Andrade et al., J Clin Case Rep 2013, 3:12
DOI: 10.4172/2165-7920.1000323

Journal of Clinical Case Reports

Case Report Open Access

Tiapride Associated Toxic Epidermal Necrolysis in an HIV-Infected Patient

Paulo Andrade[1]*, Nuno Rocha Pereira[1], Cândida Abreu[1], Paula Egipto[3], Daniel Moura[2] and António Sarmento[1]

[1]*Department of Infectious Diseases, Hospital de São João, Porto, Portugal*
[2]*Burn Unit, Hospital de São João, Porto, Portugal*
[3]*Department of Pharmacology, Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

Abstract

Toxic epidermal necrolysis is a rare but severe and often fatal adverse cutaneous drug reaction. Early diagnosis and prompt discontinuation of the culprit drug is of the utmost importance, making drug causality assessment the mainstay when managing this condition. We present the first reported case of toxic epidermal necrolysis induced by tiapride, in a 43 year-old male Caucasian with a history of liver cirrhosis and HIV infection. This case report should raise awareness on the medical community to a potentially fatal reaction to a frequently prescribed drug in alcoholic patients. It also underlines the importance of further research regarding HIV infection, immune deregulation and adverse cutaneous drug reactions.

Keywords: Tiapride; HIV; Toxic epidermal necrolysis

Abbreviations: TEN: Toxic Epidermal Necrolysis; SJS: Stevens-Johnson Syndrome; BSA: Body Surface Area; SMX/TMP: Sulfamethoxazole/Trimethoprim; MHC: Major Histocompatibility Complex; HAART: Highly Active Antiretroviral Therapy; CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus

Introduction

Toxic epidermal necrolysis (TEN) is a severe adverse cutaneous drug reaction characterized by mucosal erosion and epidermal detachment [1]. It is usually distinguished from Stevens-Johnson Syndrome (SJS) by the extent of affected body surface area (BSA): SJS when less than 10% of BSA is affected, TEN when BSA affected is more than 30% and when 10 to 30% of BSA is affected as SJS-TEN overlap [1,2]. TEN is a rare condition, with an estimated incidence of 0.4 to 1.9 per million people annually [3-5]. Reported incidence in HIV infected patients is higher, as much as 1 per 1000 people annually [6]. Some of the most frequently implicated drugs are anti-infective sulfonamides, phenytoin, carbamazepine, phenobarbital and allopurinol [7]. We present the first reported case of TEN attributable to tiapride, a neuroleptic drug mainly used in alcoholic withdrawal syndrome.

Case Report

A 43 year-old male Caucasian was admitted to the emergency room of our tertiary care hospital with a two day history of fever, headache and malaise, followed by bilateral conjunctivitis, oral enanthem and a maculopapular exanthema in the entire body surface, except for the scalp and perineum. He had been admitted to the emergency room of another hospital with acute alcohol intoxication 7 and 5 days earlier, had been treated with intravenous fluids, thiamine and pyridoxine on both occasions and was started on tiapride.

He had HIV infection and alcoholic liver cirrhosis, both diagnosed 6 years earlier when he was also diagnosed with pulmonary tuberculosis and was started on isoniazid, rifampin, pyrazinamide, ethambutol and pyridoxine, as well as highly active anti-retroviral therapy (HAART), sulfamethoxazole/trimethoprim (SMX/TMP) for opportunistic infection prophylaxis and oxazepam for alcohol withdrawal syndrome. He had been treated previously with thiamine, due to several prior episodes of acute alcohol intoxication. He was compliant for 5 years (until 12 months before emergency room admission), when he abandoned follow-up and resumed alcohol consumption. At that time he was on tenofovir, emtricitabine and efavirenz, presented undetectable blood HIV viral load and a $CD4^+$ T lymphocyte count of 312/mm^3.

