

or less while 1964 (64.9 %) had been breast-fed for more than 6 months.

Starting the child on infant formula before three months and starting complementary food early have been reported to be risk factors for asthma⁸. Our patients had been started on complementary food at month 4.5 ± 3.38 on average. 2265 (75 %) patients had been started on complementary food at various times starting from 3 months. Most of our patients had been started on complementary food after 3 months.

It is stated that the month of birth has an effect on the development of Ig E due to the inhaled allergen concentration. Children with pollen allergy are usually born March to June while those with house dust mite allergy are usually born May to October. Asthma is reported to be seen less frequently in those born during the winter. The reason for this is supposedly the increased tree and grass pollens in summer and spring and the increased house dust concentration in the fall⁵. Our results supported this and most of our patients had been born in the summer while winter was the season of the smallest number of births.

Childhood infections and vaccines are reported to have an increasing or decreasing effect on the prevalence of allergic disease. The reverse correlation between atopy and infection is explained with the stimulation of the TH-1 response in T lymphocytes with recurrent infection. Viral infections may trigger asthma attacks but asthma prevalence is low where respiratory infections are common and their protective role in becoming sensitized to allergens should be noted. The increased prevalence of asthma, especially in developed countries, is explained with the hygiene theory. The improved hygiene and decreased incidence of infection is seen as a factor in the increase of atopic diseases. Infections stimulating the TH-1 response may suppress the development of asthma⁹. A study on African children has shown that past measles infection is a protective factor against atopy¹⁰. Manticardi et al¹¹ report that children who have had infections spreading by the orofecal route have a significantly lower prevalence of atopy than those who have had viral infections spreading by air (MMR, varicella, CMV, HSV1). 538 (17.8 %) of our patients reported an episode of mumps, 598 (19.8 %) of measles and 964 (31.8 %) of varicella, all air-borne diseases.

Although allergic sensitivity to aspirin is well-known, nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin and ibuprofen may initiate an asthmatic crisis mostly by a non-allergic mechanism¹². Atopy is not a predisposing factor for the development of penicillin sensitivity and it may be said

that fatal anaphylactic reactions develop more easily in these persons¹³. Of our patients, 114 (3.8 %) had a history of drug allergy. The most common of these was allergy to penicillin, present in 72 patients.

It has been reported that patients who have cow milk and egg intolerance before two years of age more commonly develop sensitization to aeroallergens by four years of age⁸. 127 (4.2 %) of our patients had a history of food intolerance.

The main personal risk factor for bronchial asthma is atopy in the individual or his/her family. The most important risk factor is atopy in the family. Some genes related to concurrent atopy, Ig E response and asthma have been found. These genes are located on chromosomes 5, 11 and 14^{3,9,14,15}. Children whose parents do not have extrinsic asthma have an asthma prevalence of 8 %, which increases to 15 % with asthma in one parent and 28.6 % with asthma in both parents. The incidence of asthma in first-degree relatives is 3-6 times of normal². Of our patients, 1743 (57.6 %) had a history of atopy in the family making it an important risk factor for our patients as well.

Findings indicate that passive smoking increases the sensitivity of upper and lower respiratory airways, has a negative effect on lung function parameters and lung development and that is also increases symptoms and hyperreactivity in asthmatic children. Smoking at home seems to increase emergency service visits, number of attacks, hospital admissions and the dosage of the medication used^{14,16}. Although the role of passive exposure to cigarette smoke in the development of asthma is debatable, studies indicating that it increases the severity of asthma are becoming more convincing¹⁵. F. Demirel et al¹⁷ have reported the rate of passive smoking as 72.1 % for asthmatic children while this rate is 28 % in the USA¹⁸. 1626 (53.8 %) of our patients reported passive smoking and 1549 (51.2 %) reported cigarette smoke as one of the factors increasing the symptoms.

Exercise is a common trigger for asthma in children and young adults. Exercise increased symptoms in 754 (24.9 %) of our patients.

The symptoms increased in the spring and winter months in 2262 (74.7 %) patients and only in the winter months in 1195 (39.5 %) patients. This indicates that the symptoms are related to the increased pollen count in the spring and to the infections and air pollution in the winter.

Asthma in children and young adults is seen more often in cities while adult asthma is not affected by the place of residence. The asthma prevalence and mortality is increased in minorities living in financial difficulty in cities with inadequate health systems^{15,19}. There has been a significant increase in air pollution

in socioeconomically advanced or developing countries due to increased industrialization and urbanization. Correspondingly, 2807 (92.8 %) of our patients lived in the city.

Allergic sensitization is a risk factor for the development of an allergic disease. Exposure to allergens during the early stages of life make it easier for specific diseases to develop later on, possibly due to the developing immunological sensitivity. House dust mites, cockroaches, pollens, animal epithelium are the most important sources of allergens leading to sensitization in the early stages of life¹⁵. The bed, pillows and quilts are important sources for house mites. The most common material for the beds (1238, 41 %), pillows (1380, 45.6 %) and quilts (1188, 39.3 %) of our patients was wool. This indicates that wool beds, pillows and quilts are a factor in sensitization.

