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Penicillin allergy—a rare paediatric condition?

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SUMMARY A total of 298 children with a history of adverse reactions in connection with oral penicillin treatment were investigated with a radioallergosorbent test for penicillin metabolites, the skin prick test, and oral challenge with penicillin V. No severe reactions were seen. In 30 (10%) of the subjects slight to moderate skin reactions were observed on the seventh to 10th day of the challenge period. Between one to four years after the oral challenge 222 children were reinvestigated by interview. One hundred and ten had been given treatment by penicillin and 103 (94%) of these children tolerated the new treatment well and without any adverse reactions.

We conclude that the term 'penicillin allergy' is often misused. Such a diagnosis should be established by clinical investigation.

During early childhood oral treatment with penicillin is common and cutaneous reactions and gastrointestinal symptoms are not uncommon in connection with antibiotic treatment.[1] Many children who react in this way are considered allergic to penicillin, and for fear of severe reactions the treatment is usually stopped. Subsequently, in many cases an alternative treatment with erythromycin, cephalosporin, or trimethoprim-sulphamethoxazole is given. None of these drugs, however, can be regarded as the primary drug of choice in the treament of respiratory tract infections in children. Erythromycin is rarely considered to produce any allergic reactions[2]; however, frequent use of it has created resistant Gram positive coccus strains, and its efficacy against *Haemophilus influenzae* infections in children has been reported to be limited.[3] Cephalosporins are reported to cause an increase in the frequency of side effects[4 5] and a cross reactivity with penicillin exists.[6 7] Trimethoprim-sulpha-methoxazole may give rise to undesirable side effects, immunological reactions, and bone marrow depression. These adverse effects have most often been reported in adults.[8] Thus penicillin still seems to be the first line antibiotic.

Side effects after treatment with penicillin are seldom IgE mediated,[9 10] and severe reactions are very rare in childhood.[11 12] The diagnosis of penicillin allergy cannot be established without thorough investigation.

The aim of this prospective study was to study the possibility of identifying or excluding 'penicillin allergy' in children who had a history of adverse reactions in connection with prior oral penicillin treatment by means of a radioallergosorbent test, the skin prick test, and oral challenge and to determine whether the diagnosis of 'penicillin allergy' is overused.

Subjects and methods

A total of 298 children, 1–15 years old (median age 3 years) with a history of side effects in connection with prior oral penicillin treatment were investigated. They were all outpatients in the Sachs' Children's Hospital or the paediatric department of Huddinge Hospital during the period 1982–5 and all tests were performed using routine procedures.

Most children were investigated within six months of the suspected side effect. A careful history of the adverse reaction was obtained and, where possible, the facts were compared with previous medical records.

Specific IgE to the penicillin metabolites, penicilloyl V and G, was determined with the radioallergosorbent test (Phadebas RAST) in 277 children following the recommendations of the manufacturer. In 22 children the reaction had taken place more than six months previously, therefore no test was performed. In these patients the titres for the test may have decreased and they were not therefore regarded as reliable.

Skin prick tests on the forearm, using benzylpenicillin (0·06 g/ml) and phenoxymethylpenicillin (0·05 g/ml), were made in all patients using saline and histamine (1 mg/ml) as negative and positive controls respectively. A weal larger than 2 mm was considered to be positive.

Oral challenge was performed with phenoxymethylpenicillin in 297 patients when there was no clinical evidence of infection. The challenge dose with a suspension or tablets was set at 25 mg/kg body weight twice a day for 10 days. The first one or two doses were given in the hospital and the patient was observed in the office for two hours. After the 10 day oral challenge period the patients filled in a questionnaire concerning symptoms during the penicillin challenge. If any side effects of importance occurred, the patient was seen at the office after three weeks and in relevant cases a new radioallergosorbent test was performed

FOLLOW UP

In order to evaluate the impact of the penicillin allergy testing and the later antibiotic treatment a follow up investigation was made one to four years after the oral challenge test. A questionnaire was given to those 234 patients who had been subjected to challenge more than one year earlier; 222 families (95%) answered it.

Results

A heredity to atopic disease was present in 137 (46%) of the children. At the time of the initial adverse reaction 225 (76%) were less than 7 years of age (table 1). A total of 185 (62%) of the children had been treated with phenoxymethylpenicillin, 75 (25%) with amoxycillin/ampicillin, and 39 (13%) with cephalosporins, erythromycin, or other unstated preparations. In a third of the children the main symptom was an exanthem without pruritus and 168 (56%) had an exanthem with pruritus or urticaria, in some cases in conjunction with facial oedema or swollen joints (table 2). No asthmatic or anaphylactic reactions were reported. The time when the side effect occurred was mainly between day zero to day three or after one week of treatment (table 3). Skin prick tests were negative in all 298 children.

