Allergy to Penicillin

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SUMMARY

Since Fleming discovered Penicillin, it has been one of the most widely used antibiotics due to the combination of its bactericide efficiency, low cost and scare side effects.

Among the latter, the most frequent ones that restrict its use in the common clinical practice are precisely the phenomena of both real or suspected hypersensitivity. Not in vain does penicillin head the list of drugs capable of precipitating allergic reactions, estimating that these can affect 2% of the general population at some moment in their lifetime. An idea of the real importance of this problem can be given with the observation that, for every 100,000 penicillin injections there are between 10 and 40 hypersensitivity reactions, 2 of which can be fatal anaphylactic reactions. Thus, only in the United States of America, some 300 persons per year die from this cause.

We will explain some features of the hypersensitivity to penicillins in the following, concentrating on its pathogeny, clinical manifestations and diagnostic possibilities.

PATHOGENY

Penicillin is a low molecular weight molecule, of about 300 Daltons, and thus is incapable of precipitating an immune response by itself. It must, therefore, bind to a high weight molecular molecule, generally a protein, that will act as a carrier, the hapten-carrier complex being the truly immunogenic one. From this, the production or non-production of an immune response and the nature of this response will depend on both the features of the hapten and the carrier as well as the characteristics of the individual's immunological response.

Penicillin, in its native state, lacks the free radicals necessary to securely bind, by covalent linkages, with the corresponding macromolecule. Thus, there arises the importance of knowing its metabolic routes, since it is through these that the capacity of functioning as a hapten is acquired. Figure 1 shows a summary of the principal routes of metabolization of penicillin, as well as both its main major and minor antigenic determinations that are truly responsible for the existence of the hypersensitivity reactions of these.

ANTIGENIC DETERMINANTS OF PENICILLIN

The antigenic determinants of penicillin can be classified as major and minor (Table I). Each one of them is associated to the preferential development of one type of immune response that gives rise to different types of clinical manifestations (Table II).

Benzyl-penicilloyl:

It is estimated that 95% of the penicillin administrated to a subject is capable of binding to a carrier through a beta-lactam ring, which is made up of a non-polar phenylacetamide nucleus and a thiazolidine group with carboxyl endings, thus forming benzyl-penicilloyl (BPO). This is the best characterized antigenic determinant, against which most of the synthesized antibodies are directed in both man and animal. That is why it is considered the major antigen determinant. It basically gives rise to the production of the IgG and IgM antibodies that mediate the accelerated or retarded urticarial reactions.

Minor antigenic determinants

The minor antigenic determinants are formed in much lesser quantities. Penicillenate, penicillamine, polypenicoyl, penaldate, benzyl-penicilloic acid and penalmadic acid stand out. Basically, they induce IgE synthesis and are the main responsible agents of the immediate reactions, urticaria, angioedema,

