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CASE STUDY

Occupational asthma induced by cephalosporins

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Occupational asthma induced by cephalosporins. J. Sastre, S. Quirce, A. Novalbos, M. Lluch-Bernal, C. Bombín, A. Umpiérrez. ©ERS Journals Ltd 1999.

ABSTRACT: A 20-yr-old pharmaceutical worker who developed attacks of shortness of breath and wheezing 9 months after beginning work on a process in which cefadroxil powder was bottled or encapsulated will be described.

Skin test with cefaxodril was negative. Baseline spirometry and methacholine inhalation test were normal. A controlled bronchial challenge test was carried out in a closed-circuit system with assessment of respirable dust concentration.

Exposure to cefadroxil powder at a mean concentration of 10 mg·m^{-3} for 10 min elicited an isolated immediate asthmatic response, but no response was observed to control challenge with lactose. Single-blind oral challenge test with amoxicillin up to 500 mg was well tolerated, whereas the oral challenge with cephalexin (25 mg) elicited an immediate asthmatic response.

This patient had developed occupational asthma caused by inhalation of cefadroxil as confirmed by specific inhalation test. Since she tolerated oral amoxicillin, a synthetic penicillin with the side-chain identical to that of cefadroxil, it seems that she may be sensitized to the dihydrothiazine ring of cephalosporins.

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Several drugs may cause asthma in those inhaling them during their manufacture [1]. Although asthma attacks have been recognized as part of the clinical manifestations of an anaphylactic reaction to systemic administration of antibiotics, occupational asthma (OA) induced by β-lactam antibiotics has been reported only in the last few years [2–9]. A case is reported of a pharmaceutical worker in whom OA developed after inhalation of cefadroxil powder in her workplace. A single-blind oral challenge test with cephalexin elicited an immediate asthmatic reaction, whereas no reaction was observed to orally administered amoxicillin. The chemical structures of cefadroxil, cephalexin and amoxicillin are shown in figure 1.

Case report

The patient was a 20-yr-old female, a nonsmoker, who had been employed in a pharmaceutical company for a year as a production worker. She had no history of asthma or atopy. Her work consisted mainly of the operation of a dispenser of drugs in powder form, including cefadroxil, which was produced in batches. In the last 5 months she had experienced three short-lived attacks of shortness of breath, chest tightness, dry cough and sneezing which developed when cefadroxil powder was being bottled or encapsulated. These symptoms subsided spontaneously in the first episode by avoiding exposure to cefadroxil but required emergency treatment with inhaled β-agonists and systemic corticosteroids on the other two occasions. The patient had no symptoms when other drugs where processed, and she became asymptomatic after being transferred to a different section of the company. She had taken oral amoxicillin on several occasions without any adverse effect, and she did not recall having received any treatment with cephalosporins.

Blood differential count, serum biochemistry, chest and paranasal sinus radiographs showed no abnormalities. Spirometry revealed a forced vital capacity (FVC) of 4.48 L (122% predicted), a forced expiratory volume in one second (FEV_1) of 3.47 L (108% pred) and FEV_1/FVC of 77%.

Skin tests

Skin prick tests were carried out with a battery of common aeroallergens (ALK-Abelló, Madrid, Spain), as well as with thragacant, arabic, and karaya gum extracts at 10 mg·mL^{-1}. Prick and intradermal skin tests were also performed with penicilloyl-polylysine 5×10^{-5} M (Allergopharma, Reinbek, Germany), minor determinant mixture 1×10^{-2} M (Allergopharma), benzylpenicillin 10,000 U·mL^{-1} (Pharmacia & Upjohn, Madrid, Spain), amoxicillin 25 mg·mL^{-1} (Beecham Pharmaceuticals, Madrid, Spain), and purified cefadroxil 25 mg·mL^{-1} (Bohn Laboratories, Madrid, Spain). Histamine phosphate 10 mg·mL^{-1} and normal saline were used as positive and negative controls, respectively.

Specific immunoglobulin E measurements

Specific immunoglobulin (Ig)E to penicillin G, penicillin V, amoxicillin, ampicillin and cefaclor were determined in serum by the CAP system (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions, and results >0.35 kU·L^{-1} were considered positive.

