

Selective allergic reaction to oral cloxacillin

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Summary

Background Previous observations indicate that in some instances subjects allergic to penicillins may experience an allergic reaction after taking the drug by one route but have good tolerance after being administered the same drug by a different route.

Objective The purpose was to establish if cloxacillin (CLX) induced a selective response only after oral route administration in a suspected case and to study if there were differences between the oral and parenteral formulations.

Methods Skin tests were carried out using benzylpenicillin (BP) conjugated to poly-L-lysine (BPO-PLL), minor determinant mixture of benzylpenicillin (MDM), ampicillin (AMP), amoxicillin (AX) and cloxacillin (CLX). Radioallergosorbent assay (RAST) was carried out using BPO-PLL, AX-PLL and CLX-PLL sensitized discs. In the case the skin tests and RAST were negative, a controlled challenge administering the drug by both oral and parenteral route was made. Urine samples were taken at prechallenge (basal levels) and at three periods after challenge (1–3, 3–6 and 6–9 h). Analysis of oral and parenteral formulations was made by HPLC chromatography.

Results All skin tests and RASTs were negative. With the challenge tests the patient tolerated parenteral BP and oral phenoxymethyl penicillin (PV) and oral and parenteral AMP up to therapeutic concentrations. Parenteral CLX (500 mg) was also tolerated but 30 min after administering 50 mg by the oral route progressive generalized erythema with pruritus, facial angioedema and tachycardia developed. Urine samples taken during the challenge tests showed an increased excretion of N-methyl histamine (N-MH) 3 h after challenge with oral CLX but no change in N-MH levels after challenge with parenteral CLX or the other penicillins, indicating that histamine was released during the allergic episode with oral CLX. HPLC analysis of the oral and parenteral CLX formulations indicated that there were no differences and that neither polymers nor other contaminant materials were present.

Conclusion Although the nature of the allergenic determinant involved in the induction of the reaction is not yet known, the oral route may have favoured the production of a metabolite not generated by the parenteral route.

Keywords: allergy, selective, cloxacillin

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Introduction

Allergic reactions to penicillins can occur by several immunological mechanisms [1], although type I (IgE-mediated) and type IV reactions (cellular-mediated), are most commonly reported [2–4]. The most common

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determinant structure involved is the penicilloyl which can be formed from most penicillins but there is increasing evidence that the side-chain structure may make an important contribution to the antigenic determinant [5] and therefore the specificity of the response. This appears to be particularly important for AX allergy. In a recent study one-third of penicillin allergic subjects were found to be selectively allergic to AX and able to tolerate other

penicillins [6]. The possibility of side-chain specificity has also been suggested for other semisynthetic penicillins [7,8] including cloxacillin [9].

In the present study we have examined a patient who had reacted to a combination of parenteral amoxicillin and oral cloxacillin after previously tolerating both drugs. A range of penicillins, including cloxacillin, and related reagents were employed in skin tests, RASTs and challenge tests. The latter used oral and parenteral administration together with measurements of urinary N-MH during the challenge phase.

Materials and methods

Case report

The patient was a 43-year-old man who had previously been treated with BP and AX with no untoward side-effects. He was suffering from a pharyngeal infection which was being treated with simultaneous administration of parenteral AMP and oral CLX. On the third treatment he experienced immediate generalized erythema and pruritus with facial angioedema. The symptoms resolved, spontaneously, 4 h later.

Skin tests

Skin tests were carried out using the following reagents: BPO-PLL 5×10^{-5} M, MDM 2×10^{-2} M (ALK), AX 20 mg/mL (Beecham), CLX 20 mg/mL (Beecham), AMP 20 mg/mL (Antibioticos S.A., Leon, Spain).

Specific IgE antibodies determination, RAST

RAST assays were carried out as described by Blanca *et al.* [10] with reagents prepared using poly-L-lysine conjugates of benzyl penicillin (BPO-PLL), amoxicillin (AX-PLL) and cloxacillin (CLX-PLL). The assays were validated using a serum that recognized the common structure to the penicillins used, the new antigenic determinant.

Challenge protocol

The patient was challenged with BP parenterally and PV orally and AMP and CLX by the oral and parenteral routes with a 1 week interval between the individual drugs. On each occasion the patient was challenged at the same time of day. For PV, AMP and CLX the patient was initially given 10 mg followed by 50 mg, 100 mg, 250 mg and finally 500 mg provided there were no adverse effects. For BP the doses were 10^3 , 10^4 , 10^5 , 25×10^5 , 50×10^5 and 10^6 units.