Animal fur was a significant cause of sensitization and 394 (13 %) of our patients had a pet in their house. Demirel et al¹⁷ have reported the percentage of those keeping a pet as 20 %. The percentage of those keeping a pet at home has been reported as 53 % in the USA¹⁸.

Ig E levels are high in 75-83 % of children with allergic asthma. However, a normal or low value does not eliminate the diagnosis of asthma. It is rare for children to have high Ig E levels without an allergic disease⁴. The average total Ig E level of our patients was high at 402.7 ± 646 IU/ml (min: 1- max: 4000).

Specific Ig E determination in the blood is less sensitive, more expensive and more time-consuming than the skin prick test but less traumatic. The skin reactivity to histamine and allergens is low in infants and young children and this is therefore a preferred method in young children, those with extensive eczema or dermographism and children who carry a risk of anaphylaxis due to hypersensitivity⁴. The test was positive in 325 (48 %) of the 625 patients that we tested with specific mix Ig E.

Aeroallergens, and especially in-house aeroallergens, lead to sensitization in many parts of the world. Mites, cockroaches and animal species are the most important in-house aeroallergens. The main aeroallergens outside the home environment are pollens and fungal spores²¹. House dust mites are important aeroallergens in many countries (8, 21-23). 1902 of our 3025 asthmatic patients had received the skin prick test while others did not receive the test because they were too young or because of other reasons. 1146 (60.9 %) of the 1902 patients receiving the skin prick test were atopic. The most common allergens were house dust mites, observed in 726 patients (63.3 %). Pollen allergy was second with 565 (49.3 %) patients.

Although there are many studies on asthma that have led to a better understanding of its physiology and major advances in its treatment its incidence is increasing. Asthma is also an important health problem in our country. New research on the epidemiology, risk factors and clinical characteristics of asthma will provide better information.

We emphasized the risk factors of a large number of patients, followed-up with a diagnosis of asthma, retrospectively. We believe a comprehensive approach considering all details of the disease is required when confronted with allergic patients.

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Treatment of pemphigus vulgaris. An overview in Mexico

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ABSTRACT

Pemphigus is an autoimmune skin disease that can present in a variety of forms and can prove challenging to manage and treat. An overview of the condition in Mexico is presented. Emphasis is placed on management of the condition, with description of the most commonly used treatments (glucocorticoids, azathioprine), the second line therapies (cyclosporine and mycophenolate mofetil), and additional alternative treatments (cyclophosphamide and dapsone).

Key words: Pemphigus. Pemphigus vulgaris, treatment. Steroids. Adjuvants.

INTRODUCTION

The term pemphigus encompasses a group of potentially fatal diseases characterized by blister-like skin and/or mucosal lesions (table I)^{1,2}. Pemphigus vulgaris (PV) is one of the more serious presentations that very often leads to serious patient conditions that are difficult to manage on an outpatient basis, and frequently requires intensive care³.

A close association has been observed between the disease and Major Histocompatibility Complex (MHC) class II antigens in certain ethnic groups such as those of Mediterranean origin that are susceptible to PV⁴.

The physiopathology of PV is characterized by the production of circulating antibodies targeted to desmoglein-3, and in some patients to desmoglein-1 (fig. 1). This in turn conditions the diagnostic options and monitorization of the course of the disease^{5,6}.

Importance is placed in this study on the existing treatment options, of which the most common are steroids, azathioprine, tetracycline, cyclophosphamide, mofetil mycophenolate, dapsone and methotrexate.

PEMPHIGUS VULGARIS

Clinically, PV is characterized by the appearance of blisters with subsequent ulceration on the skin and mucosal membranes (fig. 2). The condition often begins in the oral mucosa and rapidly spreads to the skin (fig. 3). The disease is infrequent, with no patient sex predilection, and exhibits two peak incidences in the third and sixth decades of life, respectively⁷. The diagnosis is based on clinical factors, though a histopathological study is practically mandatory (revealing intraepidermal blisters containing acantholytic cells) (fig. 4), along with direct immunofluorescence (DIF) evaluation (revealing the presence of IgG deposits in intraepidermal keratinocytes, with a honeycomb pattern) (fig. 5).

Treatment first aims to achieve disease remission, and this is frequently possible as a result of intensive therapy (often on an in-hospital basis). Such management is then followed by maintenance therapy to stabilize the disease with the administration of systemic medication in progressively decreasing doses.

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Table I
Classification of pemphigus

| |
|---|
| Superficial pemphigus |
| Foliateous pemphigus |
| Endemic (or <i>fogo salvagem</i>) |
| Erythematous or seborrheic pemphigus |
| Isolated |
| Associated to systemic lupus erythematosus (Senear-Usher) |
| Deep pemphigus |
| Pemphigus vulgaris |
| Pemphigus vegetans |
| Paraneoplastic pemphigus |

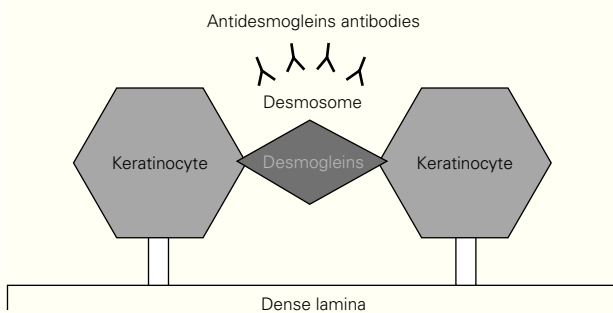


Figure 1.—Pathogenesis of pemphigus vulgaris.



