

Anaphylactic Shock Associated with Cefuroxime Axetil: Structure–Activity Relationships

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Structure–activity relationship (SAR) describes the relationship between chemical structure and pharmacologic activity for a series of compounds.¹ The SAR of a given molecule can be determined by assessing the biological effects of gradual changes in its chemical structure. Using the same reasoning, it is also possible to determine the potential toxicity of the metabolites of a given compound.

In the field of allergy, SAR testing is commonly conducted in the area of contact dermatitis.² In immediate immunoglobulin (Ig) E–mediated drug hypersensitivity, this type of approach is less commonly used. An SAR study can, however, help specify the antigenic determinants of low-molecular-weight compounds (covalent binding with proteins). This method has been applied to the determination of the IgE-binding sites of sulfamethoxazole.³ More recently, study of the immunogenicity of sulfamethoxazole (antigenic determinants recognized by T-cells) has described this type of approach.⁴ Few studies have used this method in the determination of the specificity of IgE antibodies in the case of penicillin⁵ or cephalosporin⁶ hypersensitivity.

Antibiotics with β -lactam rings (mainly penicillins and cephalosporins) are commonly prescribed and are responsible for the majority of immediate drug hypersensitivity reactions.^{7,8} Cross-reactivity among different generations of cephalosporins varies between 0% and 68.8%, with third-generation cephalosporins being less cross-reactive than first- or second-generation ones.⁹ Furthermore, 12–38% of patients who are allergic to penicillins have been shown to react to cephalosporins with a similar side-chain; it has been reported that patients who are allergic to penicillins have a

OBJECTIVE: To present a predictive model of allergenicity based on a structure–activity relationship analysis of β -lactam antibiotics using appropriate skin testing procedures.

CASE SUMMARY: A 39-year-old woman was diagnosed with anaphylactic shock a few minutes after taking a 500 mg tablet cefuroxime of axetil and was admitted to the emergency department with dizziness, facial angioedema, generalized skin rash, and inferior cardiac ischemia. Skin testing confirmed the involvement of cefuroxime as the cause of the anaphylactic reaction, and the reaction was defined as probable according to the Naranjo probability scale. We then performed skin testing to study cross-reactivity between different β -lactam antibiotics. In addition to this initial assessment, a structure–activity relationship (SAR) analysis was done. It showed that the patient was sensitized to β -lactam antibiotics presenting a methoxyimino group, but not to similar compounds lacking this chemical group (eg, amoxicillin or penicillin G or V). Challenge with amoxicillin under intensive medical monitoring was tolerated up to a cumulated dose of 1 g, administered intravenously over 2 hours.

DISCUSSION: This study demonstrates that SAR analysis could be useful to predict potential adverse reactions to related antibiotics and to select alternative strategies when antibiotic administration is essential.

CONCLUSIONS: An SAR-based approach could help physicians and pharmacists provide allergic patients with relevant advice and propose viable alternatives regarding drug therapy.

KEY WORDS: anaphylactic shock, cefuroxime axetil, drug allergy, structure–activity relationship.

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fourfold risk of developing an allergic reaction to a cephalosporin compared with patients with no penicillin allergy.¹⁰

We report a case of an immediate allergic reaction to cefuroxime axetil and describe an SAR analysis based on skin tests to predict the likelihood of adverse reactions to related antibiotics.

Case Report

A 39-year-old woman was admitted to the emergency department with anaphylactic shock that occurred a few minutes after she took a 500 mg tablet of cefuroxime axetil (Zinnat, GlaxoSmithKline, Genval, Belgium) used to treat acute bronchitis. Her past medical history included depression, psoriasis, and chest pain without identified coro-

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naropathy. The patient was taking Deanxit (consisting of flupentixol 0.5 mg and melitracin 10 mg), trazodone 100 mg, lormetazepam 2 mg, and aspirin 100 mg, all on a daily basis. Cefuroxime axetil was taken as self-medication (first dose that day). The patient had received treatment with cefuroxime axetil before this event occurred.

On admission, the woman's systolic blood pressure was 60 mm Hg; symptoms included faintness, dyspnea, facial angioedema, and generalized skin rash, and transitory inferior cardiac ischemia was diagnosed. The electrocardiogram showed subendocardial lesions in the inferior territory. The reaction was defined as probable according to the Naranjo probability scale.¹¹ Treatment consisted of blood volume expansion, epinephrine, and corticosteroids and complete recovery was achieved, including normalization of the electrocardiogram.

