

1.1. Flucloxacillin and acute generalized exanthematous pustulosis

Introduction

Flucloxacillin is a narrow-spectrum beta-lactam antibiotic of the penicillin class. It is used to treat infections caused by susceptible Gram-positive bacteria. Unlike other penicillins, flucloxacillin has activity against beta-lactamase-producing organisms such as *Staphylococcus aureus* as it is beta-lactamase stable. Flucloxacillin is indicated for the treatment of *respiratory tract infections and infections of skin and soft tissue* [1]. Flucloxacillin has been approved for the international market since 1970.

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute eruption characterized by the development of numerous nonfollicular sterile pustules on a background of edematous erythema. Fever and peripheral neutrophilia are usually present. In approximately 90 percent of cases, AGEP is caused by drugs, most often antibiotics (e.g. aminopenicillins and macrolides), the calcium channel blocker diltiazem, and antimalarials. The eruption develops within hours or days of drug exposure and resolves spontaneously within two weeks after drug discontinuation [2]. The EuroSCAR study group has developed an AGEP validation score to distinguish AGEP from other pustular cutaneous reactions. The score elegantly balances the morphology, course and histopathology of the event and results in an overall score defining the probability that the cutaneous reaction is AGEP [3]. The estimated incidence of AGEP is one to five per million per year. AGEP can occur at any age, although it most often affects adults. In a study including 97 validated cases of AGEP, the mean age was 56 years. Both sexes are affected, with a slight female predominance [2].

Reports

Between November 2011 and June 2015 Lareb received three reports of AGEP associated with the use of flucloxacillin.

Case A (166535)

This serious report from a dermatologist concerns a female aged 31-40 years, with AGEP (60% of skin had papular and pustular erythema partly confluenting to plaques) following administration of flucloxacillin 500 mg three times daily orally for an axillary abscess with a latency of 4 days after its start. The patient was hospitalised for 14 days. Flucloxacillin was withdrawn. The patient was treated locally with zinc oxide, ketoconazole, betamethasone and fusidic acid and recovered in two weeks. Concomitant medications were betamethasone, folic acid, hydroxocobalamin, dobutamine and methotrexate. The medical history of this patient includes psoriatic arthritis and psoriasis. Histopathology was compatible with AGEP and flucloxacillin as causative medicine was confirmed by a positive patch test for flucloxacillin.

Case B (201398)

This serious literature report [4] concerns a female aged 21-30 years, with AGEP following oral administration of flucloxacillin 500mg three times daily for suspected erysipelas of the leg with a latency of 5 days after its start. On admission, her history revealed Down syndrome, mild psoriasis vulgaris and an earlier maculopapular rash after flucloxacillin therapy. She was switched from flucloxacillin to clarithromycin. The next day, she was hospitalised and subsequently shifted to an ICU on the same day because of severe systemic involvement, including hemodynamic instability, and respiratory problems, while under the suspicion of toxic epidermal necrolysis and sepsis. On day 10, she showed complete healing of the skin. During a 12-month follow-up, no recurrence of acute generalised exanthematous pustulosis was noted. A definite diagnosis of acute generalised exanthematous pustulosis with toxic epidermal necrolysis -like features was made (score 9 of the EuroSCAR validation score). Three months after discharge, patch testing with flucloxacillin was positive, and showed a (vesiculo) pustular reaction.

Case C (130092)

This serious report from an internal medicine specialist concerns a female aged 80 years and older, with AGEP following administration of flucloxacillin for erysipelas with a latency of 5 days after start. Flucloxacillin was withdrawn and the patient is recovering. Concomitant medication was not reported. The medical history of this patient includes rheumatoid arthritis, osteoporosis, eczema and glaucoma.

Other sources of information

SmPC

The Dutch SmPC of flucloxacillin does not mention AGEP. Other cutaneous reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme are mentioned [1]. Information about the US SmPC of flucloxacillin is not available since flucloxacillin is no longer used in the US.

Literature

Besides the literature report received at Lareb (Case B), several other case reports describe the occurrence of AGEP suspected to be caused by flucloxacillin.

Murad and Murphy [5] describe a man in his 40s who developed a severe cutaneous adverse reaction following treatment of septic arthritis three days after starting flucloxacillin and clindamycin. The eruption had overlap features of cutaneous vasculitis and, based on the EUROSCAR diagnostic criteria, AGEP. Initially, clindamycin was stopped but the eruption progressed. In view of this progression, flucloxacillin was also stopped and he was started on methylprednisolone and daptomycin. His condition improved significantly after three days of treatment.

