PRESCRIBING IN GENERAL PRACTICE 1

Adverse penicillin reactions in the records of a general practice 1973 to 1975

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Introduction

THE penicillins are safe as well as useful drugs. They are generally accepted to be non-toxic to man and animals (Stewart, 1964), yet allergic reaction are their most common and significant side-effects (Idsoe *et al.*, 1968). Sensitivity can be induced and anaphylaxis provoked by any type of penicillin, administered in any conventional vehicle, and by any method of administration. Penicillin allergy is the commonest of all drug allergies (Feinberg, 1961; Maha, 1961).

Coombs and Gell (1968) described four main types of allergic reactions. All of them can be induced by penicillin sensitivity. The clinical types of drug reaction seen with the penicillins include: anaphylaxis, serum sickness, pyrexia, local painful swelling at the site of injection (Arthus-like reaction), haemolytic anaemia, systemic lupus erythematosus, and skin reactions (erythema multiforme, toxic erythema, angioneurotic oedema, urticaria, and fixed drug eruptions).

Penicillin hypersensitivity reactions may be immediate or delayed. The antigenicity of penicillin is due to the conjugation of the basic nucleus 6-amino pencillanic acid (6-APA) with a serum protein or to its breakdown products, penicilloylated proteins. These are responsible for the immediate reactions (most notably in parenteral administration). Delayed reactions include some reactions to protein residues of the fermentation stage of penicillin production and thus are ultimately capable of being eliminated. The timing of reactions will indicate clinically a distinction between humoral mechanisms and the cell-mediated mechanism of delayed hypersensitivity.

During the first nine years of its use only two fatalities were reported (Kern and Wimberley, 1953). By 1957, Peters and his colleagues estimated that there had been up to 1,000 deaths in all due to penicillin therapy. Even small amounts of the drug such as those used in intradermal testing have been known to produce anaphylaxis and death.

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Idsoe *et al.* (1968) reporting for the World Health Organization described 151 fatalities after penicillin administration. They underlined the importance of the patient's history in avoiding tragedy, environmental measures in eliminating accidental exposure, and adequate and ready therapeutic measures if and when crisis occurred.

Penicillin reactions in general practice

This topic is important particularly in general practice where these drugs are most used. The penicillins will provide the family doctor with most of the drug sensitivity reactions that he is likely to meet; yet there are comparatively few detailed reports from general practice about these reactions.

The patients studied here are not considered to have proven hypersensitivity (allergy), but required management simply because their previous records indicated a reaction sufficiently adverse to have caused them to stop a course of treatment of their own accord or to have been instructed to do so.

In this practice simple inked stamps were introduced 17 years ago to denote children for whom vaccination was to be avoided, patients receiving particular drugs (steroids, anticoagulants, monoamine oxidase inhibitors), patients requiring follow-up of a particular observation—for example a dubious cervical smear—and adverse drugs reactions. Seven years ago, coloured stickers were attached to the records of patients when a specific drug reaction was either noted or reported. From a joint list of 5,200 patients, details of such patients and the suspected drug were entered into a special register.

The register

On 30 June 1973 there were 263 patients registered who had experienced some alleged adverse reaction to medication, and in 183 of these a penicillin was implicated. Thus, just over one in 20 on the practice list had reported a drug reaction; for one in 28 this was a penicillin reaction.

The practice figures (3.6 per cent of all patients, i.e. not specifically of treated patients) are within the range found by Idsoe and his colleagues, but are not strictly comparable. In 1959, in a US practice, 3.2 per cent of treated patients (Moore and Woody, 1960) had reactions. In another population, 2.6 per cent of Finnish soldiers (Peltonen *et al.*, 1963) had allergic reactions after treatment. Since the total number of patients who at any time had treatment with a penicillin could not be known, it is not suggested that practice figures indicate prevalence.

Interest lay in the precise description of the phenomenon as a practical day-to-day problem of general practice, a problem of therapeutics and medical care. With these reservations, the figures suggest that a doctor with an average list might have as many as 90 patients with such a history.

First stage of the enquiry

All 183 patients on the register (or their parents) were asked to complete a form designed to include full details of the incident identified as a sensitivity reaction, the nature of the response, whether immediate or delayed, other known sensitivities, history of atopy, family history, and safe experience of a penicillin since the incident.

One hundred and sixty-three patients completed the form. All forms were completed by January 1974. The volunteers were then systematically tested and all replies were cross-checked against previous clinical records. Because of discrepancies, a further seven records were ultimately eliminated from the survey, leaving 156 patients.