The concentration of serum tryptase, sampled at the acute stage of the reaction, was 200 µg/L (normal <14). Three weeks after the reaction, the level of tryptase returned to normal (5.75 µg/L). Thus, systemic mastocytosis was excluded.

Skin tests were performed 4 weeks later with cefuroxime (Zinacef, GlaxoSmithKline, Genval, Belgium), following the guidelines previously reported.^{12,13} The prick test was positive at a concentration of $2 \cdot 10^{-2}$ mg/mL (wheal of 5 mm in diameter; positive control with codeine phosphate 9%: 4 mm). The intradermal test (IDT), which was carried out with cefuroxime and read after 20 minutes, was clearly positive at a concentration of $2 \cdot 10^{-6}$ mg/mL, with the wheal expanding from 3 to 14 mm. The human basophil activation test, using CD63 expression, was positive with cefuroxime.

The diagnosis of anaphylactic shock due to cefuroxime allergy was established as a result of this initial assessment.

Additional cutaneous tests for assessment of cross-reactivity were performed to complete the diagnosis. Prick tests and IDT were carried out on the forearm, with increasing concentrations up to a maximum of 2 mg/mL for cephalosporins and 25 mg/mL for penicillins, as described elsewhere^{12,13} (Table 1).

Cefotaxime ($2 \cdot 10^{-5}$ mg/mL), ceftriaxone ($2 \cdot 10^{-3}$ mg/mL), and cefepime ($2 \cdot 10^{-2}$ mg/mL) produced the lowest threshold concentrations regarding IDT. Amoxicillin, cefaclor, cefazolin, ceftazidime, and penicillins G and V yielded negative skin tests.

The patient provided written informed consent for a challenge with increasing doses of amoxicillin under intensive medical monitoring. This investigation revealed that amoxicillin was well tolerated up to a cumulated dose of 1 g, administered over 2 hours intravenously.

Discussion

We used different β-lactams in the SAR analyses in an attempt to relate the structure of each molecule to skin reactivity. All of the antibiotics that showed positive results

carried either a methoxyimino group (cefuroxime axetil, cefotaxime, cefepime, ceftriaxone) or an isoxazole group with a methyl substituent (oxacillin), which is a bioisostere of the methoxyimino group (Figure 1).

On the other hand, amoxicillin, cefaclor, cefazolin, and penicillins G and V, which have no methoxyimino group, showed negative results to skin tests. Ceftazidime, also yielding negative results, has an alkoxyimino group that cannot be considered as a bioisostere of the methoxyimino moiety because of a greater steric hindrance (Figure 2).

This analysis reveals that our patient was sensitized to β-lactams with a methoxyimino group, but was not sensitized to antibiotics without this chemical group, such as amoxicillin or penicillin G or V. Because of similar indications for treatment, amoxicillin can be regarded as a valuable alternative to cefuroxime.

A cross-reaction between cefuroxime and cefotaxime, documented by in vitro and/or in vivo tests, has been reported.^{6,14,15}

The methoxyimino group, as well as the methyl-substituted isoxazole moiety, has been introduced in the side chain of β-lactam antibiotics to enhance their stability to β-lactamases.¹⁶⁻¹⁸ Thus, we raise the hypothesis that, due to their role of steric shielding, the methoxyimino group and its bioisostere could comprise the site of IgE recognition.

Conclusions

This case study emphasizes the usefulness of SAR-based investigation in drug allergy. Such an approach could prove beneficial in deciding which molecules should be avoided and which could reasonably be used to treat further infections in allergic patients. However, SAR-based approaches should not be used in isolation in deciding whether there is a potential for cross-reactivity.

Through this SAR analysis, the importance of the β-lactam side chain in triggering the IgE-mediated mechanism has been confirmed. In this case, we further postulated that

Table 1. Skin Tests Carried Out with Different β-Lactams

Drug	Prick Tests	IDT
Amoxicillin	–	–
Benzylpenicillin	–	–
Cefaclor	–	not done
Cefazolin	–	–
Cefepime	–	+
Cefotaxime	+	+
Ceftazidime	–	–
Ceftriaxone	+	+
Cefuroxime	+	+
Oxacillin	–	+
Phenoxymethylpenicillin	–	not done

IDT = intradermal testing.

the methoxyimino group and its bioisostere are directly responsible for binding of the molecule to IgEs.