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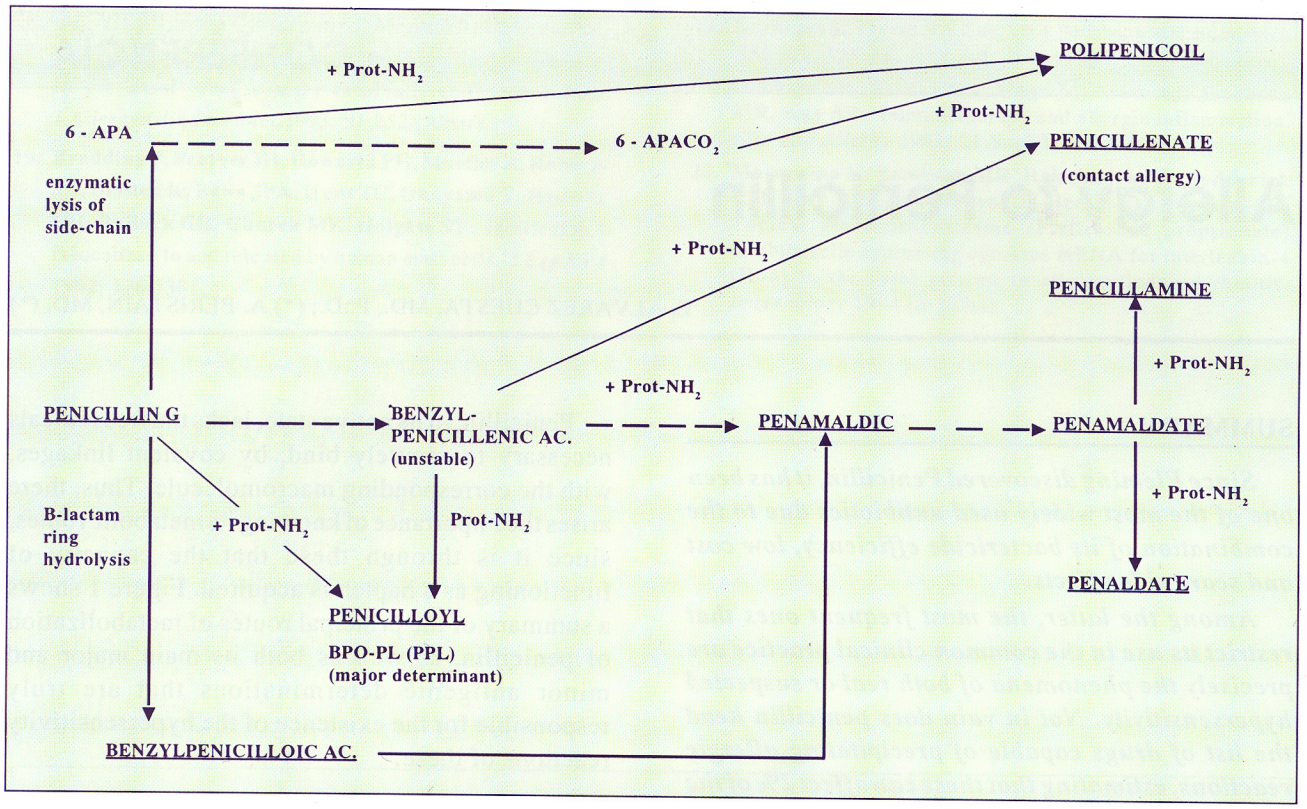

Figure 1 - Penicillin metabolism

bronchospasm, that can give rise to anaphylactic shock, and to a lesser degree, to the accelerated reactions.

Table I

ANTIGENIC DETERMINANTS OF PENICILLIN

1. **Major antigenic determinant**
   - **Benzyl-penicilloyl (BPO)**
2. **Minor antigenic determinants**
   - **Penicillenate**
   - **Penicillamine**
   - **Polypenicoyl**
   - **Penaldate**
   - **Benzyl-penicilloic acid**
   - **Penalmadic acid**
3. **Other antigens:**
   - **Impurities**
   - **Penicillin polymers**

Other possible antigens

- ***Impurities:*** These are basically exogenous proteins that appear in the process of penicillin production. It seems that they are capable of binding to benzyl-penicilloyl groups, thus acquiring immunogenic capacity. Given the improvements introduced into the manufacturing process, the concentration of these impurities is lesser and lesser, and thus their clinical importance is decreasing.

Table II

PATHOGENY OF THE ALLERGY TO PENICILLIN

Immunology of the reactions to penicillin

TYPE OF REACTIONS ACCORDING TO CLINICAL PICTURE		ANTIGEN	ANTIBODY	TYPE OF REACTION GEL & COOMBS
anaphylactic		minor determinants	IgE	I
accelerated reactions		major determinants	IgE	I
late reactions	Hemolysis	BPO fixed to the red cell membrane	IgG, IgM	II
	Interstitial Nephritis	BPO fixed to the tubular membrane	IgG, IgM	II
	Serum Sickness	major determinants	IgG, IgM	III
	Maculopapular Rash	BPO?	IgM?	
				delayed Hypersensitivity

- ***Penicillin polymers:*** It seems that these have the same specificity as the penicilloyl determinant.