Figure 2.—Presence of ulcerations on the face – some covered with blood crusts.

The principal systemic therapeutic options currently available in Mexico are described below. Their indications, contraindications and side effects are summarized in table II.



Figure 3.—Dissemination of the disease, with involvement of the chest. Note the characteristic ulcerations.

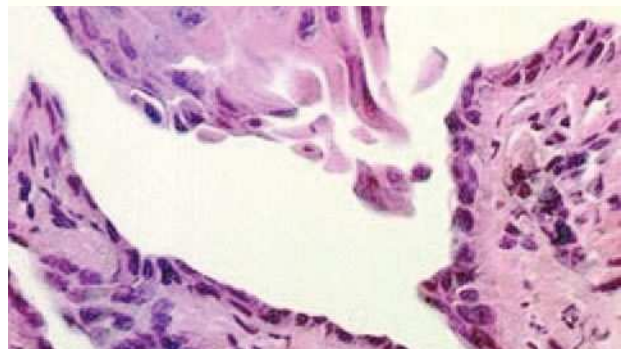


Figure 4.—Histological view, showing an intraepidermal blister containing acantholytic cells. Hematoxylin-eosin stain, 40x.

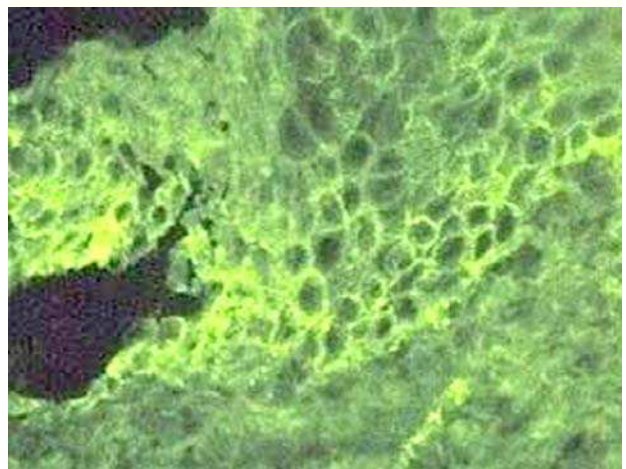


Figure 5.—Direct immunofluorescence labeling with IgG deposits among the intraepidermal keratinocytes, forming a honeycomb pattern.

Oral steroids

Oral steroids are a basic option for the management of PV in any phase of the disease, and since

Table II
Systemic treatments for pemphigus vulgaris

| |
|--|
| Steroids |
| Oral |
| Prednisone |
| Pulses |
| Methylprednisolone |
| Dexamethasone |
| Immunosuppressors and immunomodulators |
| Azathioprine |
| Methotrexate |
| Cyclophosphamide |
| Gold salts |
| Cyclosporine A |
| Chlorambucil |
| Mofetil mycophenolate |
| Intravenous immunoglobulin |
| Plasmapheresis |
| Extracorporeal phototherapy |
| Antibiotics |
| Tetracyclines |
| Dapsone |
| Others |
| Nicotinamide |
| Anticholinergic agents |

their introduction have contributed to improve patient survival^{8,9} – though it is well known that PV can improve even in the absence of treatment, with increased survival over the middle or long term⁹.

The benefits afforded by oral steroid use with or without the Lever scheme are great. At conventional doses, these drugs reduce blister outbreaks within 2-3 weeks¹⁰, with complete disease remission in up to 29 % of cases¹¹.

Prednisone dosing via the oral route is arbitrary, since different management schemes have been developed, and no general consensus has been reached over the best treatment option for PV. The drug dose is empirically adjusted to the severity of the disease, though in most cases a dose of 0.5-1 mg/kg body weight is prescribed, reaching 2 mg/kg/day as required¹².

Steroid dose reduction should be carried out gradually. In our practice we apply weekly 5-mg reductions to 20 mg, followed by weekly 2.5 mg reductions in an attempt to completely obviate the need for such medication while ensuring control of the disease^{4,12}.

Methylprednisolone or dexamethasone pulses

Steroid pulses have been widely applied to am-pullar diseases, and fundamentally to PV, to avoid the

complications and side effects of chronic daily oral steroid dosing¹³.

The term “pulse” refers to discontinuous intra-venous infusion of supratherapeutic drug doses in a short period of time¹⁴. Pulse therapy is recommend-ed as an adjuvant to the initial management plan for patients with more severe PV involvement¹⁵. Methyl-prednisolone (and dexamethasone) is the most com-monly intravenous glucocorticoid. The dose corre-sponding to each pulse has not been standardized, but ranges from 10-20 mg/kg in the case of methyl-prednisolone, and 2-5 mg/kg in the case of dexamethasone with a three-hour infusion in 500 ml of 5 % glucose solution. In this context, 500 mg of the for-mer and 100 mg of the latter medication are consid-ered equivalent to 625 mg of prednisone¹⁴.