At the emergency room (D1) the patient presented fever (38.8°C), tachycardia (110 hbpm) and tachypnea (24 cpm), as well as oral enanthem, bilateral conjunctivitis and a non-pruriginous coalescent maculopapular exanthema distributed to the face, neck, trunk, limbs, hands and feet, including the palms and soles and sparing the scalp and perineum. Laboratory results were the following: haemoglobin 11.4 g/dL, white blood cell count 35×10^9/L, thrombocytes 42×10^9/L, albumin 25.9 g/L, AST 51 U/L, ALT 48 U/L, total bilirubin 8.3 mg/L, urea 1.8 mg/L, creatinine 7 mg/L, aPTT 37 sec, PT 13.7 sec and C-reactive protein 48 mg/L. His $CD4^+$ T lymphocyte count was 71/mm^3 and HIV viral load was 633.000 copies/mm^3. He was admitted to the Infectious Diseases Ward with a diagnosis of suspected TEN associated to tiapride and all medication was discontinued. On D2 after admission, due to cutaneous tenderness and dorsal bullae, the patient started intravenous corticosteroids. On D4, diffuse bullae formation was observed and positive Nicholsky sign localized to the dorsum was elicited. A skin biopsy was performed on D5, confirming epidermal necrosis and detachment as well as discrete inflammatory infiltrate in the superficial dermis. Blood, sputum and urine cultures were all negative. Serological testing revealed past infection by CMV, HSV1, *Mycoplasma pneumoniae and Chlamydia pneumoniae* and no prior contact with HSV2, HBV, HCV, *Treponema pallidum or Toxoplasma gondii*. Serum cryptococcal and CMV antigens were negative. Peripheral blood polymerase chain reaction for HSV1 and 2, CMV, *Mycoplasma pneumoniae and Chlamydia pneumoniae* were negative. Clinical worsening ensued with sheet like epidermal sloughing which eventually covered about 90% of total body surface (Figures 1 and 2). On D7 corticosteroids were discontinued. The patient was transferred to the Burn Unit where hemodynamic stability was maintained with

***Corresponding author:** Paulo Andrade, Department of Infectious Diseases, Hospital de São João, Porto, Portugal, Tel: +351967247061; E-mail: andrade.pf@gmail.com

Received November 20, 2013; **Accepted** December 16, 2013; **Published** December 18, 2013

Citation: Andrade P, Pereira NR, Abreu C, Egipto P, Moura D, et al. (2013) Tiapride Associated Toxic Epidermal Necrolysis in an HIV-Infected Patient. J Clin Case Rep 3: 323. doi:10.4172/2165-7920.1000323

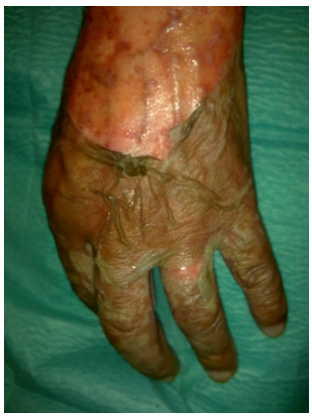

Figure 1: The patient upon transfer to the Burn Intensive Care Unit. Notice sheet like epidermal sloughing of the trunk and left arm.

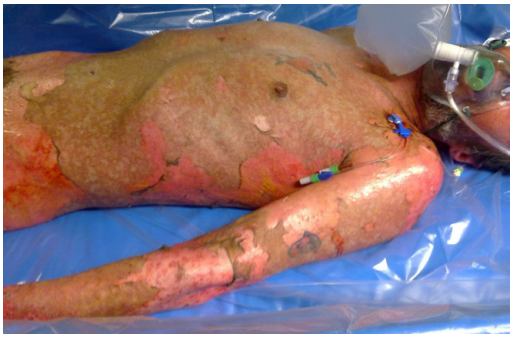

Figure 2: Close-up of the patient`s hand upon transfer to the Burn Unit. Notice epidermal detachment originating a glove-like appearance.

fluid therapy and inotropic support. Neither invasive mechanical ventilation nor parenteral nutrition was required. Wound care, under intravenous sedation and analgesia, was performed with the use of topical antiseptics and hydrotherapy on a daily basis. No surgical debridement was necessary. Gradual clinical improvement with progressive cutaneous healing and re-epidermization occurred and the patient was transferred to the Infectious Diseases ward on D70. Oxazepam, SMX/TMP and HAART with emtricitabine, tenofovir, lopinavir and ritonavir were reintroduced. The patient was discharged on D106 with no sequelae apart from minor cutaneous scarring. He resumed outpatient follow-up and achieved undetectable HIV viral load, alongside with sustained alcohol eviction.