CLINICAL MANIFESTATIONS

The clinical manifestations can be quite variable depending on the mechanism involved. Their approximate frequency is shown in Table III:

According to Levine [1], they can be classified in function of their appearance in time in:

- Immediate reactions.
- Accelerated reactions.
- Late reactions.

Table III

CLINICAL PICTURES: FREQUENCY OF APPEARANCE

URTICARIA	46%
ANGIOEDEMA	
GENERALIZED EXANTHEMA	17%
HYPOTENSION	12%
SERUM DISEASE	10%
CONTACT DERMATITIS	3%
BLOOD DYSCRASIA	32%
PRURITUS	2%
ASTHMA	0.7%

1. ***Immediate reactions:***
These occur during the first hour after administering the drug. The most frequent manifestation is urticaria, with or without angioedema, this being followed by hypotension, that has the greatest vital risk since it can end up in frank anaphylactic shock, and by wheezing dyspnea.
They result from the activation of the mastocytes and/or circulating basophils by the union of the antigen with the specific IgE located in their respective membranes. In most of the cases, the responsible antibodies are directed against the minor determinants of the penicillin, although at times they can be against the BPO [2]. In principle, this is paradoxical, since the synthesis of specific IgE against BPO is estimated to be five times greater than against the minor determinants. In an attempt to explain this situation, it has been postulated that the presence of the antigen in very small quantities - as is the case of the minor antigenic determinants - would give rise to the synthesis of a very high specific IgE affinity that would not be counterbalanced by the presence of the specific IgG blocker antibodies since these would need greater quantities of circulating antigen for their synthesis. The BPO, present in greater quantities, would have a clearer IgE response but a lower affinity, together with the synthesis of specific IgG blockers.

2. ***Accelerated reactions:***
These take place between one to 72 hours after the administration of the penicillin. They are basically represented by urticarial/angioedema type reactions and other exanthematic eruptions. They seem to be mediated by specific IgE antibodies against BPO, present at the onset of the treatment with the drug. They sometime disappear even though the antibiotic treatment is continued, this having been seen to temporally correlated to an increase in the concentraton of specific IgG against BPO.

3. ***Late reactions:***
They occur from the third day after the onset of the treatment with the penicillin. The most representative manifestations are exanthematic eruptions, although in this case, the clinical as well as physiopathological variety (Table II) is great. Thus, the urticaria with or without angioedema, dermatitis exfoliative, Stevens-Johnson's syndrome, drug fever and serum disease are also typical.
Other manifestations, much less frequent, include the interstitial nephritis, hepatitis, blood dyscrasia (neutropenias, thrombocytopenias and hemolytic anemias), pulmonary infiltrative pathology and vasculitis, that can even develop into lupoid reactions.

DIAGNOSTIC TESTS

For many years, all those subjects who reported a clinical history of adverse reaction compatible with penicillin were considered to be allergic to penicillin. Already by 1969, Levine [3] had stated that any of the "allergic" subjects to penicillin could tolerate it without important problems. Since then, this overdiagnosis has been confirmed in several occasions. [4, 5]

Among the reasons explaining why a subject who had previously presented a typical reaction to penicillin can later tolerate it, there are two that stand out:

- the symptoms that had been considered to be allergic ones were really produced by the original infection.
- the subject had lost his sensitivity to the medication. [6]

Given that the clinical history is not sufficient to reach an unfailing diagnosis of hypersensitivity to penicillin, it is necessary to develop other tests that complemented it so as to detect those patients who truly have a risk of developing a new allergic reaction after re-exposure to penicillin. To do so, we can count on a series of "*in vivo*" and "*in vitro*" tests (Table IV), some of which we will comment on.

