Case Study

Occupational Rhinitis and Bronchospastic Reaction in a Worker Exposed to Imipenem

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Hypersensitive reactions to drugs are poorly understood. Most are believed to be immunological, often expressions of Gel and Coombs Type I reactions mediated by IgE1. The immune mechanism and the immunochemistry of these reactions, especially to common offending agents, such as penicillin and other β-lactam antibiotics, have been extensively characterised2. Hence skin testing procedures and standardisation of intradermal allergens for confirmation of a suspected IgE-mediated allergy to such agents have been validated and are in common use3–6. Although adverse drug reactions are commonly observed in patients after the administration of antibiotics, occupational asthma due to penicillins has been described in healthcare and in pharmaceutical factory workers7. Imipenem is a β-lactam broad spectrum antibiotic, used in treatment for Gram positive and negative, aerobic and anaerobic bacteria8. Occupational exposure can also occur via inhalation in the manufacturing of the compound. The commercialised antibiotic is a 1:1 mixture of N-formimidoyl-thienamicyn, a proximate principle, and cilistatin, an inhibitor of dehydropeptidase enzyme, which enhances urinary concentrations of an active drug. In this report we describe the case of a worker who presented with respiratory symptoms which were initially underestimated. The symptoms seemed to be related to the activity in the workplace (on-off test positive). Our goal was to establish the cause of such symptoms. The human study was conducted in accordance with the recommendations outlined in the Declaration of Helsinki. The authors obtained informed consent from the study subject.

Case

A 33 year-old female has been employed as a technician in a pharmaceutical factory for 2 yr. The worker was exposed to the product in a powder state, while controlling the mixing of both N-formimidoyl-thienamicyn and cilistatin in a sterile room. One year after starting her job the patient developed conjunctivitis, infections, dry and irritating cough, itchy nose, rhinorrea and headache. The patient underwent a physical check up, routine tests and a check for respiratory symptoms and rhinitis, that consisted of:

- Skin tests for a panel of common commercial allergens such as grass, tree and weed pollens, animal danders, moulds, yeast and house dust mite. All tests were read at 15 min and a wheal with a diameter of 3 mm or more was regarded as positive.
- Skin and intradermal tests for penicillins according to a standardised diagnostic methods for antibiotics, testing both the determinants, major and minor β-lactam antibiotics, G penicillin, ampicillin and amoxicillin4. Evaluation was assessed after 20 min, and again 48 h later. Histamine as a positive control and saline as a negative control were employed. Reactions at least 3 mm > than controls for skin test and 5 mm for intradermal test were considered positive5. Serum total IgE and specific IgE for penicilloyl G, penicilloyl V, ampicillin and amoxicilline, but not imipenem, which is not commercialized, were detected by the commercial CAP-SYSTEM (Pharmacia Upphon Uppsala Sweden) following the manufacturer’s methods.
- Basal respiratory function and bronchial challenge with methacoline6.
- Aspecific nasal challenge with distilled water (5 ml in each nostril).
- Specific nasal challenge with thienamycin and cilistatin directly instilled into the nose (2 mg in each nostril mixed with 2 mg of lactose). Before each nasal challenge baseline function was assessed (within 10% of that on control days).

The anterior nasal airflow resistance and the measure of FEV-1 by spirometer, as a control of respiratory function, were recorded at: 5, 15, 30, 60, 240, 300, 360 min after the nasal challenge. The nasal challenge was considered positive if anterior nasal airflow resistance increase was >100% of the baseline. The symptoms (rhinorrea, nasal irritation, stuffy nose and sneezing) were assessed from a scale of severity which was recorded by either the patient or the observer10.

Our observation showed:
- the on-off test was positive,
- specific inhalation challenge with imipenem revealed bronchoconstriction and a positive nasal response, whereas cilistatin challenge and lactose challenge (control test) were negative.

Only the nasal challenge with imipenem provoked a rapid increase in anterior nasal airflow resistance after 5

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min, which persisted for 4 h together with positive symptoms. The measurement of FEV-1 (forced expiratory volume-1) also showed a significant fall (>20%) in the first hour (Fig. 1). All other tests were negative. It was possible to remove the worker from the risk site (she spent two weeks at home). At the following check up the nasal symptoms had disappeared nor did she have bronchospastic reactions.

Discussion

To date, no cases of occupational rhinitis and/or asthma due to imipenem have been described in the literature, even if penicillins are selected amongst the major causes of occupational respiratory diseases.

The symptoms improved in this case when the worker was removed from the specific inhalatory risk. The increase in nasal resistance and the rhinitis symptoms have been associated with a specific bronchial obstructive reaction. These data suggest that imipenem specifically acts on the respiratory tract, even though we are not able to identify the mechanism. The diagnosis of occupational rhinitis due to imipenem has been supported by a clinical history and by a positive nasal challenge, oculo-rhinitis symptoms after the challenge, associated with a bronchospastic reaction. We could not assess the eosinophilic leukocytes in nasal discharge in the nasal challenge test because the recovery of secretions by lavage did not permit simultaneous, objective measures of the physiological response to the challenge, as also reported in the literature. Nevertheless, it does not result in very sensitive detection of eosinophils, whose number is extremely variable: it seems reasonable that eosinophils at least betray a hyperreactive state.

No response to cutaneous and intradermal test and specific IgE for the antigenic determinants of penicillins was observed, even if it is suggested that cross reactivity and allergic reactions to imipenem could occur in patients known to be allergic to penicillin as determined by the IgE antibodies titre. We cannot exclude a possible IgE mediated mechanism. Indeed, it should be considered that there is a different sensibility and specificity between the radioallergosorbent test (RAST) and the CAP SYSTEM (Pharmacia Upjohn Uppsala Sweden).

Saxon et al. found that close to 50% of individuals who had penicillin-positive skin tests demonstrated reactivity to one or more of the imipenem determinants, but Patriarca has recently considered it safe to administer carbapenems to patients with previous adverse reactions to β-lactams. Nevertheless, in our opinion, negative specific IgE antibodies do not exclude allergy to penicillins, and a correct diagnostic approach, other than skin tests, is often due to the challenge test. Moreover occupational challenge tests have a medico-legal value.

Our observation is probably due to the different structure of the antigenic nucleus. In fact imipenem is a carbapenem β-lactam antibiotic, differing from the molecular structure of penicillins, in that the 5-membered ring is unsaturated and contains a carbon (-CH2-) other
than a sulphur atom. Even the antigenic determinants made up of the side chains are notably different in imipenem (eg. the p-hydroxy group is missing) and the hydroxyethylic side chain is joined to the $\beta$-lactamic ring in the trans position (Fig. 2). The cases in the literature of cross reactivity of imipenem and penicillin suggest that they exist, in vivo, in homologous conformations 14).

Primary prevention (elimination of the agent from the workplace by substitution or process change) was obviously not possible, but a reduction in exposure has been achieved through isolation, enclosure and improved local exhaust.

The periodic examination of workers in high risk industries can lead to early recognition and early removal from exposure sources. The relocation of the patient in order to reduce exposure and the provision of respiratory protection can help to reach low or occasional exposure levels, although the worker would remain under medical supervision. This was the solution for the patient investigated in this study, who was employed in a monitored work place, not directly exposed to the compound, and protected by a positive pressure helmet respirator.

Further epidemiological studies are needed to evaluate the prevalence of the respiratory symptoms among workers in pharmaceutical industries, and to obtain better knowledge of the immunological mechanism.

References