The mechanism of action of the glucocorticoid pulses comprises the inhibition of acantholysis in-duced by IgG in PV, as a result of which the spread of keratinocyte deterioration is reduced. The maximum effect is recorded 3-5 days after administration – in agreement with the observation of animal studies¹⁶.

The utilization of these megadoses has revolution-ized the treatment of PV, for although such therapy is not the first choice management option, it almost al-ways improves patient prognosis when prescribed on an opportune basis.

ADJUVANT DRUGS

The treatment options for PV include substances known as adjuvant drugs, which are agents that sup-port the effect of steroids administered fundamen-tally via the oral route. Some of these adjuvants act as “steroid sparing agents”. The principal represen-tatives are azathioprine and cyclophosphamide. Some of the characteristics of these drug substances will be dealt with briefly.

Azathioprine

Azathioprine is one of the most common adjuvants to PV therapy, and has been shown to be effective in application to many diseases apart from PV, such as bullous pemphigoid and atopic dermatitis^{17,18}.

While its utility is increasingly acknowledged, the principal side effect of azathioprine (potentially severe myelosuppression) has led to the recommendation of thiopurine methyltransferase testing as a predictor of azathioprine-mediated myelosuppression¹⁸.

The administration of azathioprine as adjuvant therapy in PV increases percentage disease remis-sion up to 45 %. While the drug can be administered

as sole therapy, its use in monotherapy (and even more as initial treatment) is not advised, due to the frequency of side effects involved¹⁹.

Azathioprine offers better results when administered at a dose of 1-3 mg/kg for 6 weeks. After this period of treatment, bone marrow function must be carefully monitored²⁰.

Oral cyclophosphamide

The use of oral cyclophosphamide as steroid-sparing adjuvant therapy in PV has been documented in many reviews published in the literature²¹⁻²³. The use of oral cyclophosphamide in monotherapy entails many side effects such as hematuria, overinfection and bladder carcinoma, and remission takes too long to achieve (8 months). In this period of time, the aforementioned side effects very often appear. Consequently, oral cyclophosphamide is not recommended as monotherapy or as a first treatment option²⁴.

Pulses of cyclophosphamide with methylprednisolone or dexamethasone

PV treatment in the form of mixed pulses or DCP (dexamethasone-cyclophosphamide pulses) has been shown to be effective in application to recurrent PV and refractory presentations of the disease. Introduced by Pasricha in 1988²⁵, this therapeutic modality has yielded good results in many patients to date²⁶⁻²⁸.

The DCP scheme consists of the monthly administration on intravenous dexamethasone (136 mg, which is adjusted to 100 mg for easier use) during three consecutive days, with the addition on the second day of a 500-mg pulse of cyclophosphamide. Posteriorly, 50 mg of oral cyclophosphamide or oral prednisone 0.5-1 mg/kg/day is started, until partial remission is achieved (after about 6 months) – the oral dose being continued for up to one year, when complete remission is achieved²⁷.

The number of DCPs required to induce clinical remission varies according to the severity of PV and the complications of the disease. In a key study on treatment it was considered that 49 % of patients require 6 or fewer pulses to achieve clinical remission – though up to 11 % require more than two years of pulse therapy. On the other hand, over 60 % of the patients achieve complete remission (for over two years in 40 % of cases, and for over 5 years in 15 %)²⁹.

Among the most common side effects of DCP, mention should be made of some mild intensity dis-

orders such as facial rubor, hiccup, diffuse alopecia, insomnia, headache, joint pain, and numbness of the feet. Other effects manifesting with greater intensity comprise hypertension, hyperglycemia, blurry vision with the development of glaucoma, and posterior subcapsular cataracts, palpitations, swelling of the legs, malaise and asthenia. Serious side effects in turn comprise seizures, apnea and even death. The effects tend to be more frequent between 1-2 weeks after the therapeutic pulse³⁰.

Despite the above effects, the DCP scheme constitutes only a somewhat more aggressive alternative to conventional therapy, and is defined in the third line of treatment for PV. Apparently, it offers prolonged control of the disease, and thus an improved patient prognosis.

Mofetil mycophenolate

Mycophenolic acid has been used for the management of psoriasis during the past three decades; at present, it has been re-formulated as mofetil mycophenolate and is used as an immunosuppressor in transplantation patients (Food and Drug Administration (FDA) 1995)³¹. In recent years it has been found to be useful in the management of gangrenous pyoderma, ampullar lichen planus, systemic lupus erythematosus (SLE) and PV³².

The current uses of mycophenolate in PV have focused on active and steroid-refractory presentations of the disease. When administered as coadjuvant, the drug has been shown to reduce the activity of PV³³. It has been reported that complete remission can be achieved after 9 months of treatment in up to 70 % of cases, apparently with only minimal side effects^{34,35}.