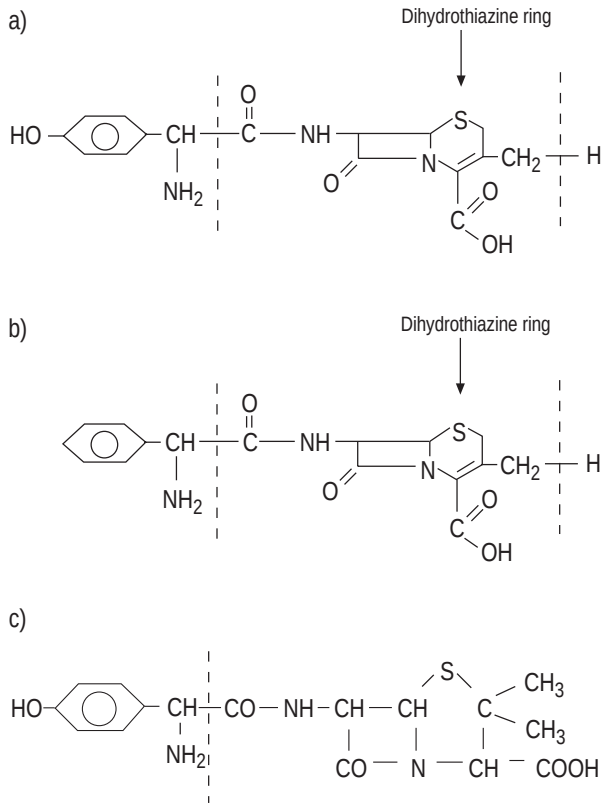

Fig. 1. – Chemical structure of a) cefadroxil, b) cephalexin and c) amoxicillin. - - - - : Separate the nuclear structure of β-lactam molecules from the side chains.

Methacholine inhalation test

This test was performed according to COCKCROFT *et al.* [10] with some modifications. The aerosolized particles were generated by a continuous pressurized nebulizer model DeVilbiss 646 (DeVilbiss Co, Somerset, PA, USA) with an output of 0.28 $mL \cdot min^{-1}$. The result of this test was expressed as the provocative concentration of methacholine causing a 20% fall in FEV1 (PC_{20}).

Specific bronchial challenge test

A controlled bronchial challenge test was carried out in a closed-circuit system for exposure to particles that is based on a similar validated system [11]. The apparatus consisted of three parts: a particle generator (small-scale powder disperser, TSI model 3433; TSI, St Paul, MN, USA); an aerosol delivery system (plexiglass cylinder 60×11 cm) that was connected to an orofacial mask; and a monitor of respirable particles (DustTrack, aerosol monitor, model 8520; TSI). The concentration of aerosolized powder in the chamber was regulated to obtain the desired concentration, adjusting the air flow and speed of rotation of the plate where the powder is located in the disperser and by the flow of the exhaust system. The aerosol was inhaled by the patient at tidal volume. A hole in the wall of the cylinder allowed the subject to breathe the aerosol through a face mask with an unidirectional membrane, which prevented particles from escaping through the face mask if the subject was not breathing through the apparatus. During aerosolization, powder concentration was measured in real time. The patient withheld all medications for several weeks prior to the test. As a control bronchial challenge, the patient was exposed to lactose powder (up to 10 $mg \cdot m^{-3}$) for 30 min on the first day. The following day, increasing concentrations of cefadroxil were given by inhalation, starting with 1.5 $mg \cdot m^{-3}$. The dose was increased at intervals of 10 min and FEV1 and FVC were measured at 5 and 10 min after inhalation of each concentration. The bronchial challenge test was discontinued when there was a fall in FEV1 of ≥20% from the baseline value or when the highest concentration had been given. At the end of the inhalation challenge test, spirometry was performed at 20, 30, 40 and 60 min, then hourly for 8 hrs after challenge, and again the following day. From that moment, peak expiratory flow rate (PEFR) measurements were performed hourly for 24 h after challenge, respecting sleeping time. A fall in FEV1 of ≥20% from baseline within 60 min of challenge was considered a positive immediate reaction, while a fall in PEFR >25% between 2 and 24 h after challenge was considered a positive late reaction if no change was observed during the control day.

