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TITLE: Selective immediate responders to amoxicillin and clavulanic tolerate penicillin derivative administration after confirming the diagnosis.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

ABSTRACT

Background

An increasing number of patients show immediate selective hypersensitivity reactions to clavulanic acid (CLV), and amoxicillin (AX), probably due to their increased prescription. The maintenance of this response should be established.

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Objective

To assess that the immediate hypersensitivity selective response to AX or to CLV is maintained after repeated administration of Penicillin G (PG)/Penicillin V (PV) and AX.

Methods

Patients with proven immediate hypersensitivity to AX (Group A) or CLV (Group B) were included. Diagnosis was performed using skin tests with major and minor determinants of PG (PPL/MDM), AX and CLV and by drug provocation test (DPT) if required. Selectivity was established by confirming tolerance to PG/PV (Group A) and to PG/PV and AX (Group B). The maintenance of the selective response was verified by repeating DPT, 15 days after the initial investigation, with the same procedure.

Results

Of 51 patients, 78% belonged to Group A and 22% to Group B. Most had anaphylaxis. In Group A, 72% were skin test positive; 28% required DPT. In Group B, 63% were skin tests positive; 37% required DPT. Only two AX selective cases developed positive responses after re-provocation with PG/PV. No cases selective for CLV developed a positive response to PG, PV or AX.

Discussion

The selective response to AX appears consistent and a response to penicillin determinants only develops in a minority of cases. For the case of CLV, the selective response appears not to be modified by exposure to penicillin determinants, meaning that patients with CLV allergy can take penicillin derivatives safely.

KEY WORDS: Immediate response, selective, amoxicillin, clavulanic acid, penicillin derivatives, cross reactivity, tolerance

INTRODUCTION

Allergic reactions to Betalactam (BL) antibiotics can be mediated by different mechanisms, mainly IgE (immediate reactions) and T cell (non-immediate reactions) (1,2). Six major groups of BLs exist: penicillins, cephalosporins, monobactams, carbapenems, clavams and oxacephems (3,4). Penicillins are the most frequently involved in allergic reactions (5), this group comprises narrow and broad spectrum penicillins, penicillase resistant penicillins and combinations with betalactamase inhibitors (5). The inclusion of betalactamase inhibitors, such as clavulanic acid (CLV) has made the evaluation of hypersensitivity reactions to BLs more complex, because CLV, initially considered non immunogenic (6), has been shown to induce hypersensitivity reactions (7-9).

Two major groups of responders exist according to their clinical tolerance to different BLs: selective and cross-reactive (1,2). The former includes patients that react to one BL while tolerating others and the latter includes patients reacting to similar BL structures (1,4). Cross-reactivity can be due to similarities in the common BL structure and selective reactions due to recognition of the side chain structure (10). However, immunochemical studies indicate that although side chain specific structures are determinant for selective immunological recognition and clinical response, the whole molecule is required to induce a reaction (11). There was little evidence for side chain-specific hypersensitivity to penicillins until the 1980s when individuals with skin test-positive to AX only were initially identified (12-14). These results have been confirmed in different countries, for a wide range of cases (13-19).

Patients with penicillin selective responses maintain the selectivity after subsequent BLs re-exposures (20-22), although more studies are needed to confirm this observation. In fact, antibody specificity may vary with subsequent re-stimulation with closely related haptens (20,23,24). Moreover, AX is now prescribed in combination with CLV, which can also induce selective reactions, and affect IgE recognition (1).

In this manuscript we describe a study of a large group of patients with immediate hypersensitivity selective reactions to AX or to CLV who were re-exposed to Penicillin G (PG) and PenicillinV (PV), and also to AX in the case of selective reactions to CLV.

MATERIAL AND METHODS

Patient selection

The study group was carried out in a prospective way from the 268 subjects who attended the Allergy Service of the Infanta Leonor Hospital between January 2009-July 2013 with a history indicative of immediate hypersensitivity reaction to AX or AX-CLV. Study subjects had an index reaction of urticaria or anaphylaxis classified as described (1,25) and also confirmed selective immediate-type hypersensitivity to AX (Group A) or to CLV (Group B) based on positive skin test or oral challenge results.

For diagnosis we followed the general guidelines published for the evaluation of immediate reactions to BLs (26) with some modifications. Group A was defined as patients with proven immediate hypersensitive to AX and Group B as patients with proven immediate hypersensitive to CLV. The groups were defined as outlined in Figure 1.