Quantitation of N-MH in urine after drug challenge

Urine samples were obtained at basal levels (prechallenge) and 3 hourly intervals during three consecutive periods (1–3, 3–6 and 6–9 h) after the drug was administered. N-MH was determined by radioimmunoassay using a commercially available kit (Pharmacia, Uppsala, Sweden). The intra-assay coefficient of variation of the method was 8.9% and the inter-assay coefficient of variation was 12.5%. All samples were determined in triplicate and in the same assay.

Analysis of CLX by HPLC

An analysis of both the oral and parenteral CLX formulations was carried out using ion pair HPLC chromatography with a 250×4 mm ID Ultrasphere ODS column (Beckman). The mobile phase consisted of an aqueous solution of 0.01 M TBA and 0.01 M phosphate buffer (pH adjusted to 4 with phosphoric acid), and acetonitrile. A 20% (w/v) aqueous solution of parenteral (solution cloxacillin) and oral (acid cloxacillin) was passed through the column. Ampicillin polymers prepared by the method of Bundgaard *et al.* [11] were used as controls.

Results and comments

When studying suspected penicillin allergic subjects we initially use a standard range of skin-test reagents utilizing BP-PLL, MDM, AX and AMP together with RASTs using BPO-PLL and AX-PLL. Our subject had

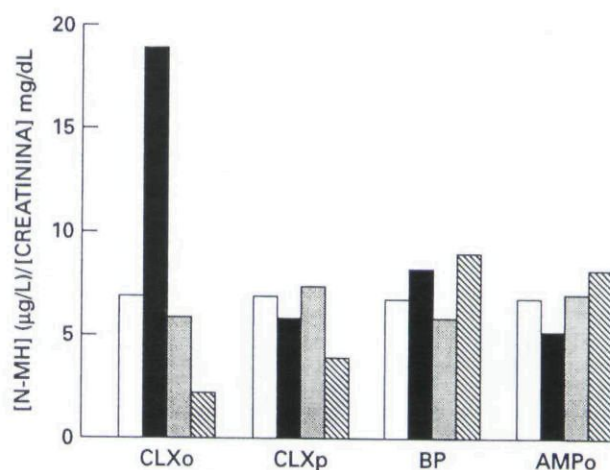
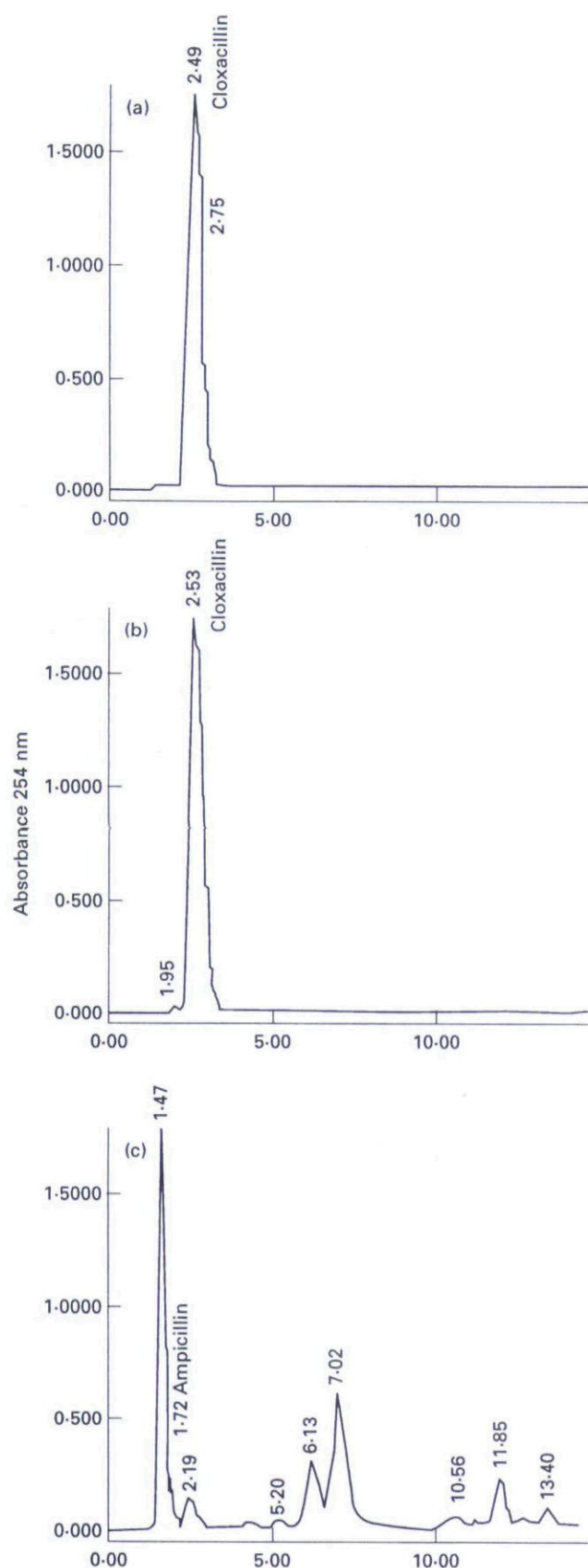


