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## Oral Adverse Reaction to Cefuroxime Axetil

V. Vucicevic Boras<sup>1\*</sup>, V. Brailo<sup>1</sup>, D. Vidovic Juras<sup>1</sup>,  
S. Ljubojevic Hadzavdic<sup>2</sup> and D. Gabric Panduric<sup>3</sup>

<sup>1</sup>Department of Oral medicine, School of Dentistry, University of Zagreb and Clinical Hospital Center Rebro, Kispaticeva 12, Zagreb, Croatia.

<sup>2</sup>Clinic for Dermatology, Clinical Hospital Center Rebro, Kispaticeva 12, Zagreb, Croatia.

<sup>3</sup>Department of Oral Surgery, School of Dentistry, University of Zagreb, Croatia.

### Authors' contributions

*This work was carried out in collaboration between all authors. Author VVB wrote the first draft of the manuscript. Authors VB and DVJ managed the literature search. Author SLJH made dermatological tests. Author DGP made corrections according to the reviewer's suggestions. All authors read and approved the final manuscript.*

**Case Study**

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### ABSTRACT

A 62 year old female patient was referred to the Department of oral medicine due to the severe oral reaction two days after she started to use cefuroxime axetil. Buccal and sublingual mucosa was very inflamed and covered with thick pseudomembranes. Patient was otherwise healthy and did not take any medication. She was advised to stop the suspected drug intake immediately and was given intramuscular methylprednisolone injection (40mg, i.e. 1mg/kg) as well as chlorhexetidine mouthwash with local anaesthetic (Xylocaine) to be used at home three times a day. After seven days the lesions healed completely. Two months after the adverse drug side effect, allergic tests were performed. *In vitro* tests (indirect degranulation of basophile granulocytes and blast transformation of lymphocytes) as well asepicutaneous test were negative to cefuroxime axetil.

**Keywords:** Cefuroxime axetil; oral adverse reaction.

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\*Corresponding author: Email: boras@sfzg.hr;

## 1. INTRODUCTION

Every medication applied locally or systemically can cause adverse side effects on various parts of the human body. The oral lesions of unwanted drug side effects are not typical and therefore not easy to diagnose. Cephalosporins have been used for more than 25 years in order to treat upper and lower respiratory infections (sinusitis, otitis, tonsillitis and bronchitis), skin infections such as erythema migrans associated with early stage Lyme disease and urinary tract infections [1]. Shin et al. [2] collected data from six Korean Centers on 1418 cases and reported that the most prevalent causative drugs of adverse reaction were antibiotics (31.6%), contrast dyes (14%), non-steroidal anti-inflammatory drugs (11.1%), antipsychotics (5.4%), anticonvulsants (5.2%), cardiovascular agents (4.8%), antineoplastics (4.6%) and opiates and non-opiate pain killers (3.5%). Among the antibiotics, cephalosporins (8.1%) were the most common cause of adverse drug reactions, followed by anti-tuberculosis agents (5.7%), quinolons (4%), vancomycin (3.1%) and penicilin (2.8%).

To our knowledge there are no published cases upon exclusively oral adverse side effect of cefuroxime axetil so far.

## 2. CASE REPORT

A 62 year old female patient was referred to the Department of oral medicine due to the severe oral reaction two days after she started to use cefuroxime axetil. The patient signed informed consent prior to evaluation at our Department. Otherwise the patient was healthy and didn't take any medication. However, due to the urinary infection she was prescribed cefuroxime axetil 500mg bid. The patient developed severe oral reaction two days after the beginning of the therapy, i.e. roughly two hours after last cefuroxime axetil tablet intake. Buccal and sublingual mucosa was very inflamed and covered with thick pseudomembranes (Picture 1,2,3). The patient refused oral mucosal biopsy. The patient was advised to stop the suspected drug immediately and was given Depo Medrol (methylprednisolone, 40mg (1mg/kg) by intramuscular injection as well as chlorhexetidine mouthwash with local anaesthetic (Xylocaine) to be used at home three times a day. After two days she was given again Depo Medrol as intramuscular injection together with same mouthwash. Three days after as the lesions haven't subsided completely, she was given intramuscular Depo Medrol injection again and after two days lesions subsided completely. She was free of any oral lesions after seven days. Re-challenge test was not preformed due to the ethical reasons. Two months after the adverse reaction, skin and *In vitro* (indirect degranulation of basophile granulocytes and blast transformation of lymphocytes) tests were performed and were negative to cefuroxime axetil.

