Acta Dermatovenerol Croat 2008;16(3):133-137 CASE REPORT

Fatal Toxic Epidermal Necrolysis and Severe Granulocytopenia Following Therapy with Cefuroxime

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Received: December 27, 2007
Accepted: July 21, 2008

SUMMARY Toxic epidermal necrolysis (TEN) is one of the most threatening adverse reactions to various drugs. No case of concomitant occurrence TEN and severe granulocytopenia following the treatment with cefuroxime has been reported to date. Herein we present a case of TEN that developed eighteen days of the initiation of cefuroxime axetil therapy for urinary tract infection in a 73-year-old woman with chronic renal failure and no previous history of allergic diathesis. The condition was associated with severe granulocytopenia and followed by gastrointestinal hemorrhage, severe sepsis and multiple organ failure syndrome development. Despite intensive medical treatment the patient died. The present report underlines the potential of cefuroxime to simultaneously induce life threatening adverse effects such as TEN and severe granulocytopenia. Further on, because the patient was also taking furosemide for chronic renal failure, the possible unfavorable interactions between the two drugs could be hypothesized. Therefore, awareness of the possible drug interaction is necessary, especially when given in conditions of their altered pharmacokinetics as in case of chronic renal failure.

KEY WORDS: epidermal necrolysis, toxic; Stevens-Johnson syndrome; cefuroxime; furosemide; kidney failure, chronic; neutropenia

INTRODUCTION

Toxic epidermal necrolysis (TEN) or Lyell's syndrome is a life threatening cutaneous reaction most commonly induced by various drugs (1-4). The incidence of TEN and Stevens-Johnson syndrome (SJS) has been estimated to 0.4-1.2 cases *per* million *per* year based on retrospective studies (5-8). In a prospective study from Germany the incidence of SJS and TEN was calculated to be 1.89 cases *per* million *per* year (3). The dominant causative agents are various drugs although association with some other conditions has also been described (e.g., graft *versus* host reaction, malignant disorders, infections, etc.) (1-4). Drugs most frequently associated with TEN are

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sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, chlormezanone and allopurinol (9). Among recently marketed drugs, nevirapine, lamotrigine and sertraline have been significantly associated with TEN (10). Controversies regarding the possible role of corticosteroids as causative agents in several cases of TEN (9) have not yet been resolved as they have been usually prescribed along with some other drugs with a known potential for TEN induction (10). Although the pathogenetic mechanisms responsible for TEN have not yet been fully clarified, it is widely accepted that it is a hypersensitivity reaction mediated dominantly by cytotoxic CD8+ lymphocytes (11).

The onset of the disease usually occurs within 4 weeks of the initiation of causative agent therapy and manifests with general symptoms such as fever, malaise and arthralgias, which are followed by mucocutaneous eruptions that appear 1-3 days later (12) and progress rapidly to bullous formation and detachment of large areas of the epidermis (1-4,10). Etiologic diagnosis is based on the dynamics of events that occur within a typical period of time after particular drug exposure. *In vitro* hypersensitivity tests are neither specific nor sensitive enough, whereas *in vivo* provocation tests confer high risk since re-exposure is likely to elicit a new episode of TEN of increased severity (4,13). Medications and procedures reported to be efficacious in the treatment of TEN include corticosteroids (14), cyclophosphamide (15), cyclosporine A (16), plasmapheresis (17), and intravenous immunoglobulins (IVIG) (18). Despite all these measures the mortality is still high and reaches 30%-40% (1,2). In a certain number of cases granulocytopenia occurs along with TEN. Based on the analysis of cases and series of patients reported so far, granulocytopenia, impaired renal function and older age have been recognized as variables associated with worse prognosis (19,20).

Cefuroxime induced TEN is an extremely rare condition anecdotally registered by the manufacturer during the post-marketing follow up. In medical literature only a single case report has been published so far (21). However, no case of simultaneous occurrence of TEN and severe granulocytopenia following the treatment with cefuroxime has been described until now. Furthermore, the possible unfavorable influence of concomitantly prescribed medications through different pathways of interactions on the development of these threatening conditions is emphasized.