Summary of results of first stage

There were no significant findings in association with age or sex or the persistence of symptoms.

Under previous history, one in ten gave a history of intolerance to some other drug, an allergic reaction to food, or immunization procedures and, most important of all, one in five gave a specific history of atopy. Eighteen of those with mainly skin manifestations (122 in all) had also reacted to skin plasters (6) or had had nickel dermatitis (12). In 79 cases (nearly half) a penicillin had been safely administered before; in 58 there had been no known exposure. Seven pairs of patients in immediate families shared a history of reaction; 38 others (one in three) claimed to have a relative with such a history. It was not possible to quantify the reasons for the administration of a penicillin at the time of the incident, nor could dosage be accurately described.

The time lapse since the event was sometimes considerable, the longest being 20 years—this, interestingly, was a reaction to a skin preparation, and this patient was still positive to testing. In 75 cases the time lapse was less than five years, in 77 it was more.

In one third of cases, the patient had initially suspected the reaction. One third occurred in hospital practice.

In 39 patients, parenteral administration was responsible for the reaction, in 124 an oral preparation was responsible. Skin preparations had caused four, and eye ointment one. In 14 patients more than one episode was indicated. The preparations used were identified in 162 cases (one in four had an ampicillin reaction), but it was not possible to determine whether the different types of penicillin caused reactions in proportion to their use; and whether, for example, procaine preparations were used less and the paediatric preparations and ampicillin disproportionately represented.

Immediate symptoms (within half an hour) were described by five after injection, six on an oral preparation, and one applying an eye ointment. In all, 48 patients developed symptoms within the first half day, and 22 receiving injections had a reaction within 24 hours.

Analysis of reactions

Patients were asked to indicate their reactions in terms of simple symptoms grouped as:

1. General.
2. Skin manifestations.
3. Gastrointestinal symptoms.
4. Special reactions.

General and special reactions. The first group of 54 patients, and Group 4 (11 patients) are considered together. The 54 include all in whom anaphylaxis might be suspected. The symptoms noted were: pallor, weakness, faintness, shortness of breath, palpitations, and wheezing. In 43 cases parenteral administration was involved, and in 68 an oral preparation was given; 11 patients experienced two or more of the above symptoms and eight had some skin manifestation as well. There was one near death from an *oral* preparation in a hypersensitive individual, a severe asthmatic.

The special reactions included: severe headache (two patients); vestibular disturbance (two); loss of consciousness (two); confusion (two); typical drug fever (two); an Arthus-type reaction (one); rigidity, dyspnoea and tetany (one). The difficulties of interpretation of this group need no emphasis, especially in patients with bronchitis or pre-existing cardiovascular disease.

Skin reactions. These were reported by 122 patients (Table 1). Two had a severe bullous eruption, one a pustular eruption, and two described peeling of the hands and feet.

The large number with a possible toxic erythema indicated a difficulty of diagnosis in more than half of the 163 who co-operated in the survey. In effect, by far the commonest sign was precisely that which would give the examining doctor the greatest difficulty in attributing a cause. On the other hand, few (23) had this sign alone.

Four patients had had ampicillin rashes associated with glandular fever.

Table 1. Skin reactions to penicillin taken orally or injected in 122 patients.

	Route of administration Injected	Oral
Erythema	20	76
Angioneurotic oedema	11	35
Macular eruption	8	26
Urticaria	10	23
Purpuric reaction	0	5

Gastrointestinal symptoms. These were reported by 44 patients. Seven of the patients described had, by the time of the survey, received a penicillin since the original episode with no ill-effect.

Second stage of the enquiry

The assistance of the Department of Medicine of Guy's Hospital and of Professor Maurice Lessof were sought in evaluating the cases. In completing the questionnaire all patients had been asked if they were willing to attend the hospital for skin testing and for the analysis of blood samples. Initially, 110 volunteered to attend. Since the analysis of the original 163 patients' records, 18 patients had moved, and six (four women and two men) had died. Finally, 78 patients from the practice attended and completed the tests.

Independently of me, Dr Suzanne Alexander, a dermatologist and research worker, saw the patients in the Department of Medicine and carried out skin and cellular tests. To avoid the risk of anaphylaxis, skin tests were carried out by the prick method and patients were observed for 30 minutes. During this time a history was again taken and blood was obtained. The cellular tests carried out at that time were lymphocyte transformation tests (LTT) (Alexander and Forman, 1971) and macrophage migration inhibition tests.