Although it was initially suggested that the drug could be used in monotherapy with favorable effects over more than 6 months, it is now believed that mycophenolate is better used as adjuvant in cases of active PV – yielding superior results and shorter recovery times when administered in this manner^{36,37}.

Mycophenolate is recommended for recalcitrant cases, or in situations where azathioprine or cyclophosphamide cannot be used³⁸.

Methotrexate

While the utility of methotrexate as monotherapy for PV has always been the subject of discussion, it is most widely accepted as an adjuvant. In effect, the combination of high doses of methotrexate (up to 125 mg a week are advised) with prednisone

0.5-1 mg/kg/day appears to bring the disease under control within 6 months³⁹.

Despite evidence of the effectiveness of methotrexate as an adjuvant to therapy in patients with PV, in practice it is difficult to use because of its side effects (mainly at hepatic level). These effects are more likely when such high doses of the drug are used^{38,39}.

Thus, methotrexate as adjuvant is reserved for those cases of PV in which it is not possible to use some other adjuvant substance such as azathioprine or cyclophosphamide³⁸.

Tetracycline and nicotinamide

The combination of these two drugs has been tested not only in application to PV but also to patients with foliaceous pemphigus^{40,41}, discoid lupus erythematosus⁴², pemphigus vegetans⁴³, linear IgA dermatosis⁴⁴ and bullous pemphigoid⁴⁵.

The combination has been shown to be useful for the treatment of both cutaneous⁴⁶ and oral PV⁴⁷.

The usually recommended posology is 1.5 g of nicotinamide and about 2 g of tetracycline a day⁴⁸, or 50-200 mg of minocycline⁴⁹. Adequate treatment responses have been reported with this regimen, though the existing results are not conclusive. In any case, this combination gives rise to few side effects when used as adjuvant therapy, and therefore can be considered in situations where it is not possible to use azathioprine or cyclophosphamide.

Dapsone

Dapsone is one of the most useful agents in application to many diseases, including leprosy. There have been isolated reports on the utility of dapsone in application to PV. In this context, the drug has been postulated to control the levels of antibodies in PV, though the results of an experimental study suggest that dapsone exerts no effects upon serum antibody levels in PV⁵⁰. Despite this, case studies have been made involving the use of this drug. It has not been shown to be of use in monotherapy, but can be used as an adjuvant. In any case, the data available to date are not conclusive⁵¹⁻⁵³.

OTHER TREATMENTS

Many other treatments for PV are also under study, and some have demonstrated good efficacy compared with steroid treatment. Some of these

therapies, such as gold salts⁵⁴, chlorambucil⁵⁵ and cyclosporine⁵⁶, are used as adjuvants in the treatment of PV, in association to prednisone or (as in the case of cyclosporine) for the control of disease remission. Such therapies are not recommended as first choice management options, however. Other treatments such as intravenous immunoglobulins⁵⁷, plasmapheresis⁵⁸ and extracorporeal photopheresis⁵⁹ have been more extensively documented. Their application in industrialized countries appears to be frequent, though only in cases that prove resistant to conventional treatment⁶⁰, or in relapsing disease. As such, they are viewed as last choice options in the management of PV.

DISCUSSION

While many treatments have been developed for pemphigus vulgaris (PV), none have been shown to offer absolute efficacy in controlling the disease. The management of choice is steroid therapy via the oral or intravenous route, which offers an adequate response and favorably modifies the prognosis.

The drugs described above are only part of the repertoire currently available for the management of PV. The more salient options have been described, in view of their ease of use and accessibility in this country – though in the not too distant future we hope also to be able to introduce photodynamic therapy and specific plasmapheresis, among other therapeutic options.

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Allergy to cloxacillin with normal tolerance to amoxicillin and cefuroxime

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ABSTRACT

Background: Cloxacillin is a semisynthetic penicillin widely used in nonmethicillin resistant *Staphylococcus aureus* infections. Several hypersensitivity reactions to cloxacillin have been reported, although IgE-mediated allergic reactions to the drug are rare and there is little information about possible tolerance to other semisynthetic penicillins or cephalosporins in patients with cloxacillin allergy. We present 2 patients with demonstrated IgE-mediated allergy to cloxacillin and tolerance to amoxicillin and cefuroxime.

Case reports: Case 1. A 47-year-old woman began treatment with cloxacillin due to acute cellulitis. After ingesting 500 mg of the drug, she experienced generalized maculopapular eruption and facial angioedema. Case 2. A 55-year-old woman presented an episode of acute urticaria and labial angioedema 60 minutes after ingesting 500 mg of cloxacillin for a skin abscess.

Methods and results: Skin prick tests were positive to cloxacillin in case 1 and negative in case 2. However, an intradermal test was positive to cloxacillin (2 mg/ml) in case 2. Simple-blind oral challenge tests with amoxicillin (1 g) and cefuroxime (500 mg) were well-tolerated by both patients.

Conclusions: We present 2 patients allergic to cloxacillin with normal tolerance to other betalactam antibiotics, confirming that cross-reactivity among these antibiotics seems to be uncommon. Complete allergy study, including an oral challenge test, should be considered in these patients.

Key words: Amoxicillin. Cloxacillin. Hypersensitivity. Tolerance. Allergy.