Table IV

DIAGNOSTIC TECHNIQUES

- "IN VIVO" TEST:
  - SKIN TEST
  - SPECIFIC PROVOCATION TEST
- "IN VITRO" TEST:
  - RAST
  - OPTIC BASOPHIL DEGRANULATION

Skin tests

Skin tests are indicated in those subjects having a previous history of hypersensitivity reaction after the administration of penicillin that are susceptible of having been IgE mediated. Therefore, they have no predictive value in serum disease, cytopenias, dermatitis exfoliative, interstitial nephritis, drug fever or maculopapular rash.

The following products are commercialized:

- Penicilloyl polylysine (PPL): synthetic conjugate of BPO with a non- immunogenic carrier.
- Disodic benzyl-penicilloate, representing the minor antigenic determinants (MDM).
- Penicillin G.

In general, the skin test with PPL detects between 35% and 75% of the subjects allergic to penicillin, its sensitivity being increased if the minor antigenic determinants and penicillin G are also tested. [7,8]

We use undiluted PPL, in a concentration of 6×10^5 M =, benzyl-penicilloate up to a concentration of 0.5 mg/dl and penicillin G up to 10,000 U/ml for the skin tests. The concentration used at onset and its subsequent doses depends on the characteristics of the clinical history. We always begin with the prick test, and if this is negative, we then use the intradermoreaction. We evaluate both techniques according to that established in the international literature. [9]

In our experience [7,8], the effectiveness of the skin tests in predicting the tolerance to the re-exposure to penicillin (negative predictive value) is 97%. The remaining 3% presented reactions that at no time were life threatening. On the contrary, a positive skin test strongly suggests non-tolerance to the readministration of penicillin (high positive predictive value).

Regarding the safety of this technique, in our experience [10] only 0.4% of the patients presented a slight pruriginous urticaria with MDM or penicillin G, that was easily controlled with the normal medication. In any case, as three cases of death have been described with this technique [11], we recommend that the tests only be used in the presence of a qualified allergologist and after suspension of drugs that may strengthen the anaphylactic reactions (beta--blockers, for example).

All things considered, the skin tests with PPL, MDM and penicillin G, done by experienced personnel, are a rapid, safe and effective method to predict the risk of suffering an allergic reaction to the readministration of penicillin.

Determination of specif IgE: RAST technique

This is a solid phase radioimmunoassay technique described by Wide and Juhlin in 1971 [12]. This technique has several problems in the diagnosis of hypersensitivity to medicaments in general and therefore applicable to the diagnosis of allergy to penicillin: [13]

- As its nature is a non-protein antigen and therefore it lacks amine groups, it has difficulties in its linkage to the solid phase.
- It is difficult to know exactly what transformations the drug undergoes in the organism as well as the exact structure of the hapten--carrier complex that will be needed to bind to the solid phase.

It has some advantages regarding the skin tests:

- The allergen is stable in the solid phase.
- They are preferable to the skin tests in patients with dermographism, extended dermatitis and in general in all the occasions in which the former tests are not possible.
- The results are quantitative, and therefore, easily comparable.

The main disadvantages are:

- Its specificity [7, 13] is less than that of the skin tests.
- It is an expensive technique in relation to the "*in vivo*" studies.
- It is only possible to detect abnormalities with the major antigenic determinant since none of the minor ones are commercialized, the latter, as we have indicated, being the main cause of anaphylactic shock.

In general, it is a sensitive and specific method [7, 13], although its results are inferior to those of the skin tests.

Basophil degranulation test

With this test, we are attempting to quantify the specific degranulation of the IgE mediated antigen of the basophils of the peripheral blood. Although technically it is available to any minimally equipped laboratory, in practice, its use is not very extensive due to the difficulty of the technique.

Ureña et al [14] established the limits of positivity of this test in 35% of degranulation for penicilloyl (52% sensitivity, 86% specificity) and 25% for the minor determinants (61% sensitivity and 72% specificity). In principle, it would be less reliable than the skin test and slightly more than the RAST.

Specific provocation

It is by far the best diagnostic technique, although it should only be used by experienced allergologists, because of the possibility of inducing severe systemic reactions. The false positive reactions are rare, occurring when the attacks are evaluated in the acute phase. The false negative reactions are also rare, although they can occur if we test the drug during the refractory period or if we have induced tolerance.