Natkunarajah and Ostlere [6] describe a 19-year-old woman who was prescribed flucloxacillin for a localized skin infection. By day three the patient had developed multiple painful vesicles and bullae on the neck and trunk with targetoid lesions noted on the legs. She was transferred to the intensive care unit and treated with ciclosporin. A skin biopsy was taken and subcorneal pustules were found, with marked papillary oedema without full-thickness epidermal necrosis, findings consistent with AGEP. Over the next seven days the eruption resolved. The final diagnosis was AGEP with overlapping features of TEN triggered by flucloxacillin.

Koehler et al [7] present a 30-year-old man with an acute abscess of the left thigh. He was hospitalized and treated by incision and drainage of the abscess as well as with systemic flucloxacillin 3g/day. Three days later he was discharged, continuing with oral flucloxacillin. The following day he presented with fever and acute diarrhea. Flucloxacillin was replaced by intravenous amoxicillin/clavulanic acid. Within 24 hours he developed a generalized maculo-pustular exanthema with intertriginous accentuation. A biopsy was performed and AGEP was diagnosed. After discontinuation of amoxicillin/clavulanic acid and treatment with systemic prednisolone the patient recovered. In this case report it cannot be ruled out that amoxicillin/clavulanic acid may have caused AGEP.

Databases

Table 1. Reports of AGEP associated with the use of flucloxacillin in the Lareb, WHO and Eudravigilance database [8,9].

| Database | Drug | Number of reports | ROR (95% CI) |
|----------------|----------------|-------------------|------------------|
| Lareb | flucloxacillin | 3 | 16.5 [5.2-52.3] |
| WHO | flucloxacillin | 24 | 15.4 [10.3-23.0] |
| Eudravigilance | flucloxacillin | 25* | |

*The Eudravigilance database contains 25 cases of AGEP associated with the use of flucloxacillin. Closer inspection of these cases reveals, besides the three cases that are also present in the Lareb database, six other unique cases of which five are literature cases. In three of these five literature cases other suspect drugs (terbinafine, amoxicillin and clindamycin) are reported besides flucloxacillin.

Prescription data [10]

| Drug | 2010 | 2011 | 2012 | 2013 | 2014 |
|----------------------------|---------|---------|---------|---------|---------|
| Flucloxacillin (Floxapen®) | 262,170 | 267,120 | 270,270 | 280,140 | 290,280 |

Mechanism

The pathomechanism of AGEP has been only partially elucidated. AGEP is a T cell mediated neutrophilic inflammation involving drug-specific CD4+ T cells, cytotoxic CD8+ T cells, and inflammatory cytokines and chemokines. Drug-specific CD4+ T cells produce large amounts of CXCL8 and GM-CSF. CXCL8, a chemokine inducing neutrophil chemotaxis, and GM-CSF, which reduces neutrophil apoptosis, are both involved in tissue accumulation of neutrophils. T helper 17 (Th17) cells also may be involved in the recruitment, activation, and migration of neutrophils in AGEP [2]. The exact mechanism by which flucloxacillin causes AGEP is unknown.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received three reports of AGEP associated with the use of flucloxacillin. Although a wide spectrum of cutaneous diseases or reactions can cause pustular eruptions, most of them can easily be differentiated from AGEP. However a couple of diseases remain where differentiation from AGEP may cause problems, such as pustular psoriasis, pustular vasculitis or toxic epidermal necrolysis [3]. We were not able to determine an AGEP validation score using the EuroSCAR criteria because not all information regarding morphology, course and histology was available in the reports. However, case B that was reported in literature, can be considered an index case in view of the additional information in the literature report. Moreover, the diagnosis AGEP in case A was made by a dermatologist, and in all cases the course was compatible with the typical course for AGEP in showing an acute onset and rapid resolution of the eruption after drug discontinuation. The causality of flucloxacillin in two of our reports was confirmed by a positive patch test.

The association of flucloxacillin and AGEP is supported by a statistically significant disproportionality in the database of Lareb and WHO. Due to all the duplicates in the EudraVigilance database it was not possible to determine a ROR for this database. In the literature several case reports are described where AGEP occurred while using flucloxacillin. It cannot be ruled out that concomitant medication also played a role in two of these literature reports. However, flucloxacillin is a beta-lactam antibiotic. Antibiotics of this class are frequently reported as causative drugs for AGEP [3]. Therefore this association is not surprising.

- AGEP should be mentioned in the SmPC of flucloxacillin

References

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