The search for practical laboratory tests is motivated both by increasing knowledge of the mechanisms involved and the wish to avoid risk to patients. A random group such as the one presented here from one practice seemed ideally suited to this type of enquiry. In addition to the tests mentioned above, it was hoped to determine total and penicillin-specific IgE. The radioallergosorbent (RAST) test quantitatively measures the potentiality for reagin-dependent Type 1 reactions, but has the disadvantage of technical difficulty and cost. The test correlates with skin test results and thus could be used to avoid dangerous clinical tests. While a programme of further tests is under consideration for this group of patients, the results so far are given below.

Of 78 patients from the practice, 73 were included in the original survey. As indicated above, the patients' reply to questioning might relate to an episode 20 years before. Such a lapse of time dims exact recollection and also diminishes sensitivity. Of the 79 who had had penicillin safely before the incident, about one third had had it within three to six months of the episode. Timing is relevant in several ways:

1. Unless patients are systematically tested after reaction, there may be good grounds for uncertainty. Yet, in general practice, they will present to the doctor with this element of doubt about a previous reaction.

2. If testing is considered, the test should be made within three months of the original reaction (Idsoe *et al.*, 1968) when 90 per cent may be expected to react positively (Budd *et al.*, 1964).

3. Yet, by contrast, a decline in demonstrable sensitivity may indicate that it is safe, with due care and avoiding parenteral administration, to give a trial of penicillin in cases where the grounds for such treatment are adequate and logical. In the practice test group, the lapse of time from the reported reaction varied between more than five years (34 patients) and less than one year (ten).

Results from the second stage

The details of the smaller test group were as follows (age was classified by decade): in the first decade there were eight, in the second 22, in the third four, in the fourth 12, in the fifth nine, in the sixth eight, in the seventh eight, and in the eighth two. In 57 cases an oral preparation was involved in the original reaction, in 14 a parenteral preparation was responsible, and in three a topical preparation had been used.

Twenty-nine had experienced an immediate reaction (defined as within minutes but less than 12 hours); 41 had had delayed reactions. In nine of the fourteen cases which reacted to injection, there had been a very rapid immediate reaction. The reactions had included: six major anaphylactic episodes—one nearly fatal—four cases of angioneurotic oedema, and 45 urticarias of greater or lesser severity.

Nineteen gave positive histories of atopy, ten of other skin sensitivities, and seven women gave specific histories of nickel dermatitis. Four had serious chronic illness with complicating immunological factors, and a further four had typical ampicillin reactions during glandular fever. In all, seven had safely had some form of oral penicillin since the original reaction, and before testing.

The results of testing were as follows: thirty-one gave unequivocal evidence of sensitivity in one or more of the tests. Skin tests were positive in 18 cases (four delayed positives), coinciding with some but by no means all of those whose clinical history had been most severe and rapid in onset, and including two cases in which vague general symptoms might not have seemed likely to be due to penicillin—one was known to have had an oral penicillin safely before the test, and the other had developed an ampicillin rash in glandular fever. Skin tests were positive in eight out of 34 whose reaction had been over five years before, and in only one out of ten who had experienced a reaction less than one year before.

Lymphocyte transformation tests were positive in ten

and dubious in three. Only three of these coincided with positive skin tests, one with a glandular fever ampicillin rash; two were positive in cases where the patient had safely taken a penicillin since the original reaction. Six patients whose reaction dated from over five years ago gave a positive LTT result; two gave doubtful responses.

Macrophage migration inhibition tests were positive in 13 cases (dubious in one), coinciding with five positive skin tests and five positive LTT results. In three cases (including one positive skin reaction and a positive LTT result) penicillin had been safely taken since. MIT testing was positive in six cases where the original episode was over five years ago.

The above tests were made with the major and minor determinants of penicillin and with specific penicillins, such as ampicillin. Thus, the more costly tests were not superior in establishing a safe policy to careful history taking and skin testing; but in 13 unequivocal and two doubtful cases (half), one or other was positive where the skin test was not.

Third stage

At this point, after completing the above tests, it was possible to reclassify the test group as follows:

Group 1 — warning retained

Group 1 consisted of patients who had experienced severe, well-documented reactions, and particularly those of rapid onset (regardless of negative test results); all who gave a positive result to one or more of the tests (skin, LTT, MIT); patients with a history of atopy, of chronic illness associated with abnormal immune processes, and with strong histories of skin disorder. All of these patients should retain the original warning notice on their cards. There were 43 patients in Group 1.