INTRODUCTION

Cloxacillin is a semisynthetic penicillinase-resistant penicillin widely used in non-methicillin resistant *Staphylococcus aureus* infections. Most frequent side effects of cloxacillin are gastro-intestinal manifestations like vomiting or diarrhea, although there have been reported different hypersensitivity reactions^{1,2}. However, IgE-mediated allergic reactions to the drug are rare and there is little previously reported information about the management of allergic patients to cloxacillin in order to demonstrate tolerance to other semi-synthetic penicillins or cephalosporins³. We present two different patients with demonstrated IgE-mediated allergy to cloxacillin with normal tolerance to amoxicillin and cefuroxime.

CASE REPORT

Case 1. A 47-year-old woman diagnosed of chronic lymphedema after a radical mastectomy, began treatment with cloxacillin due to an acute cellulitis.

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Shortly after the intake of *Orbenin*® 500 mg (Glaxo-SmithKline-Beecham, Toledo, Spain) she experienced generalized pruritic maculo-papular eruption, hives and angioedema of the face.

Case 2. A 55-year-old woman, with a personal background of smoking, who had taken cloxacillin 500 mg for an abscess involving the bulbous end of a finger. 60 minutes after the intake of the first pill, she presented an episode of acute urticaria and labial angioedema. Both patients were completely recovered after the administration of parenteral treatment (40 mg of 6-methyl-prednisolone and intravenous diphenhydramine). They both had previously taken cloxacillin without any reaction and they had not eaten any food or had not been doing exercise in the previous 4 hours.

ALLERGIC STUDY

In the Allergy Unit at our Hospital, Skin prick tests (SPT) with benzylpenicillin (10.000 U/ml), major and minor determinants mixture of benzylpenicillin (BPO and MDM, Diater, Madrid, Spain), cloxacillin (20 mg/ml), amoxicillin (20 mg/ml) and cefuroxime (200 mg/ml) were performed 30 days later according to standardized procedures⁴. If they were negative, intradermal tests were carried out. Prick test was positive only to cloxacillin in case 1 with a mean diameter of the obtained wheal of 5 mm. Prick tests were all negative in case 2, but the intradermal test was positive to cloxacillin (2 mg/ml) presenting a 14 mm wheal of mean diameter, double that of the histamine wheal (1 mg/ml) at the 20 min. reading. All the other tests were negative and no positive results were obtained at the 24 h reading. Simple-blind oral challenge tests with increasing doses until an accumulative dose of amoxicillin (1 g) and cefuroxime (500 mg) were performed, being well-tolerated in both patients.

DISCUSSION

Adverse reactions to betalactam antibiotics constitute a major hazard in medical practice. Although the use of cloxacillin is widely extended, data of immediate allergic reactions after using this drug are very

scarce. It could be explained due to it is not frequently involved in allergic reactions⁵ but there could exist an insufficient communication that leads to remain cloxacillin allergic reactions to be underdiagnosed. This fact could explain the lack of reported experience in clinical management of those patients. There is a general tendency to avoid using other betalactam antibiotics due to that there are similarities in chemical structure between them to justify a cross-reactivity mechanism between cloxacillin and amoxicillin or cephalosporins. However, if we remember that many of the allergic patients to penicillin or amoxicillin tolerate any cephalosporin, the allergologist might be asked to find out which of the other betalactam antibiotic could be used as secure alternatives in cloxacillin allergic patients. We should not forget that previous observations indicate that, in some instances, subjects allergic to cloxacillin may experience an allergic reaction after taking the drug orally but have good tolerance after being administered the same drug by parenteral route⁶.

In conclusion, we present two different patients allergic to cloxacillin with normal tolerance to other betalactam antibiotics, confirming that cross-reactivity seems to be uncommon among those tested antibiotics. A complete allergologic study, including an oral challenge test, should be considered in these patients.

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Patch tests for diagnosis of delayed hypersensitivity to cephalosporins

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ABSTRACT

Background: Few studies have reported delayed hypersensitivity reactions to systemically administered cephalosporins. The diagnostic procedures and extracts for these reactions are not standardized, and little is known about the extent of cross reactivity among different cephalosporins.

Cases report: We report 2 cases of delayed hypersensitivity reactions due to cephalosporins presenting as erythrodermia.

Case 1. An 80-year-old man developed generalized pruritus and erythema 2-3 days after starting treatment with cefuroxime. The drug was stopped and antihistamines and corticosteroids were administered. The patient improved 5-6 days later, and mild superficial desquamation was observed.

Case 2. A 66-year-old woman experienced similar symptoms 4-5 days after beginning cefazolin. She reported a similar reaction with ceftazidime 8 years previously.

Methods and results: Skin prick tests and specific IgE against penicillin G and V, amoxicillin, ampicillin

and cephalosporins were negative. Intradermal tests with ceftazidime and cefazolin were positive in case 2 at delayed reading. Patch tests using benzylpenicillin, ampicillin, amoxicillin, several cephalosporins, aztreonam and imipenem were positive to all the cephalosporins tested (at 48 and 96 hours) and were negative to the other betalactams. Controlled administration of amoxicillin, benzylpenicillin, aztreonam and imipenem was well tolerated by both patients.