Skin testing

Skin tests were done by prick, and if negative by intradermal tests as previously described (26). The maximum concentrations used were: PPL $5 \times 10^{-5} \text{M}$, MDM $2 \times 10^{-2} \text{M}$, AX 20 mg/ml, CLV 20 mg/ml (9,27). In those cases with a history of severe anaphylaxis we performed the test with increasing dilutions before reaching the maximum concentration as described (26). All skin test reagents were provided by DIATER laboratories (Diater-Ferre, Madrid, Spain).

Drug Provocation Test (DPT)

In subjects with negative skin tests to PPL and MDM, DPT with PG was performed by parenteral route in a single dose of 10^6 units. This was followed by a 3-d therapeutic course of PV of 500 mg/8-h.

If DPT with PG and PV was negative and skin test was negative to AX, a DPT with AX was performed. AX DPT was performed using 5 oral doses of 5, 50, 125, 250 and finally 500 mg with ½ hour of observation between doses until reaching 930 mg of cumulative dose (26). This was followed by a 3-d therapeutic course of AX 500 mg/8-h.

When AX-CLV was involved, after confirming good tolerance to AX, in those cases with negative skin test with CLV, an AX-CLV DPT was performed as described for AX (22). We used 4 oral doses of AX-CLV containing 50/12.5, 125/31.25, 250/62.5 and 500/125 mg of AX and CLV respectively, with ½ hour of observation between doses, until reaching a cumulative dose of AX-CLV of 925/231.25 mg. This was followed by a 3-d therapeutic course of AX-CLAV 500/125 mg/8h.

Re-provocation for assessing maintenance of tolerance to PG/PV and AX

Patients with selective reactions to AX (Group A) were re-evaluated 15 days after the first study by repeating skin testing and if negative repeating DPT with PV as described above.

In those with selective reactions to CLV (Group B), re-evaluation with skin testing and DPT with PV and AX was performed.

Statistical studies.

The comparison of the time intervals between those cases with skin test positive to AX and skin test negative were made by T-tests. This was also performed for the CLV selective responders. The ages of the Group A subjects versus those of Group B were also compared. The relative frequencies of patients presenting urticaria or anaphylaxis were compared using Chi squared tests.

RESULTS

Of the 268 subjects evaluated, 58 (21.6%) were confirmed as having immediate hypersensitivity. Seven (12.1%) of them were allergic to benzyl-penicillin determinants and were not considered for further study. Fifty-one cases were finally included, 40 (78%) were classified as AX selective responders with good tolerance to PG and PV (Group A) and 11 (22%) as CLV selective responders with

good tolerance to PG, PV and AX (Group B). AX was the drug implicated for 20 of these cases, and AX-CLV for 31. From this last subgroup, 20 were found to be selective to AX and 11 to CLV, indicating that 35% of our patients taking AX-CLV developed a selective response to CLV. The time interval between the original occurrence of the reaction and the performance of the study had no influence on the allergy testing results.

Data on the clinical characteristics and the allergological evaluation of Group A are shown in Table 1. A predominance of female versus male was observed (23 F versus 17M); in 50% of cases AX-CLV was implicated and in the other half AX alone; 77% developed anaphylaxis and 23% urticaria.

Twenty-nine (72%) cases had positive skin test results, 9 by prick and 20 by intradermal (Table 1). Analysis of prick and intradermal results did not show statistical differences between anaphylaxis and urticaria.

Two cases developed systemic symptoms after intradermal testing with AX: case 6 in Table 1 was a patient with a history of anaphylaxis who developed generalized pruritus and erythema with nausea and vomiting and case 33 was a patient with a history of anaphylaxis, who developed mild systemic pruritus and facial erythema. In both cases the reactions occurred with the maximum concentration 20 mg/ml. Symptoms were controlled with the administration of intramuscular antihistamines and adrenaline. No case developed symptoms at lower concentrations.

In the remaining 11 cases (10 with anaphylaxis and 1 with urticaria) of Group A who had negative skin test results to AX, a DPT with AX was required to establish diagnosis. The time interval of response after the challenge, the symptoms induced and the triggering dose are shown in table 2.

A total of 11 cases were classified as selective responders to CLV after the intake of AX-CLV (Group B). This represents 21% of all the cases included and 35% of those where AX-CLV was the culprit drug. Clinical characteristics, allergological study

and DPT results are shown in Table 3. No systemic reactions to CLV occurred in these patients after skin testing.

