doctors have prescribed drugs which are documented in the notes

as causing allergies, when there has been no consultation or discussion of the rationale for trying the suspect agent. In contrast, if the original event was life-threatening, or if the mechanism suspected was anaphylactic (immediate) allergy then it is probably best to avoid re-exposure. Downstream assessment may of course make it possible to define the risk more accurately.

Investigation

For most drugs there are no validated *in vivo* or *in vitro* tests. Where it is safe to do so, provocation with the native drug is the 'gold standard', but this may not always be practical or wise. Skin testing for drug allergy has been best studied in relation to penicillin and anaesthetic agents. For penicillin, we have good data indicating that in patients with a good history of immediate reactions to penicillin, a negative skin test means the risk of an adverse event on subsequent exposure to penicillin is little more than the risk of an adverse event in the general community [6, 7]. Conversely a positive skin test means that there is about a 75% risk of adverse reaction to penicillin and a 5–7% risk of adverse reactions to cephalosporins (perhaps less with some of the third generation cephalosporins). Aztreonam, meropenem and imipenem may also be tolerated. In all cases, if a decision is eventually made to proceed with these agents, they should be administered cautiously under close clinical supervision.

Testing usually involves a graded series of skin prick tests followed by intradermal tests. These should ideally be done with the intravenous preparations of benzylpenicillin, amoxicillin and any beta-lactam that is being contemplated, as well as with penicillin derivatives. Many allergic reactions are to the penicilliloyl metabolite. Unfortunately, it has been difficult to obtain the penicilliloyl derivatives in recent years, but these are now available again in the US, and some specialist units have imported supplies. These tests (for IgE to benzylpenicillin and penicilloyl-lysine) have a high negative predictive value in patients with suspected type 1 penicillin allergy and should be more widely used in Europe than they currently are. Some guidance is available for investigation on non-immediate reactions to penicillins [8] but these remain largely an area of research.

Skin tests to cephalosporins also show good positive and negative predictive value in patients with suspected type 1 beta-lactam allergy [9, 10]. However, there has been no systematic assessment of cross reactivity between different cephalosporins. The limited data available indicate that about 54% of patients with proven cephalosporin sensitivity are skin test positive only to the suspect agent, while 46% reacted to the suspect agent and other cephalosporins. The clinical implications of these data remain uncertain.

For anaesthetic agents, investigation proceeds on two levels. Some useful information on the nature of the index event can be obtained by measuring mast cell tryptase at the time of the event. Tryptase is stable in blood and has a half-life of several hours, so if samples are taken immediately and 24 h after the index event, this will help confirm (or exclude) anaphylaxis. Taking these samples should not be allowed to interfere with the immediate management of the event, as the enzyme persists for several hours in the blood. A positive result is very helpful, but negative results cannot fully exclude an adverse drug reaction. The most common agents to cause problems are muscle relaxants (suxamethonium, vecuronium, rocuronium, etc.). These agents all have a quaternary ammonium moiety, which is thought to be the principal component involved in causing allergic reactions. Some patients are allergic to all muscle relaxants, while others only show skin reactivity to one of these. In all instances, the skin test results need to be cross-checked with the clinical history before coming to any conclusion about which drugs were responsible and which would be safe for future anaesthetics. Reactions to propofol, latex and antibiotics can also occur and there are good skin testing protocols to detect sensitivity to these agents [11].

Management

The main principles of management are accurate diagnosis and risk assessment, followed by drug avoidance and reducing the risks of inadvertent administration.

In general, drug allergies should always be clearly indicated on clinical notes but with some rider as to probability. Inevitably this estimate will be both imprecise and a matter of judgement. However, the decision-making process on whether to prescribe a suspect drug will differ depending on whether the event is thought to be a 'definite reaction' as opposed to a 'possible but unlikely reaction'. Clinical notes should be labelled consistently, and validated drug allergy information should also be included in all referral letters and correspondence, even if it seems irrelevant at the time.

Where a definite medical need exists for the suspect medication, it may be possible to induce tolerance or to perform a graded challenge. The choice of procedure depends on the history of the previous reaction and the likelihood that the patient is currently allergic to the agent. The purpose of a graded challenge is to administer cautiously the drug to assess whether it is safe to give the drug. This is used in patients who are unlikely to be currently allergic to the drug. In contrast, induction of drug tolerance is used to modify a patient's response to allow treatment to be given safely. This is suitable for patients who are known to be or highly likely to be allergic to the drug but have a strong clinical indication. For example it may be useful to give aspirin to patients with aspirin-exacerbated reactive airways disease needing recurrent oral steroids, recurrent nasal polyps needing resection, for

prophylaxis following coronary stent surgery, or for antiphospholipid syndrome and pregnancy. Drug desensitization should only be undertaken by clinicians who are familiar with the procedure, and in particular it should be noted that this approach is never appropriate for patients who have experienced severe non-IgE mediated reactions (Stevens-Johnson syndrome, toxic epidermolysis, etc.). Graded challenges usually start with about 1/100 of the normal dose; dose steps may be at 30 min intervals where the suspected reaction is IgE-mediated (e.g. urticaria) but only at intervals of a few days where non-IgE-mediated mechanisms would be more likely (e.g. an exanthematous reaction attributed to a statin). Induction of drug tolerance may involve progressive depletion of mediators (e.g. penicillin) or internalization of receptors (aspirin), although the precise mechanisms are not entirely understood. In any event, very small doses (about 1/10 000 of the usual dose) are given with a progressive escalation of dose over 6–12 h. Tolerance is generally maintained for as long as the drug is continued, but will be lost if the patient ceases to take the drug.

Patients should be advised to ensure their next of kin are aware of any important drug allergies, and they may wish to carry information about drug allergies on their person, in the form of a Medicalert bracelet or locket. This is particularly relevant for drugs that might be given in an emergency setting where the patients might be unable to give a clear account of themselves. However, this is less critical for drugs which are only likely to be given as long-term therapy.

Conclusion

Drug allergy is a common problem, but not every patient who believes they are allergic to medication is in fact allergic. Accurate diagnosis depends on taking a full and detailed history, supported by tests where these are appropriate and available. Different approaches are needed for patients who present acutely with illnesses that might be due to drug allergy, those who give a history of drug allergy but have no immediate need for treatment and those who are acutely ill and may be best treated with a drug for which they give a history of adverse reactions. Investigation of drug allergy is an inexact science, but can improve the precision of decision-making. Management consists of making as accurate a diagnosis as possible, and then taking efficient and effective avoidance measure, except in those situations where the suspect drug is far and away the best treatment for the patient's condition. In selected situations, repeated exposure may be the best option, but should only be done with expert advice and informed consent.

Competing Interests

There are no competing interests to declare.

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