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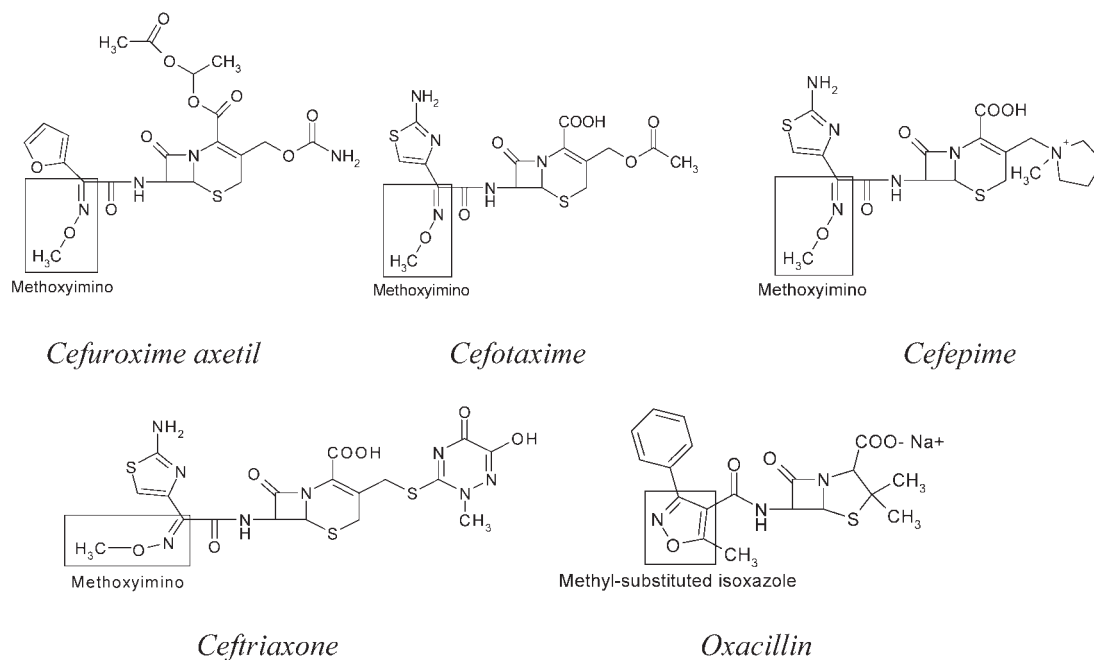


Figure 1. Structure of molecules yielding positive results in skin tests.