Conclusions: 1) We report 2 cases of delayed hypersensitivity reactions due to cephalosporins presenting as erythrodermia. 2) Epicutaneous tests were useful for diagnosis. 3) Both patients tested positive to all cephalosporins and negative to other betalactams.

Key words: Cephalosporins. Cross reactivity. Delayed hypersensitivity. Erythrodermia. Patch tests.

INTRODUCTION

Few studies have reported delayed hypersensitivity reactions to systemically administered cephalosporins. The most typical clinical manifestation is a maculopapular rash¹⁻⁶. Diagnostic procedure and extracts for these reactions are not standardized, and little is known about the extent of crossreactivity among different cephalosporins. We report 2 cases of delayed reactions due to cephalosporins suggesting erythrodermia, and confirmed by patch tests. We have not found this clinical presentation in the literature for delayed reactions with cephalosporins.

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CASE REPORTS

Case 1

A 80-year-old man was treated orally with cefuroxime (250 mg twice a day) because of a respiratory infection. Two days after starting this treatment, he developed generalized pruritus and erythema involving all the skin. He was admitted to hospital. Laboratory testing revealed leukocytosis ($15400/\text{mm}^3$) with eosinophilia (9 %). This drug was stopped and antihistamines and corticosteroids were administered. The patient improved slowly, observing a slightly superficial desquamation 5-6 days later. The complete resolution of the symptoms occurred in 10 days. A skin biopsy at the second day of the eruption showed moderated acanthosis and hyperkeratosis, and lymphohistiocytic infiltrate in the dermis with numerous eosinophils. The patient had not presented adverse reactions to drugs previously and he had no history of allergic diseases. He did not remember if he had taken cefuroxime before, and he has avoided betalactams after the reaction.

Case 2

A 66-year-old woman began treatment with cefazolin i.m. (500 mg/12 h) and metamizole (500 mg/8 h orally) after the implantation of a knee prosthesis. Forty-eight hours later she presented with a pruritic rash that started on her trunk and then spread to her entire cutaneous surface, including her palms and

soles. Physical examination at fourth day revealed widespread fine scaling and diffuse erythema. She gradually improved after discontinuation of both drugs and systemic administration of antihistamines and corticosteroids in 7 days. She had taken cephalosporins 8 years before and she remembered a similar reaction with ceftazidime. She has tolerated amoxycillin and metamizole after the last episode without problems. The patient had no history of skin disorders or atopy.

METHODS AND RESULTS

Two to four months after the reactions, we studied both patients after obtaining informed consent. Prick tests with penicillin G (10,000 UI/ml), amoxycillin (20 mg/ml), ampicillin (20 mg/ml) and cephalosporins (ceftazidime, cefazolin, cefuroxime, cefonicid, cefotaxime and cefepime at 2 mg/ml)⁷ were negative. No specific IgE antibodies against the same allergens were found. Prick and intradermal tests with penicillin determinants (PPL and MDM) proved negative. Intradermal tests with ceftazidime and cefazolin (2 mg/ml) were positive in case 2 at delaying reading (48 h). Patch tests (20 % pet) on healthy back skin using benzylpenicillin, ampicillin, amoxycillin, aztreonam and imipenem were negative (at 48 and 96 hours). Patch tests with cephalosporins were performed with commercialized forms diluted at 20 % in pet (patient 1)⁸ or using the marketed preparations *as is* (patient 2)^{3,4} on the back (normal skin) using Curatest® (Lohmann Rauscher, Germany) covered by Mefix® (Mölnlycke Health Care AB, Sweden) with 48 hours of occlusion. All of them resulted positive (table I), but negative in 10 control patients. Controlled administration of amoxycillin (750 mg orally), benzylpenicillin (1.000.000 UI im), aztreonam (500 mg im) and imipenem (250 mg im) on different days was well tolerated for both patients.

DISCUSSION

Nonimmediate reactions are those occurring more than 1 hour after drug administration. The main nonimmediate reactions are maculopapular or morbilliform exanthems, although other reactions are possible as urticaria/angioedema, exfoliative dermatitis, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc. The mechanisms involved in these reactions seem to be heterogeneous⁷. Regarding cephalosporins, only a few articles report about these reactions and in all of them maculopapular rashes are observed¹⁻⁶.

Table I

Patch tests with cephalosporins

| Drug | Patient 1 | Patient 2 | Results (48 and 96 h) |
|-------------|-----------|------------|--------------------------|
| Cefazolin | 20 % pet | 200 mg/ml* | positive |
| Cefalexin | 20 % pet | np | positive |
| Cefaclor | 20 % pet | np | positive |
| Cefuroxime | 20 % pet | 125 mg/ml* | positive |
| Cefoxitine | 20 % pet | np | positive |
| Cefonicid | np | 200 mg/ml* | positive |
| Ceftriaxone | 20 % pet | np | positive |
| Cefixime | 20 % pet | np | positive |
| Cefminox | 20 % pet | np | positive |
| Cefepime | 20 % pet | 200 mg/ml* | positive |
| Cefotaxime | 20 % pet | 200 mg/ml* | positive |
| Ceftazidime | 20 % pet | 200 mg/ml* | positive |

*Commercialized form *as is*.

pet: petrolatum; np: not performed.