In four cases with negative prick and intradermal tests to CLV, DPT with AX-CLV was performed. These were patient 43 of Table 3, who was positive to 31 mg of CLV (125 mg of AX-CLV acid), and patients 45, 47 and 50, who responded to 12.5 mg of CLV (50 mg of AX-CLV acid). The symptoms elicited were in all cases systemic pruritus and abdominal pain. Patient 3 also developed hypotension. All cases were treated with intramuscular adrenalin and antihistamines with complete recovery.

An analysis of the skin test with AX and CLV determinants showed a sensitivity of 72% for the AX selective group and 64% for the CLV selective group. A combined analysis of both determinants indicates that in patients with an immediate reaction to AX or CLV, the overall sensitivity was 71%. In the remaining cases the diagnosis could not be confirmed unless a DPT was undertaken.

Results of the re-provocation in Group A with PV 15 days after performing the evaluation showed that two cases (patients 7 and 15 of Table 1) became positive to PV. Patient 7 developed systemic pruritus accompanied by wheals and lips angioedema after being administered 50 mg of PV (cumulative dose 55 mg) and patient 15 developed nausea, systemic pruritus and chest pain after taking 125 mg of PV (cumulative dose 180 mg). Both patients received immediate treatment with adrenalin and antihistamine and recovered completely within an hour. For Group B re-provocation was carried out using PV and AX as described above. No positive reactions occurred.

DISCUSSION

Although different studies have shown that selective reactions to BLs occur and that this is particularly relevant within the penicillin groups (14,22), only one study has verified that patients maintain selectivity (20). In that study a small group of subjects with selective responses to AX tolerated several therapeutic

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courses of PG and PV but only one case became skin test positive to BPO in the second year of re-evaluation. It has also been shown that patients with immediate selective reactions to AX that converted to skin test-negative over time were again sensitised to AX after re-exposure to non-therapeutic concentrations of AX (22). In order to verify and replicate these findings in a different population ten years after the previous study (20), we have evaluated the response to PG and PV in a well-defined group of selective responders to AX (Group A). In contrast with the previous work, in the population of this study AX-CLV was taken by a very high proportion of cases, and given that selective responders to CLV have also been reported (7-9), we therefore decided to also study patients with selective response to CLV (Group B).

In more than 50% of patients included the BL involved in the reaction was AX-CLV, of which 35% were selective reactors to CLV, data similar to those previously reported (9).

In our study the number of subjects with negative skin tests that required DPT for establishing diagnosis was 28%, similar to other work (28). Previous work indicates that subjects with a long time interval between drug intake and performance of the studies can become negative (29,30). A comparison of the time of the occurrence of the allergic reactions and the performance of the study between subjects diagnosed by positivity of skin tests and those diagnosed by DPT showed that there were no statistical differences, indicating that the negative results were not related to the time interval between drug intake and the occurrence of the episode. Although the mean age of subjects with hypersensitivity reactions to CLV was lower than those with AX there were no statistical difference, as found in a previous study (9). Further research, including a larger group of cases is needed to confirm previous data indicating that those at younger ages, more exposed to the combination of AX-CLV have higher chances of become selective to this drug.

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In Group A, it is important to note that 31% were prick test positive to AX, a figure higher than published previously (24,31). This may be related to the time interval between the reaction and the study, in our case this was lower than in previous studies (28,29,32). The remaining skin test positive patients were diagnosed by intradermal AX. Sixteen were positive at the maximum dose of 20 mg/ml, with only a small proportion being intradermal positive to lower doses. Recommendations for the concentrations used for skin testing depend on the severity of the reaction and the time interval between allergic episode and the allergological evaluation (33,19). In more severe cases, starting at much lower doses than the maximum recommended can decrease the occurrence of systemic reactions (28,32). In fact in our study only 5% of patients developed systemic symptoms after skin testing and in all instances these reactions were mild and well controlled by appropriate treatment. Other studies have shown higher figures (28). A detailed analysis of those with side effects showed that these occurred at the maximum concentration used (20 mg/ml) by the intradermal route, which indicates that in spite of negative prick testing a reaction can occur (26). An analysis of those selective cases to AX who were diagnosed by DPT showed that 64% of subjects responded to the lower doses administered, in most instances 50 mg, with the remaining requiring higher doses for eliciting a positive response.

It is of relevance to note the number of CLV selective cases from the total number of patients evaluated. They account for 21% of all the cases included and 35% of those for whom AX-CLV was the culprit drug. Although the sensitivity of the skin test was found to be lower for group B, this was not statistically significant.