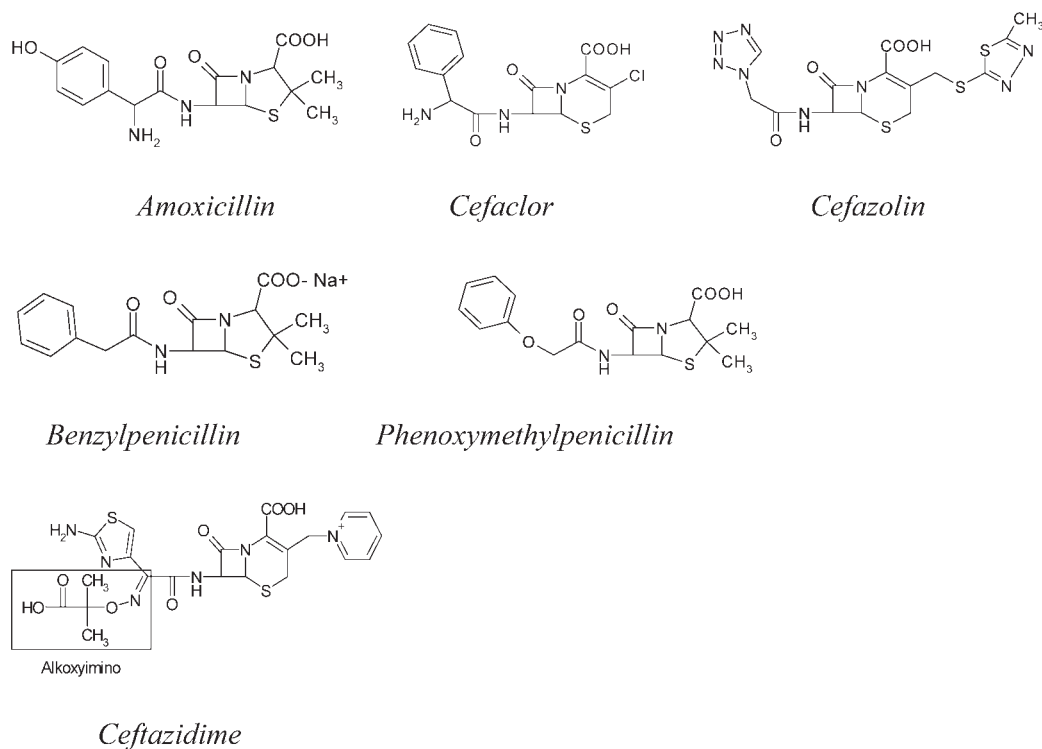


Figure 2. Structure of molecules yielding negative results in skin tests.

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EXTRACTO

OBJETIVO: Presentar un modelo para predecir la alergenidad basado en el análisis de la relación estructura-actividad de los antibióticos β -lactámicos utilizando procedimientos de test cutáneos apropiados.

RESUMEN DEL CASO: Se diagnosticó un shock anafiláctico a una mujer de 39 años pocos minutos después de tomar un comprimido de cefuroxima axetilo y posteriormente fue ingresada en un servicio de urgencias con mareos, angioedema facial, rash cutáneo generalizado e isquemia cardíaca inferior (la reacción fue clasificada como probable conforme a la escala de probabilidad de Naranjo para las RAM). Las pruebas cutáneas confirmaron la implicación de cefuroxima como causa de la reacción anafiláctica. Posteriormente realizamos un test cutáneo para estudiar las reacciones cruzadas entre diferentes antibióticos β -lactámicos. Además de esta valoración inicial se hizo un análisis de la relación estructura-actividad (SAR). Éste mostró que la paciente estaba sensibilizada frente a antibióticos β -lactámicos que presentan un grupo metoximinio, pero no frente a compuestos similares sin ese grupo químico (pe, amoxicilina o penicilina G o V). Se toleró la administración de una dosis de hasta 1 g de amoxicilina a lo largo de 2 horas de perfusión bajo vigilancia médica intensiva.

DISCUSIÓN: Este estudio revela que el análisis SAR podría ser útil para predecir reacciones adversas potenciales a otros antibióticos relacionados y seleccionar estrategias alternativas cuando la administración de antibióticos es indispensable.

CONCLUSIONES: Un enfoque basado en un análisis SAR podría ayudar a los médicos y farmacéuticos a facilitar consejos apropiados a los pacientes alérgicos y proponer alternativas viables de cara a futuros tratamientos farmacológicos.

Juan del Arco

RÉSUMÉ

OBJECTIF: Présenter un modèle prédictif d'allergénicité basé sur l'analyse des relations structure-activité des antibiotiques β -lactames en utilisant des procédures de tests cutanés appropriées.

SOMMAIRE DU CAS: Une femme âgée de 39 ans a présenté un choc anaphylactique quelques minutes après avoir ingéré un comprimé de céfuroxime axétil et a été ensuite admise aux urgences avec vertige, angiooedème facial, rash cutané généralisé, et ischémie cardiaque inférieure transitoire (réaction probable selon l'échelle de Naranjo). Les tests cutanés à lecture immédiate (prick-tests et intradermoréactions) ont confirmé l'implication du céfuroxime dans la genèse du choc anaphylactique. Nous avons ensuite procédé à des tests cutanés dans le but d'étudier la réactivité croisée entre les différents antibiotiques β -lactames et réalisé une analyse des relations structure-activité (RSA). Celle-ci montre que la patiente est sensibilisée aux antibiotiques β -lactames présentant un groupement méthoximinio, mais qu'elle ne l'est pas aux composés ne possédant pas ce groupement chimique, comme l'amoxicilline ou les pénicillines G ou V. La réintroduction de l'amoxicilline sous surveillance médicale a été tolérée jusqu'à une dose cumulée de 1 g, administrée par voie intraveineuse sur une période de plus de 2 heures.

DISCUSSION: Cette étude révèle que l'analyse des RSA pourrait être utile pour prédire la réactivité croisée d'antibiotiques proches de celui ayant induit la réaction allergique et envisager des stratégies thérapeutiques alternatives quand l'utilisation d'un antibiotique de cette famille est indispensable.

CONCLUSIONS: Une approche basée sur les RSA pourrait aider médecins et pharmaciens à conseiller les patients allergiques et proposer des choix alternatifs concernant les futures prises de médicaments.

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