We describe 2 patients who suffered an erythrodermic reaction several days after beginning cephalosporin therapy (cefuroxime in the case 1, and cefazolin and ceftazidime in the case 2). We have not found in the literature previous cases reporting delayed hypersensitivity reactions with ceftazidime, neither erythrodermia as clinical presentation of delayed reactions to cephalosporins.

Our cases, as well as others from other authors, demonstrate the usefulness and safety of patch tests in the diagnosis of delayed hypersensitivity to cephalosporins. Moreover, patch tests prove useful to detect or rule out cross-reactivity to other betalactam drugs and among cephalosporins^{1-5,7}. As in other papers, our patients showed positivity to cephalosporins with different side chains but no to other betalactams^{3,4}. Romano et al suggest that the response could be directed toward a determinant shared by cephalosporins (probably at the core portion of the molecule, rather than at their side chains), but not by other betalactams⁴. On the contrary, Martin et al find a positive result only for the cephalosporin responsible of the reaction (cefonicid)². Studies on the cephalosporins as allergens are scarce, and very few have been dedicated to the determinants responsible for allergic reactions. The dihydrothiazine ring and side chains have been identified as antigenic structures, but the questions on allergenic cross-reactivities among cephalosporins, and between cephalosporins and penicillins cannot be answered with confidence.

In summary: 1) We report 2 cases of delayed hypersensitivity reactions due to cephalosporins pre-

senting as erythrodermia. 2) Epicutaneous tests have been useful for the diagnosis. 3) Both patients proved positive to all cephalosporins and negative to other betalactams.

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INFORMATION

XXX CONGRESO DE LA SOCIEDAD ESPAÑOLA DE INMUNOLOGIA CLINICA Y ALERGOLOGIA PEDIÁTRICA (SEICAP)

Tendrá lugar en Sitges (Barcelona), los días 18 a 20 de mayo de 2006, con el siguiente Programa:

Jueves 18.

Talleres y Seminarios: *Pruebas del parche. Manejo práctico del niño con sospecha de alergia a fármacos. Inmunoterapia en pediatría. Enfermedades alérgicas infantiles: técnicas de educación.* Reunión de los Grupos de Trabajo.

Viernes 19.

Mesa redonda:

Marcadores de la inflamación, moderadora Dra. M.^a T. Giner. *Marcadores de la inflamación en la enfermedad alérgica*, Dra. T. Montero. *Lavado broncoalveolar y esputo inducido*, Dra. M. Bosque. *Determinación por métodos no invasivos*, Dr. J. I. Sierra.

Sábado 20.

Mesa redonda:

Avances en el tratamiento con base inmunológica. Moderador Dr. J. M. García. *Inmunomoduladores en inmunodeficiencias*, Dra. T. Español. *Inmunomoduladores e inmunosupresores en enfermedades alérgicas y autoinmunes*, Dra. M. A. Martín Mateos. *Reconstitución inmunológica: trasplante de proge-*

nitores hematopoyéticos y terapia génica, Dr. L. Madero.

Este mismo día se celebrará la **II Reunión de Enfermería de Alergia Pediátrica** con el tema Avances en alergia pediátrica: técnicas de enfermería y educación sanitaria.

Los días 18 y 19 tendrán lugar los siguientes **Talleres para pediatras de atención primaria:** *Alimentación del lactante alérgico*, Dra. M. Piquer. *Diagnóstico diferencial del asma ¿qué es asma y qué no lo es?*, Dr. S. Nevot. *Manejo práctico de la inmunoterapia*, Dr. M. Ibero. *Actitud a seguir ante una sospecha de inmunodeficiencia*, Dr. A. Blanco.

Están previstas **Sesiones de Comunicaciones libres y de Pósteres**, para los que pueden enviarse los resúmenes hasta el día 15 de febrero por correo electrónico (seicap06comunicaciones@viajeseci.es).

Información y registros:

Secretaría técnica. Viajes El Corte Inglés. División de Congresos. Gran Vía Fernando el Católico 3 bajo. 46008 Valencia. Tf.º 963107189. Fax 963411046. seicap06inscripciones@viajeseci.es.

XXX JORNADAS ANUALES DE LA AAAeIC, XIX CONGRESO NACIONAL de la AAAeIC y XIV CONGRESO LATINOAMERICANO DE ALERGIA, ASMA E INMUNOLOGIA

Se desarrollarán de forma conjunta del 17 al 20 de agosto de 2006 en el Hotel Inter-Continental en Buenos Aires (Argentina). El objeto de estos congresos es proveer a los profesionales asistentes de conocimientos actualizados en los campos del asma, alergia e inmunología. Participarán profesionales alergistas e inmunólogos de la Argentina y del resto de Latinoamérica y profesionales de especialidades de la salud relacionados, como también se cursarán invitaciones a destacados especialistas extranjeros.

Información:

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