Radioallergosorbent tests for penicillin metabolites were negative in 274 of the 277 tested cases. In three children increased titres were found. One of these had a high IgE value as well as IgE antibodies to human serum albumin. The titre in this child was therefore regarded as non-specific. One child showed a borderline value. The third child had a high titre without a high IgE value. This patient was the only one in whom no oral challenge was done.

Of the 297 children who were given phenoxymethylpenicillin as a challenge 30 (10%) showed clinical reactions, mainly with symptoms such as urticaria, an exanthem with pruritus and, in some cases, with oedema of the face and joints. No serious reactions or anaphylaxes were seen. In 22 of 30 cases the reactions occurred on the seventh day of challenge or later. The challenge test was positive in 19 (21%) of children who had a primary reaction on the seventh day, or later, as compared with five (4%) of children who had a primary reaction during the first three days (table 3). No child with exanthem alone reacted again whereas 14 (11%) of the children with urticaria or pruritus, or both, did.

Table 1 *Age distribution in 298 children with adverse reactions during treatment with penicillin and the No (%) reacting to oral challenge with phenoxymethylpenicillin*

Age group (years)	*No of children*	*No (%) with positive challenge*
0–<4	151	8 (5)
≥4–<7	74	10 (14)
≥7–≤10	29	4 (14)
>10	27	7 (26)
Unknown	17	1 (6)

Table 2 *Type of adverse reaction during treatment with penicillin in 298 children and the No (%) reacting to oral challenge with phenoxymethylpenicillin*

Type of reaction	*No of children*	*No (%) with positive challenge*
Exanthem—no pruritus	99	0
Urticaria—pruritus	132	14 (11)
Urticaria and swollen joints and/or facial oedema	36	15 (42)
Other symptoms	31	1 (3)
Anaphylaxis	0	—

Table 3 *Time after treatment with penicillin and development of side effects in 298 children and the No (%) reacting to oral challenge with phenoxymethylpenicillin*

Time for reaction (years)	*No of children*	*No (%) with positive challenge*
Day 0–3	131	5 (4)
Day 4–6	46	4 (9)
Day 7+	90	19 (21)
Unknown	31	2 (7)

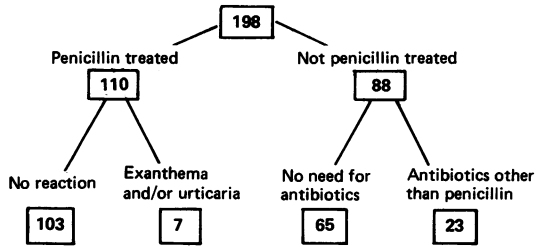

Figure *Follow up investigation in 198 cases one to four years after a negative oral challenge test with phenoxymethylpenicillin.*

Of the children with urticaria associated with swollen joints or slight facial oedema, or both, 15 (42%) reacted on challenge (table 2). Below 3 years of age only eight (5%) of the children reacted on challenge, while seven (26%) of those above 10 years of age had a reaction (table 1). The child with a borderline titre on the radioallergosorbent test developed only a mild urticaria on the seventh day after an phenoxymethylpenicillin challenge. A new radioallergosorbent test was performed in 13 of 30 children who reacted to the oral challenge and 12 still had low values. In the group with a positive heredity 16 (12%) had a reaction as compared with 13 (8%) in the group with a negative heredity for allergic diseases.

Two hundred and twenty two children were investigated using a questionnaire one to four years after the oral challenge test in order to ascertain whether side effects to penicillin treatment given for infections had occurred after the challenge. Half of the subjects (110) received penicillin again and 103 (94%) showed no side effects. Seven reacted with cutaneous manifestations, such as exanthem or urticaria (figure). All these reactions occurred on the 7th–10th days of treatment or after the end of the treatment. Furthermore one child who had a positive penicillin challenge test had no reaction later when accidentally treated with penicillin. Two of the seven children who, according to the questionnaire had reacted, were rechallenged during an infection free period and did not react on this occasion.

A total of 88 children with a negative oral challenge had not received further penicillin treatment (figure). In 65 cases there had been no need for penicillin, but in 23 cases the children had been treated with erythromycin, cephalosporin, or trimethoprim-sulphamethoxazole, partly because of concern that phenoxymethylpenicillin might cause severe reactions. This means that 17% of those children who might have needed penicillin (110+23) did not receive adequate treatment, despite a thorough investigation.