Fig. 1. Urinary N-MH excretion previous to drugs administration (basal) and after 3, 6 and 9 h of administering parenteral cloxacillin (CLXp), oral cloxacillin (CLXo), parenteral benzylpenicillin (BP) and oral ampicillin (AMPo). □, Basal. ■, 3 h. ▨, 6 h. ▩, 9 h.



experienced an allergic response after receiving AX and CLX so cloxacillin was added to the skin-test regimen and a CLX-PLL RAST was developed. This seemed particularly prudent since studies have suggested that CLX may be able to stimulate side-chain specific responses [9] which could lead to antibodies non-cross-reactive with other penicillins. Challenge tests are also an important part of our strategy and CLX was added to our usual range of BP, AMP and PV with the use of parenteral and oral administration as appropriate. In conjunction with the challenge tests we also investigated urinary excretion of N-MH as a further diagnostic aid.

All skin tests and RAST measurements were negative as were the challenge tests with parenteral AMP and CLX and oral BP, PV and AMP. However, 30 min after the administration of 50 mg of CLX by the oral route the patient experienced generalized erythema with pruritus, facial angioedema and tachycardia. The results of the N-MH measurements in urine are presented in Fig. 1. In the case of CLX taken by oral route (CLXo), a high level of N-MH was detected in the first urine sample (1–3 h collection period), representing 270% of baseline values, and then decreased at the 3–6 and 6–9 h intervals. This peak of N-MH coincided with the appearance of allergic symptoms. With the other penicillin derivatives, including CLX administered by parenteral route, no symptoms appeared and no significant increased peaks were detected after the drug administration. With CLXp, BP and AMPo the values were similar or slightly different but did not show any relevant peak after drug intake. The results confirmed that the patient had responded to CLX but only when administered by the oral route.

The difference in response to parenteral and oral CLX could have been sample dependent but HPLC analysis (Fig. 2) showed no major differences between them. Additionally, no significant extra peaks suggesting the presence of polymers or other contaminating materials were detected in either of the preparations. A control sample containing ampicillin polymers showed multiple peaks using the same HPLC conditions and column.

The immediate nature of the initial allergic reaction in our patient and the rapid response after oral CLX challenge (30 min) suggests an IgE-mediated reaction via mast cell degranulation. The increased excretion of N-MH during the first 3 h after challenge also implies the involvement of mast cells and/or basophils in the induction of the reaction. However, we were unable to confirm the presence of penicillin specific IgE antibodies even

Fig. 2. HPLC analysis of oral cloxacillin (a), parenteral cloxacillin (b) and ampicillin polymers (c).

when using CLX for skin tests and RAST measurements. Inability to detect specific IgE antibodies is not an uncommon finding for penicillin allergic subjects and to some extent reflects the heterogeneity of human responses to penicillins and a lack of knowledge of the determinants involved. Skin testing has evolved from using free BP to the use of BP related reagents such as BPO-PLL and MDM. The latter reagents have increased the number of patients who give positive responses [4,6] but some patients still do not respond. In some cases this may be because of a very specific response against a penicillin, non-crossreactive with BP. For example, studies with amoxicillin have shown that a number of subjects can react to this penicillin but safely tolerate others. This suggests a very specific response, which for many patients appears to be related to the side-chain of amoxicillin as confirmed by skin tests and RAST measurements [5,6]. However, even in this case only about half of a group of patients are positive by skin test and RAST [12] suggesting that the others are responding to another amoxicillin related determinant.

The subject of our studies clearly reacted to CLX, but only if administered orally. A number of other penicillins administered parenterally and orally were safely tolerated as was parenteral CLX. This implies sensitivity not to CLX itself but to a structure formed from CLX by the very different pH conditions of the gastric barrier through which drugs can pass to the tissues and circulation. Studies have shown that penicillins can form different determinants at low pH (oral administration) compared with neutral pH (parenteral administration) [13], which could lead to responses not amenable to diagnosis using conventional reagents and methods. Penicillic acids, which form more readily at low pH, are one possibility and they can react via a free thiol to give unusual disulphide linked determinants.

In conclusion, we present a case of a selective response to CLX where the route of administration seemed to be critical for elicitation of the reaction. Diagnostic studies could not confirm the presence of specific IgE antibodies but showed that the patient could safely tolerate a number of other penicillins by oral and parenteral administration. These results indicate that in addition to a need for specific diagnostic reagents the route of administration for challenge tests can be a crucial factor for diagnosis.

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