Recent years have seen an increase in the prescription of AX-CLV, raising the possibility of finding selective responders to either AX or CLV. By combining the skin test results to both of these drugs the sensitivity for finding selective responders to AX-CLV is increased to 71%, it therefore seems reasonable to include skin tests for both components in the routine diagnosis of allergic reactions to AX-CLV.

The question of re-sensitisation is relevant, since patients may become positive on re-exposure to the culprit drug (32,33). Results are variable, with some studies indicating that it does not occur (19) while others show a frequency of up to 16% (34). This does not only occur after drug administration but also after skin testing and even after inadvertent exposure (22). In our study we performed a single DPT with PG and if good tolerance was maintained then PV was administered to verify if a more prolonged treatment could lead to re-sensitisation, a procedure recommended by the EAACI protocols (26). Regarding testing for resensitisation we simplified the procedure by challenging only with PV. Only two cases responded to penicillin determinants, in both cases to the oral administration with PV. In no case as described in our previous study (20) subjects became skin test positive to penicillin determinants.

Concerning the response to CLV, the absence of cross reactivity with penicillins is not surprising since this BL has an oxazolidine ring instead of a thiazoline (21). Therefore all cases had good tolerance to both PG and AX. Although only a few cases were reported initially (6,8,27), there is an increasing tendency to find selective cases to CLV. Whether subjects could respond to other betalactamase inhibitors is a matter of speculation and cases with imputation have been reported but not definitively proven (35,36).

The results of this study also suggest that, regarding the algorithm proposed by the EAACI (26), in those countries where selective responders to CLV are found, initiation of the DPT by testing for CLV may be an alternative choice since some cases can be selective responders to CLV only and tolerate AX.

In summary, we have shown that AX allergic patients develop in most instances a selective response with good tolerance to other penicillins determinants with different side chains. However, any patient under treatment with AX must be surveyed in order to verify if positivisation to common penicillin determinants occur. In the case of patients taking AX-CLV and developing a selective response, two outcomes exist, either being selective to AX or to CLV. Although positivity to

both has never been found, the possibility exists and should be searched for in future studies.

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LEGENDS TO FIGURES

Figure 1. Algorithm with the general approach used to diagnose patients with immediate selective reactions to amoxicillin or to clavulanic.

Table 1. Demographic, clinical characteristics and skin tests results of patients selective responders to AX (Group A)

P	Sex	Age	D-R (min)	R-S (months)	Drug	Diagnosis	Prick AX	Drug Conc (mg/mL)	ID AX	Drug Conc (mg/mL)
1	M	48	5	0.25	AX	ANAF	NEG		NEG	
2	F	35	30	60	AX	ANAF	NEG		NEG	
3	F	16	60	0.75	AX-CLV	URT	NEG		POS	20
4	M	67	20	12	AX-CLV	ANAF	POS	20	ND	
5	F	50	5	0.1	AX	ANAF	POS	20	ND	
6	F	33	30	0.1	AX-CLV	ANAF	NEG		POS	20
7	M	49	5	240	AX	ANAF	NEG		NEG	
8	M	24	60	36	AX-CLV	URT	NEG		POS	20
9	F	72	60	12	AX-CLV	URT	NEG		NEG	
10	M	52	20	1	AX	ANAF	POS	0.02	ND	
11	M	54	20	0.5	AX-CLV	ANAF	POS	2	ND	
12	F	20	10	1	AX-CLV	ANAF	NEG		NEG	
13	M	38	30	0.5	AX-CLV	URT	NEG		POS	20
14	F	36	60	1	AX	ANAF	NEG		POS	20
15	M	75	20	108	AX	ANAF	NEG		NEG	
16	M	47	20	3	AX-CLV	ANAF	POS	20	ND	
17	M	61	60	1	AX	URT	POS	20	ND	
18	F	47	30	0.75	AX	ANAF	NEG		POS	0.02
19	F	32	15	120	AX	ANAF	NEG		POS	20
20	M	45	45	480	AX	URT	NEG		POS	20
21	M	40	20	0.25	AX-CLV	ANAF	NEG		POS	20
22	F	64	15	6	AX-CLV	ANAF	POS	0.02	ND	
23	F	40	20	120	AX	URT	POS	20	ND	
24	F	29	30	5	AX-CLV	ANAF	NEG		POS	2
25	F	45	10	2	AX	ANAF	NEG		POS	2
26	F	46	5	12	AX	ANAF	NEG		POS	20
27	M	44	10	0.5	AX-CLV	ANAF	NEG		POS	20
28	F	63	15	1	AX	ANAF	NEG		NEG	
29	M	61	60	2	AX-CLV	URT	NEG		POS	20
30	F	32	10	1	AX-CLV	ANAF	NEG		POS	20
31	F	71	30	1	AX	ANAF	NEG		POS	20
32	F	30	15	1	AX	ANAF	NEG		POS	20
33	F	64	30	0.25	AX-CLV	ANAF	NEG		POS	20
34	F	47	20	1	AX-CLV	ANAF	NEG		NEG	
35	M	59	30	96	AX-CLV	ANAF	NEG		NEG	
36	F	52	15	0.5	AX	ANAF	NEG		NEG	
37	F	37	30	3	AX	URT	NEG		POS	2
38	M	43	10	3	AX	ANAF	POS	20	NEG	
39	M	18	30	1	AX-CLV	ANAF	NEG		NEG	
40	F	26	15	1	AX-CLV	ANAF	NEG		POS	20