Discussion

This study has shown that in 298 consecutively investigated children diagnosed as allergic to penicillin a type 1 reaction to penicillin was not confirmed in 297 cases by oral challenge. One child with an increased titre on a radioallergosorbent test was not challenged for ethical reasons. These findings accord with the results of an earlier report where oral challenge was performed in 219 cases for 10 days.[11] Furthermore, the present study has shown that the results have been reliable up to four years after the investigation. Ninety four per cent of the children who had been treated with penicillin after the oral challenge showed no side effects. Only 6% had cutaneous manifestations, such as mild urticaria or an exanthem, or both, and they all occurred after the seventh day of treatment. No cases of anaphylaxis or other severe reactions were seen.

Children reacting in connection with ampicillin and cephalosporin treatment were included in the study because these compounds all belong to the β lactam group of antibiotics. Furthermore, the allergenic metabolites that can give rise to IgE mediated reactions are the same for ampicillins and penicillin V and there exists cross reactivity between cephalosporins and phenoxymethylpenicillin. Erythromycin is chemically different from the penicillins but the two children reacting on erythromycin had reacted earlier in the same way in connection with phenoxymethylpenicillin treatment and were thus included in the study.

As most children studied were below 6 years of age some reactions may be due to additives in the syrup preparations. It has not been possible to differentiate between side effects of penicillin per se and of the additives.

Metabolites of penicillin can act as allergens and after sensitisation, IgE mediated reactions may be elicited.[9 10] Type 1 allergy reactions are rare and may be caused by both major and minor determinants of penicillin metabolites. The radioallergosorbent test in its present form can only identify reactions due to major determinants and it must therefore be considered of limited value in the diagnosis of penicillin allergy. It should also be kept in mind that falsely increased titres also occur, especially when IgE concentrations are high. Increased titres may decrease with time, giving false negative results after several months.

Skin prick tests, such as those performed in this study, are of limited value; if used, they should be combined with intradermal testing, as described by

others.[11–13] Here too the use of both major and minor determinants is preferable.[14] Unfortunately, minor determinants are not commercially available for diagnostic purposes.

Today, the only reliable tool for identifying true penicillin allergy is probably oral challenge. If the purpose is to identify IgE mediated reactions it is not necessary to perform prolonged oral challenge. The type 1 reaction appears after the first dose. Later reactions should be regarded as expressions of other underlying mechanisms.

In most children who have had symptoms in connection with treatment with oral penicillin the side effects are minor and the children can continue taking penicillin as prescribed. There are no contraindications for future penicillin treatment in connection with infections. The tendency to react to repeated courses of penicillin treatment seems to be influenced by factors such as age, type of reaction, and the time of the primary reaction during penicillin treatment. A heredity of allergic diseases does not seem to be of importance.

Severe reactions with symptoms of anaphylaxis, asthma, or Stevens-Johnson's syndrome are extremely rare, but in such cases the treatment should be stopped and the child should not be given penicillin again.

Urticaria, pruritus, and oedema of the joints and face are not uncommon side effects, especially not at the end of the treatment. In these cases type 1 allergic mechanisms are not involved. It may be advisable to interrupt the treatment, however, and to investigate the patient later with skin testing and oral challenge when no infection is present.

It may be concluded that the diagnosis of penicillin allergy in connection with treatment with oral penicillin in childhood is often over used and that a thorough investigation must be done before the diagnosis can be established.

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Commentary

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Most 'drug reactions' are diagnosed on presumption: the patient's history and their previous experiences; probabilities concerning the reputation of the medicine; and timing of its administration in a particular instance. With the penicillins the rashes are a prominent feature; the commonest are urticarial, perhaps even with blistering and some are vasculitic (measles like) perhaps with purpura. A general scarlet fever like diffuse reddening without lymphadenopathy, but with a later 'branny desquamation', may be seen and less commonly an eczematous, itchy rash with widespread scaling early in the efflorescence. Scaliness may also follow the more obviously vasculitic rashes while urticaria on microscopical examination may prove to show definite vasculitis.

As a student, I clerked a patient who died of pencillin anaphylaxis catastrophically suddenly; he had perished before the houseman and his clerk got to the bedside. In 33 years of practice I have seldom prescribed penicillin. But fatal anaphylactic shock is exceptionally rare with oral penicillin. Serum sickness is commoner and much more drawn out in its development—urticaria, pains in belly and joints, distressed breathing, and fainting. The urticaria may persist for months, waxing and waning. Recurrence of urticaria for which no cause is discovered, may be guessed to be due to exposure to minute quantities of penicillin or similar cross reacting substances in the diet or as aerosol. 'Side effects' of penicillin administration should be read as 'ill effects'.