CASE REPORT

A 73-year-old woman with a history of partial strumectomy in her youth, arterial hypertension, chronic renal failure (CRF) (grade II/IV) and no previous history of allergic diathesis had been treated with cefuroxime axetil (2x500 mg/day *per os* for 10 days) for urinary tract infection caused by *Escherichia coli.* Her previous medication for hypertension and CRF included lisinopril, furosemide and $CaCO_3$. Eight days following the completion of cefuroxime therapy, fever, malaise, arthralgias, skin rash and pruritus developed. The patient was prescribed antihistaminics (loratadine tablets) by her family physician. Because this therapy proved inefficient, the patient presented to the Emergency Department of our hospital. The patient was subfebrile, complaining of arthralgias, malaise and itching. Physical examination revealed atypical target lesions densely distributed over her face and truncal region, and to a lesser extent over extremities. Several blisters filled with serous to sanguinolent fluid as well as areas of scaled epidermis were already formed on her face, dorsal regions, hands and feet (Fig. 1). Nikolsky's sign (dislodgement of epidermis by lateral pressure) was positive. Buccal mucosa and lips were affected with ulcerations, along with bilateral severe keratoconjunctivitis. There were no lesions of genital mucosa. The patient was hypertensive (180/90 mm Hg), with otherwise normal cardiocirculatory and respiratory status at that time. Complete blood count as well as cytologic analysis of bone marrow specimen obtained by sternal puncture indicated leukopenia (leukocytes $1.09x10^9$/L) with severe granulocytopenia (absolute number

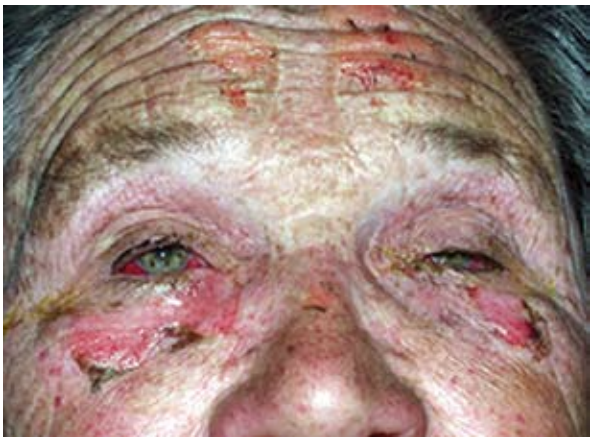

Figure 1. The patient in the initial stage of the disease. Areas of scaled, necrotic epidermis on the skin of the face and forehead, with bilateral conjunctival involvement.

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Table 1. Values of blood tests obtained 72 days prior and 19 days after cefuroxime introduction in therapy

	3 months before hospital admission (72 days before cefuroxime introduction)	At hospital admission (day 19 of cefuroxime introduction)
Serum creatinine (μmol/L)	300	213
WBC ($Nx10^9$)	7.1	1.09
Granulocytes (N/mm^3)	5100	480
Hemoglobin (g/L)	88	83
Total protein (g/L)	66	67
C-reactive protein (mg/L)	2.1	102

of granulocytes 480/μL). The relevant results of blood tests obtained 3 months prior to hospital admission during routine check-up and comparative results at hospital admission on day +19 following exposure to cefuroxime are presented in Table 1. The diagnosis of Lyell's syndrome was confirmed by skin biopsy, which revealed necrotic epidermis, subepidermal separation of the epidermis and pronounced edema of the dermis with sparse mononuclear infiltrate and no neutrophils. Direct immunofluorescence showed no immune deposits in these specimens. All medications previously used were withdrawn. Treatment with corticosteroid (methyl prednisolone 125 mg/day intravenously (iv)), antimicrobial agents (ciprofloxacin 400 mg/day iv), fluid replacement with crystalloids and colloids, along with local corticosteroid therapy, fish oil and topical antimicrobial agents (gentamicin) was started. Despite these measures, skin lesions progressed, leading to detachment of the epidermis from the entire face, hand dorsa and a large part of her back (>30% of the body surface area) (22). During the next period the condition was complicated by sepsis caused by methicillin resistant *Staphylococcus epidermidis* (MRSE) and gastrointestinal hemorrhage (hemorrhagic esophagitis). After transient improvement, leukopenia recurred and persisted throughout the course of the disease, and total serum proteins fell to 37 g/L as the result of protein loss through denuded skin. Despite intensive medical treatment at Intensive Care Unit, the patient's condition steadily worsened, with the development of multiple organ failure (MOF) syndrome, and she died 38 days from the disease onset.