Discussion

The present case report raises some interesting questions: was this TEN? If so, which was the culprit drug? Why would an HIV infected, immunocompromised patient develop a T-cell mediated disease? Why would a benzamide antipsychotic drug with a sulfonamide moiety cause TEN in a patient which had not developed TEN under treatment with a high-risk drug such as sulfamethoxazole? This patient`s clinical findings, such as a prodrome of fever and malaise, onset and type of rash, mucosal involvement, positive Nicholsky sign and epidermal detachment extension were all consistent with TEN and a skin biopsy revealing full-thickness epidermal necrosis seems to have confirmed it [1,8,9]. Rarer causes of TEN such as *Mycoplasma pneumoniae* infection, CMV reactivation or contrast agent administration were ruled out [10]. Off all the medication the patient received in the weeks ahead the onset of reaction, tiapride was the only one to which he had never been exposed to before. Since cutaneous testing or re-introduction was not done, as they were deemed unnecessary risks, drug causality was assessed using the ALDEN algorithm, with a result of "possible" [11]. Several mechanisms have been proposed to explain increased incidence of TEN and SJS in HIV infected patients [6]. Genetic predisposition seems to play an important role in adverse drug reactions, as is the case in the association between abacavir hypersensitivity and the presence of class I major histocompatibility complex (MHC) allele HLA-B5701 [12]. Other possible explanations include viral infection and reactivation, increased use of certain drugs, immune reconstitution, elevated serum IgE levels, a Th2 type of cytokine pattern, slow acetylation and decreased anti-oxidant levels [13-16]. Our case report seems to contradict some of these hypotheses. This patient had no acute viral infection or reactivation, HAART had not been started and, therefore, no immune reconstitution occurred. Type 1 hypersensitivity responses are not attributable to the sulfonamide functional group. However it is not known whether T-cell-mediated TEN is related to the sulfonamide moiety [17]. Our clinical report suggests that the immune determinant for TEN may also be different from the sulfonamide functional group because our patient was later treated with SMX/TMP without any adverse effect. Though we cannot advance a completely satisfactory overall explanation, it is worth noticing that in this case report TEN occurred during severe immunesuppression, due to exposure to an unsuspected drug and not while the patient was on HAART, with increasing CD4+ cell count and exposed to "high-risk" drugs such as SMX/TMP [7,11].

Conclusion

This is the first reported case of TEN attributable to tiapride. As it is a frequently used medication in alcoholic patients the medical community as a whole should be aware of this occurrence. Adverse cutaneous drug reactions in HIV infected patients are yet to be thoroughly understood, though the pathophysiologic mechanism seems to be multifactorial.

Acknowledgment

The authors would like to thank Dr. Cátia Caldas for her assistance.

References

1. Roujeau JC, Stern RS (1994) Severe adverse cutaneous reactions to drugs. N Engl J Med 331: 1272-1285.
2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, et al. (1993) Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 129: 92-96.
3. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, et al. (1999) Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet 353: 2190-2194.
4. La Grenade L, Lee L, Weaver J, Bonnel R, Karwoski C, et al. (2005) Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. Drug Saf 28: 917-924.
5. Lissia M, Mulas P, Bulla A, Rubino C (2010) Toxic epidermal necrolysis (Lyell's disease). Burns 36: 152-163.
6. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, et al. (2012) Incidence of toxic epidermal necrolysis and Stevens-Johnson Syndrome in an HIV cohort: an observational, retrospective case series study. Am J Clin Dermatol 13: 49-54.
7. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, et al. (2008) Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 128: 35-44.

8. Schwartz RA, McDonough PH, Lee BW (2013) Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol 69: 187.

9. Stern RS (2012) Clinical practice. Exanthematous drug eruptions. N Engl J Med 366: 2492-2501.

10. Schwartz RA, McDonough PH, Lee BW (2013) Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol 69: 173e1-173e13.

11. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, et al. (2010) ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther 88: 60-68.

12. Chaponda M, Pirmohamed M (2011) Hypersensitivity reactions to HIV therapy. Br J Clin Pharmacol 71: 659-671.

13. Rotunda A, Hirsch RJ, Scheinfeld N, Weinberg JM (2003) Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. Acta Derm Venereol 83: 1-9.

14. Smith KJ, Skelton HG, Yeager J, Ledsky R, Ng TH, et al. (1997) Increased drug reactions in HIV-1-positive patients: a possible explanation based on patterns of immune dysregulation seen in HIV-1 disease. The Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). Clin Exp Dermatol 22: 118-123.

15. Bacot BK, Paul ME, Navarro M, Abramson SL, Kline MW, et al. (1997) Objective measures of allergic disease in children with human immunodeficiency virus infection. J Allergy Clin Immunol 100: 707-711.

16. Sachdev R, Bansal S, Sinha R, Sharma N, Titiyal JS (2011) Bilateral microbial keratitis in highly active antiretroviral therapy-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a case series. Ocul Immunol Inflamm 19: 343-345.

17. Brackett CC, Singh H, Block JH (2004) Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. Pharmacotherapy 24: 856-870.