It is indicated in those patients in whom, having a suggestive clinical history, hypersensitivity to penicillin has not been diagnosed by other techniques and in whom we consider that it is essential in order to reach the final diagnosis.

We have used the subcutaneous and intramuscular route, according to the protocol presented in Table V, once we have made sure of the negativity of the skin tests. In order to avoid false negative reactions, that can occur if the provocation is done much after the initial reaction, we perform the reprovocation at 15 days. In this period, we assume that the immunological memory, if it exists, should have been activated. We begin the reprovocation with the reperformance of the skin tests, following the protocol given in Table VI.

Table V

EXPOSURE (PROVOCATION) TEST WITH PENICILLIN G

PENICILLIN CONCENTRATION	DAY	PENICILLIN UNITS DOSE	ROUTE	WAITING TIME
10,000 U/ml	1	500 1000 2000	SC	45'
	2	5000	SC	45'
100,000 U/ml		12,000		
	3	25,000	SC	45'
1,000,000 U/ml	4	100,000 200,000	SC	45'
	5	400,000 800,000	IM	45'

SC = subcutaneous; IM = intramuscular

Table VI

REPROVOCATION TEST WITH PENICILLIN G

— 15 DAYS AFTER (DAY N.º 20)

— PROTOCOL:

— SKIN TEST:
- — PENICILLOYL POLYLYSINE
- — BENZYLPENICILLOATE
- — PENICILLIN G

PRICK and INTRA

— RE-EXPOSITION WITH PENICILLIN:

- — 200,000 PENICILLIN UNITS
- — 2,000,000 PENICILLIN UNITS

45'

ATTITUDE TOWARD A REACTION AFTER THE ADMINISTRATION OF PENICILLIN

Finally, we will give a practical summary of the attitude to take when with the most frequent reactions presented in the general clinical course after the administration of penicillin.

A. Urticaria, angioedema, anaphylaxis

In principle, they are mediated by a Type I mechanism of Gell and Coombs. They are the major indication for the realization of the skin tests with penicillin G and its major and minor determinants. It is estimated that if these are negative, the possibility of presenting a hypersensitivity reaction after the readministration of the drug is low and in any case, it is generally mild and limited to the skin. Given this possibility and in order to verify or discard the

presence of hypersensivity to penicillin, another type of technique should be used, such as the RAST, basophil degranulation or even the controlled provocation up to therapeutic doses with penicillin. If the skin tests are positive, there is a high risk (50-70%) that a new administration of the drug will provoke an allergic reaction. In this case, and if the use of penicillin is essential, it is possible to begin desensitization with the drug. We recommend the review done by Lopes et al [15] to the reader for its indications and techniques for both the oral and parenteral route.

B. Blood dyscrasis, interstitial nephritis, drug fever or serum disease:

These are due to a Type II or Type III Gell and Coombs hypersensitivity mechanism. The skin tests can be useful only to discard the concomitant presence of Type I hypersensitivity.

These generally appear in the course of prolonged treatment at high doses. In a practical way, if the skin tests are negative and the administration of penicillin essential, during a short treatment, it can be slowly introduced by a doctor experienced in this subject, with a close control for the appearance of possible side effects, that, in case of appearing, would mean the suspension of the drug and the administration of high doses of systemic steroids.

C. Contact dermatitis:

This is mediated by a Type IV mechanism. It is a rare entity at present, pratically limited to the professional pathology. The prick and intradermic skin tests are not useful for its diagnosis, although patches, which are read after a period of time, can be used. The subjects with this pathology, in general, can accomplish toleration to the systemic administration of penicillin.

D. Toxic epidermal necrolysis, dermatitis exfoliative:

Their mechanisms are unknown. The performance of skin tests is not indicated. The readministration of penicillin is totally contraindicated given the possibility of provoking a potentially lethal reaction.

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