## 3. DISCUSSION

Cephalosporins may induce various hypersensitivity reactions which can be classified into immediate or non-immediate. Immediate reactions develop within the first hour of administration and manifests themselves as anaphylactic shock, urticaria and/angioedema, rhinitis and bronchospasm. Non-immediate reactions occur more than hour after the last drug administration and usually manifest as maculopapular or morbiliform rashes and delayed urticaria/angioedema [3]. It seems that within immediate reactions which are mediated through IgE, skin testing is a useful tool for evaluating such reactions reported same authors [3]. On the contrary, Yoon et al. [4] suggested that routine skin testing with cephalosporine before its administration is not useful as a predictor of immediate

hypersensitivity because of the extremely low sensitivity. When non-immediate reactions to cephalosporins occur it seems that skin tests are of little use as seen in our case. This was recently confirmed by finding of Garcia Nunez et al. [5] who concluded on the 1032 patients that sensitivity of skin testing and in vitro IgE assays regarding cephalosporins is not optimal as considerable proportion of patients are tolerant, drug provocation tests are necessary to achieve diagnosis.

Literature data usually reported severe adverse immediate type reactions to cephalosporins. Marcos Bravo et al. [6] reported anaphylactic reaction immediately after administration of intramuscular sodium cefuroxime. Grgurevic et al. [7] reported toxic epidermal necrolysis and severe granulocytopenia following 18 day long therapy with cefuroxime for the treatment of urinary tract infection which unfortunately lead to death of the patient due to the chronic renal failure. Manley et al. [8] reported bilateral renal cortical necrosis in the female patient after receiving 7 doses of cefuroxime axetil over four treatment days as well as symptoms such as arthralgias, pruritus and abdominal pain as well as progression to renal failure and thrombocytopenia. Hasdenteufel et al. [9] described a patient who developed anaphylactic shock, angioedema, generalized skin rash and inferior cardiac ischemia after taking a 500 mg cefuroxime axetil. Illhan et al. [10] reported a case manifesting as vertigo, nausea, vomiting, chest pain and generalized erythema after intake of oral dose of cefuroxime axetil. Varela Losada et al. [11] reported a case of 23-year-old woman which on day 9 of treatment with cefuroxime axetil developed an itchy maculopapular rash, throat tightness, and vomiting 5 minutes after taking a dose. The symptoms remitted spontaneously. Twelve hours later, 90 minutes after taking the next dose, she again developed an itchy maculopapular rash. The intradermal test with cefuroxime was positive as was the skin prick test with cefotaxime and ceftriaxone.

Regarding non-immediate reactions to cephalosporins on the skin there have been two case reports of cefuroxime skin reaction by Gonzalo-Garijo et al. [12] who described two cases manifesting as erythrodermia (pruritus and erythema), two to three days after starting the treatment with oral cefuroxime. The same authors [12] concluded that epicutaneous test were useful for diagnosis of the delayed hypersensitivity reactions to ceftazidime and cefazolin, however this is contrary to our result as our patient had also delayed hypersensitivity reaction but was negative on epicutaneous testing. Novalbos et al. [13] reported a patient with numerous pin head pustules without erythema in the peribuccal area after ingestion of ceftibuten and amoxicillin and all cutaneous tests were negative, unlike challenge tests.

To our knowledge, unwanted side effects of the cefuroxime axetil solely on the oral mucosa have not yet been reported.

Differential diagnosis in our patient might have included erythema exudativum multiforme (EEM), chemical burn, bullous disease, propolis induced oral lesion. As the patient was healthy and was not taking any other medication, and the lesions occurred 2 days after the beginning of the therapy it was prudent to suspect that oral reaction was due to this drug. As the patient hadn't have erosive lesions on the lips we eliminated diagnosis of EEM as well as she didn't have labial or intraoral herpes infection ever. Moreover as lesions subsided and did not recur, bullous diseases were also excluded.

Diagnostic procedures in drug induced mucosal reactions remains challenge. Apart from detailed medical history and clinical appearance of the lesions, usually skin tests, IgE, *In vitro* tests and re-challenge test are employed when there is a suspicion that drug lead to the

adverse reaction. Most of these give false negative and false positive results. Therefore, only re-challenge with the suspected drug is 100% sure, but it can be life threatening due to possibility of anaphylactic shock and is not ethical unless no other drug for the patient's condition is available [14,15].



Picture 1,2,3. Patients' oral mucosa upon admission

#### 4. CONCLUSION

This case report is to our knowledge first and only so far described oral adverse reaction to cefuroxime axetil taken per-orally. Oral manifestations of adverse reactions to drugs may vary and therefore are not easily recognized by dental practitioners. Therefore, detailed medical history together with clinical oral finding are helpful. Re-challenge remains gold standard when confirming the suspected drug, however, it is unethical and should be performed in controlled hospital setting as anaphylactic shock might develop.

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#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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