Group 2 — trial of penicillin possible

Group 2 patients were those negative to all tests, and in whom previous symptoms were mild. The history of suspect reaction and this fact (test results negative) should be indicated on the card with a different label so that if appropriate to a particular illness and under continuous clinical supervision, a penicillin could cautiously be used by the surgery doctors, avoiding parenteral use. Favourable results or recurrence of symptoms would again be recorded and reported. There were 30 patients in this group.

It has been possible since the recent completion of the present series of tests to give an oral penicillin safely under daily supervision to a further three patients whose specific illness warranted such treatment.

General observations

The recording of drug reactions on general-practice record cards gives no precise and reliable information about the frequency, variety, or severity of iatrogenic effect associated with the use of penicillin.

The numbers reflect the frequency with which treatment with penicillin is offered and contemplated, the doctor's habit of precautionary questioning of previous history, and the patient's familiarity with his treatment. There must clearly be some doubt about the patient's interpretation of any drug reaction, including the penicillins; there is an essential difference in familiarity between the penicillins and almost all drugs except aspirin or other widely self-administered preparations. There must equally be some doubt about the doctor's interpretation: thus, toxic erythemas may be associated with the illness treated or the therapy given, and combined therapy will make it more difficult to be certain which drug is responsible for the undesirable symptoms or side-effect; for example, concurrent self-administration of the salicylates. Thus, the doctor's list of reactors will usually be inflated. In this account, the casual administration of a penicillin *without mishap* to patients who had been warned not to accept such therapy reinforces the view that after an interval some may be able to take the drug safely. On the other hand, some of these individuals continued to show positive evidence of sensitivity when they later came to be tested.

Paradoxically too, all of the tests failed to confirm sensitization in a dozen cases with severe or moderately severe reactions where the history and clinical evidence was regarded as irrefutably strong. If history is not always a perfect guide, neither is testing. A negative test result does not disprove sensitivity. A positive test, however, is strong supportive evidence of its role.

Conclusions

The findings have been:

1. The importance of the clinical assessment in cases where severe or minor symptoms have been suspected of indicating penicillin sensitivity.

2. The possibility of developing a clear and safe policy for the management of such a group, within family practice.

In taking the history, the method of administration of the drug, the type, timing, severity and duration of the reaction, and where possible the type of penicillin employed and the illness for which it was given should be known. Almost equally important is anything in the previous general history leading to a suspicion of proneness to react: personal and family history of atopy above all, other allergic manifestations, the dermatological history (skin disorders other than drug sensitivity, contact dermatitis, nickel sensitivity), and other serious illness, in particular any involving an abnormality of immune mechanisms.

Increased risk is definitely associated with evidence of past or present allergic diathesis; and the risk, while generally greater in the adult group of the third to fifth decades (Feinberg and Feinberg, 1956), is greater in the allergic than the non-allergic child (Collins-Williams and Vincent, 1954).

Skin testing by the skin prick method is a useful, simple, and safe procedure which may provide confirmatory evidence. It may be carried out easily, and with proper safeguards, in the surgery.

In cases where it is essential to be sure, for example in severe illness where the penicillins may be life-saving, where several drugs might have caused the reaction, where for any reason doubt exists and certainty rather than suspicion is essential, the cellular tests employed in this survey and those not used here so far—estimations of total and penicillin-specific IgE—may be of use. In most cases, it would not be right to use them, on the grounds of technicians' time and expense. These are hospital procedures.

This analysis suggests that the repeated use of penicillin after short interruptions is to be avoided as it is liable to blunt a useful weapon and, in some cases, induce sensitivity. If it is used again selectively after such reactions the parenteral route is to be avoided.

Despite the complexities outlined, the subject is important. We must avoid iatrogenic illness. Suspicion of sensitivity is vital in daily management and in choice of therapy, and yet it may limit choice, eliminating valuable alternatives from consideration. The problem is further complicated in patients with serious or potentially serious illness. There is a particular difficulty if a patient has multiple sensitivities.

Because of many of the above general observations, a review of 'penicillin sensitivities' in a practice must start with the presumption that the register is likely to be inflated. Nevertheless, there must be a consensus in favour of caution. Just as pre-operative questioning of personal and family history indicative of proneness to bleed is essential, so also in administering a penicillin the only safeguard is to ask the patient.

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