Oral challenge test

Single-blind oral challenge tests were performed with amoxicillin and cephalexin as previously described [12]. FEV1 was measured before challenge and every 5 min during the first 30 min after oral challenge, and at 30, 45 and 60 min after challenge. Thereafter PEFR was measured hourly until bedtime and again the following day. Criteria for a positive immediate or late asthmatic reaction were the same as described above.

Results

All the skin tests performed were negative at 15 min and 24 h. Specific IgE determinations (CAP) against all the β-lactam antibiotics tested were negative. Methacholine inhalation test (up to 16 $mg \cdot mL^{-1}$) before the specific inhalation test was negative. During the control day the patient was exposed to lactose (10 $mg \cdot m^{-3}$) for 30 min and no significant changes of FEV1 or PEFR were observed during follow-up. The following day the patient was exposed to purified cefadroxil powder (Bohn), and after exposure to a concentration close to 10 $mg \cdot m^{-3}$ for 10 min a 23% fall in FEV1 was observed at 30 min (fig. 2) without late reaction. A methacholine challenge test performed 24 h after specific inhalation challenge again gave a negative result.

Controlled oral challenge test with commercial amoxicillin up to 500 mg elicited no response. However, a single-blind oral challenge test with 25 mg of cephalexin induced a fall in FEV1 of 22% at 5 min (fig. 2), without other systemic symptoms, requiring treatment with intramuscular adrenalin. No late asthmatic reaction was observed during follow-up.

Discussion

A pharmaceutical worker with occupational asthma caused by inhalation of cefadroxil, an oral cephalosporin, that was confirmed by a specific inhalation test with this

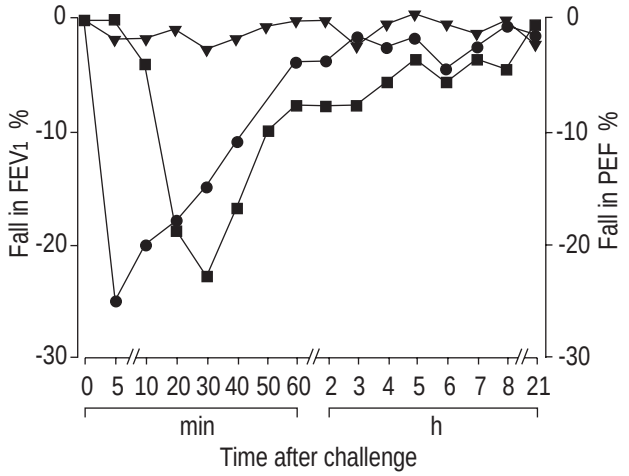

Fig. 2. – Immediate asthmatic response after a bronchial inhalation test with cefadroxil powder (10 mg·m^{-3} for 10 min; ■) and an oral challenge test with cephalexin (25 mg; ●). FEV1: forced expiratory volume in one second; PEF: peak expiratory flow. ▼: lactose control.

purified antibiotic in powder form is described. Furthermore, the patient had an immediate asthmatic attack after controlled oral challenge with cephalexin, which is unusual for a worker with OA due to an inhaled agent. However, the patient showed no reaction after oral challenge with amoxicillin, a semi-synthetic penicillin with the same side-chain as cefadroxil (fig. 1). Since the patient reacted to both cefadroxil and cephalexin it seems that she may be sensitized to the dihydrothiazine ring of cephalosporins (fig. 1) and not to the side-chain.

Interestingly, this patient developed asthma as the only manifestation of allergy to cephalosporins, as has been described in other cases of OA caused by β-lactam antibiotics [2–7]. The patient had no previous history of ingestion of cephalosporins and, therefore, the sensitization to cefadroxil probably occurred through the inhalation route. Skin tests to β-lactam antigens and purified cefadroxil were negative, as previously reported in some patients with OA caused by these antibiotics [2, 3, 9] but not in others [4, 8]. Although nonspecific bronchial hyperresponsiveness is a characteristic feature of asthma, in some cases OA may exist with negative methacholine challenge [13, 14]. In the present patient, the absence of bronchial hyperresponsiveness to methacholine after the cefadroxil-induced asthmatic reaction could be related to the isolated early asthmatic reaction after the specific inhalation test, or alternatively, to the timing (24 h) of the methacholine postchallenge test, since transient increases in nonspecific responsiveness may occur earlier [15].

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