Discussion

Our case report shows that cefuroxime, otherwise an efficacious and widely used antimicrobial (23,24), is an agent capable to induce fatal adverse effects such as TEN and severe granulocytopenia. To the best of our knowledge, this is the first description of their simultaneous occurrence following the treatment with cefuroxime. Only a single case of TEN believed to be caused by cefuroxime has been published in the literature until now (21). In that case, therapy with cefuroxime (3x1.5 g/day iv) was initiated for urinary tract infection in a cirrhotic patient that had been treated with furosemide and spironolactone for several years. Twenty-four hours later, TEN developed, followed by ischemic hepatitis on day 6, and the patient died. In our patient, TEN developed 18 days of the initiation of treatment with cefuroxime axetil. Before that, the patient had been treated with lisinopril, furosemide, acetylsalicylic acid and $CaCO_3$ for 3 months for CRF. Although all these drugs (except for $CaCO_3$) have previously been reported as causative agents in several cases of TEN (3) and no hypersensitivity testing was performed in our patient because of the known limitations and hazards of these tests, we believe that in our case the association of cefuroxime and TEN development is obvious. Namely, the development of the clinical picture upon initiation of cefuroxime therapy followed a time pattern characteristic of TEN induced by drugs. It is interesting to note that in both these cases of cefuroxime induced TEN, patients were also taking furosemide. One could hypothesize that it is probably not a coincidence that both patients went on to develop TEN. In our case, there are some additional reasons to believe so. First, drug interactions can be facilitated in conditions of their altered pharmacokinetics (and renal failure as in case of our patient is one of the best examples of such a condition). Second, the manufacturer of cefuroxime warns against simultaneous use of furosemide because of potentiated nephrotoxicity (23). And finally, in our case the dose of cefuroxime was not adjusted to the renal function. All these facts taken together allow us to conclude that cefuroxime is an agent

capable to induce these threatening adverse effects; for this scenario the interaction with furosemide might be a facilitating event (especially when occurring in a patient with impaired renal function). Along with TEN, severe granulocytopenia developed in our patient and this is the first description of such an association (following the cefuroxime ingestion). According to the manufacturer's information, granulocytopenia itself has been identified during the post-marketing follow up as one of the rare adverse events to cefuroxime, but the exact incidence could not been estimated due to insufficient data (23). Neither of these two cases of cefuroxime induced TEN was treated by IVIG, a therapeutic modality that could be efficacious in stopping the progression of the disease according to some reports (18). However, Bachot *et al*. found no benefit of IVIG treatment on either mortality or disease progression (25). Even more, the use of IVIG was associated with worse outcome, especially in patients with previously impaired renal function. Corticosteroids that were used as part of the therapeutic regimen in our patient did not stop progression of the disease, which is consistent with the reports of several authors (26,27). According to the same sources, corticosteroids may play a limited role in the very beginning of the pathologic process, but their protracted use is probably harmful rather than beneficial. It also appears that corticosteroids cannot prevent the development of SJS/TEN, the observation derived from the studies in patients that had been placed on long-term corticosteroid treatment for some other systemic disease (28). In a recently published retrospective analysis of 281 patients included in the EuroSCAR study, the authors found no strong evidence for the benefit for any specific treatment (IVIG *vs*. IVIG + corticosteroids *vs*. corticosteroids) in comparison to only supportive care (29). Only a trend of a beneficial effect of corticosteroids has been observed in that study.

In conclusion, cefuroxime is an agent capable to simultaneously induce fatal adverse reactions such as TEN and severe granulocytopenia. Interaction with furosemide might be a facilitating event for this scenario. This warns of precaution when considering drug combinations, especially in a setting of CRF.