F: Female; M: Male; D-R: Time elapsed between the intake of the drug and the appearance of the reaction; R-S: Time interval occurring between the reaction and the performance of the allergological study. AX: Amoxicillin; AX-CLV: Amoxicillin-clavulanic; ANAF: Anaphylaxis; URT: Urticaria; NEG: Negative; POS: Positive; Drug conc: Drug concentration.

Table 2. Cases of group A (selective to AX) who required drug provocation for establishing the diagnosis.

P	R-S (months)	Drug	Diagnosis	DPT- R (min)	DPT symptoms	Dose (mg)
1	0.25	AX	ANAF	20	cutaneous pruritus and wheals, lips angioedema and cough	50
2	60	AX	ANAF	10	generalized cutaneous pruritus, nauseas and hypotension	125
7	240	AX	ANAF	10	generalized cutaneous pruritus, wheals and throat tightness	125
9	12	AX- CLV	URT	20	generalized pruritus and wheals	250
12	1	AX- CLV	ANAF	30	pruritus and wheals in face and thorax	125
15	108	AX	ANAF	20	generalized cutaneous pruritus, wheals and throat tightness	50
28	1	AX	ANAF	30	cutaneous pruritus, lips angioedema and throat tightness	50
34	1	AX- CLV	ANAF	20	head and hands pruritus, lips angioedema and throat tightness	50
35	96	AX- CLV	ANAF	15	generalized cutaneous pruritus, nauseas, dyspnea and cough	50
36	0.5	AX	ANAF	15	generalized pruritus, facial angioedema and throat tightness	50
39	1	AX- CLV	ANAF	60	cutaneous pruritus and wheals in head, face and arms	500

R-S: Time interval occurring between the reaction and the performance of the allergological study. AX: Amoxicillin; AX-CLV: Amoxicillin-clavulanic; ANAF: Anaphylaxis; URT: Urticaria; DPT-R: Time interval occurring between the drug intake and appearance of symptoms in the drug provocation test.

Table 3. Demographic, clinical characteristics, skin tests and drug provocation tests results of patients selective responders to CLAV (Group B).

P	Sex	Age	D-R (min)	R-S (months)	Drug	Diagnosis	Prick CLV	ID CLV	Drug conc (mg/mL)	DPT AX-CLV	PD AX/CLV (mg)
41	F	23	30	1	AX-CLV	ANAF	NEG	POS	5	ND	
42	F	42	5	12	AX-CLV	ANAF	POS	ND	20	ND	
43	M	36	10	3	AX-CLV	ANAF	NEG	NEG		POS	125/31
44	M	57	2	48	AX-CLV	ANAF	NEG	POS	20	ND	
45	M	22	30	0.5	AX-CLV	ANAF	NEG	NEG		POS	50/12.5
46	F	45	15	2	AX-CLV	ANAF	NEG	POS	20	ND	
47	F	68	30	0.5	AX-CLV	ANAF	NEG	NEG		POS	50/12.5
48	F	32	30	0.5	AX-CLV	ANAF	NEG	POS	5	ND	
49	F	69	10	1	AX-CLV	ANAF	NEG	POS	20	ND	
50	M	43	60	1	AX-CLV	URT	NEG	NEG		POS	50/12.5
51	M	19	60	2	AX-CLV	URT	NEG	POS	20	ND	

F: Female; M: Male; D-R: Time elapsed between the intake of the drug and the appearance of the reaction; R-S: Time interval occurring between the reaction and the performance of the allergological study. AX: Amoxicillin; AX-CLV: Amoxicillin-clavulanic; ANAF: Anaphylaxis; URT: Urticaria; NEG: Negative; POS: Positive; Drug conc: Drug concentration; ND: not done; PD : Provocative dosis.