References

1. Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. Toxic epidermal necrolysis. In: Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. Dermatology, 2nd edition. Berlin: Springer; 2000. pp. 414-6.
2. Becker DS. Toxic epidermal necrolysis. Lancet 1998;351:1417-22.
3. Rzany B, Mockenhaupt M, Baur S, Schroder W, Stocker U, Mueller J, *et al*. Epidemiology of erythema exudativum multiforme majus, Stevens Johnson syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population based registry. J Clin Epidemiol 1996;49:769-73.
4. Fritsch PO, Sidoroff A. Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. Am J Clin Dermatol 2000;1:349-60.
5. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Flechet ML, Girre JP. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug etiology in France, 1981-1985. Arch Dermatol 1990;126:37-42.
6. Schopf E, Stuhmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. Arch Dermatol 1991;127:839-42.
7. Chan HL, Stern RS, Arndt KA, Langloid J, Jick SS, Jick H, *et al*. The incidence of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990;126:43-7.
8. Naldi L, Locati F, Marchesi L, Cainelli T. Incidence of toxic epidermal necrolysis in Italy. Arch Dermatol 1990;126:1103-4.
9. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.
10. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, *et al*. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR Study. J Invest Dermatol 2008;128:35-44.
11. Correia O, Delgado L, Ramos JP, Resende C, Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+ lymphocyte involvement. Arch Dermatol 1993;129:466-8.

12. Guillaume J, Roujeau J, Revuz J, Penso D, Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell syndrome). Arch Dermatol 1987;123:1166-70.
13. Roujeau JC, Albengres E, Moritz S, Piacentino A, Cuny M, Revuz J, *et al*. Lymphocyte transformation test in drug-induced toxic epidermal necrolysis. Int Arch Allergy Appl Immunol 1985;78:22-4.
14. Tegelberg-Stassen MJ, van Vloten WA, Baart de la Faille H. Management of nonstaphylococcal toxic epidermal necrolysis: follow-up study of 16 case histories. Dermatologica 1990;180:124-9.
15. Heng MC, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis. Clinical and pathophysiological aspects. J Am Acad Dermatol 1991;25:778-86.
16. Arevalo JM, Lorente JA, Gonzales-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. J Trauma 2000;48:473-8.
17. Egan CA, Grant WJ, Morris SE, Saffle JR, Zone JJ. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. J Am Acad Dermatol 1999;40:458-61.
18. Prins C, Kerdel FA, Padilla RS, Huntiker T, Chimenti S, Viard I, *et al*.; TEN-IVIG Study Group. Toxic epidermal necrolysis – intravenous immunoglobulin. Arch Dermatol 2003;139:26-32.
19. Revuz J, Penso D, Roujeau J, Guillaume JC, Payne CK, Wechsler J, *et al*. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. Arch Dermatol 1987;123:1160-5.
20. Westly ED, Wechsler HL. Toxic epidermal necrolysis. Granulocytic leukopenia as a prognostic indicator. Arch Dermatol 1984;120: 721-6.
21. Yossepowitch O, Amir G, Safadi R, Lossos I. Ischemic hepatitis associated with toxic epidermal necrolysis in a cirrhotic patient treated with cefuroxime. Eur J Med Res 1997;2:182-4.
22. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92-6.
23. GlaxoSmithKline. Ceftin (cefuroxime axetil tablets). Prescribing information. www.gsk.com
24. Perry CM, Brogden RN. Cefuroxime axetil. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1996;52:125-58.
25. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol 2003;139:33-6.
26. Kelemen JJ, Cioffii WG, McManus WF, Mason ADJ, Pruitt BAJ. Burn center care for patients with toxic epidermal necrolysis. J Am Coll Surg 1995;180:273-8.
27. Helebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg 1986;204:503-12.
28. Rzany B, Schmitt H, Schopf E. Toxic epidermal necrolysis in patients receiving glucocorticosteroids. Acta Derm Venereol (Stockh) 1991;71:171-2.
29. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol 2008;58:33-40.