

Keywords: invasive pulmonary aspergillosis, pharmacokinetics, drug toxicity, lung transplantation

*Corresponding author. SAR 2, Hôpital Haut Lévéque, avenue Magellan, 33600 Pessac, France. Tel: +33-5-57-65-68-66; Fax: +33-5-57-65-68-11; E-mail: hadrien.roze@chu-bordeaux.fr

Sir,

We describe the case of a middle-aged man who intentionally poisoned himself with 9.8 g of voriconazole, 60 mg of prednisolone, 4 g of sulfamethoxazole, 2.5 g of azithromycin and 120 mg of bromazepam. This patient with cystic fibrosis had undergone bilateral lung transplantation 7 years previously. He had been treated for several weeks with voriconazole for invasive aspergillosis. He was found at his home, on the floor, in a state of altered consciousness. Several hours after the intoxication, he was intubated for airway protection, having arrived at our hospital via a county hospital.

The patient was sedated with midazolam and sufentanil, and mechanically ventilated. The chest X-ray was normal, a pulmonary fibroscopy was carried out and some gastric fluid was aspirated from the airway; the blood gases were normal, showing no signs of hypoxaemia. The patient had moderate rhabdomyolysis, with 1500 IU/L creatinine phosphokinase, and acute renal failure, with a clearance of 22 mL/min. We did not initially find any other biological abnormalities, and soon stopped the sedation in order to evaluate his consciousness. It was estimated that the patient arrived in our department 20 h after his intoxication. HPLC was used to measure serum voriconazole. The first voriconazole blood concentration was 30 mg/L (Figure 1). Forty-eight hours post-intoxication, the patient was awake but extremely agitated. His renal function rapidly improved without any respiratory or haemodynamic failure. The patient was extubated 72 h post-intoxication. Bilirubin, alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase (ALT) and glutamyl transferase started to increase slightly every day until 126 h after the intoxication to a maximal ALT value of 600 IU/L but without any clinical symptoms of liver failure. At 144 h (day 7), the patient was no longer agitated and was discharged from intensive care. A week later, the blood tests became normal. The patient was treated for his depression and aspergillosis.

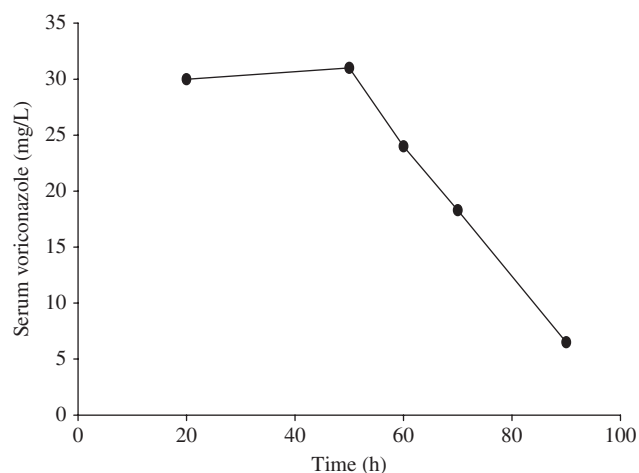


Figure 1. Serum voriconazole (mg/L).

Invasive aspergillosis is a life-threatening infection in an immunocompromised host and voriconazole is an effective treatment for this infection.¹ Voriconazole is known to have neurological toxicity and frequently hepatotoxicity with elevation of liver enzymes.^{2,3} A relationship exists between voriconazole plasma concentrations and abnormal liver function values. The risk of developing elevated liver function values increases by 7%–17% for every 1 mg/L increase in the voriconazole plasma concentration.⁴ To our knowledge there is no description in the literature of a case of massive voriconazole overdose. In this case report the patient survived the intoxication but presented with signs of immediate neurological toxicity (confusion and agitation) and a delayed increase in liver enzymes at day 3, but without any clinical signs of liver failure. In the present case it is difficult to ascertain the role of each particular drug since both voriconazole and bromazepam can lead to neurological toxicity and elevated liver enzymes.

In summary, this report shows that a very large overdose of voriconazole with high blood levels does not necessarily result in severe clinical complications or death, but the patient should be followed up for several days due to the possibility of delayed hepatotoxicity.

Funding

No external funding.

Transparency declarations

All authors: none to declare.

References

- Herbrecht R, Denning DW, Patterson TF *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347**: 408–15.
- den Hollander JG, van Harkel C, Rijnders BJ *et al.* Incidence of voriconazole hepatotoxicity during intravenous and oral treatment for invasive fungal infection. *J Antimicrob Chemother* 2006; **57**: 1248–50.
- Boyd AE, Modi S, Howard SJ *et al.* Adverse reaction to voriconazole. *Clin Infect Dis* 2004; **39**: 1241–4.
- Lutsar I, Hodges MR, Tomaszewski K *et al.* Safety of voriconazole and dose individualization. *Clin Infect Dis* 2003; **36**: 1087–8.

Journal of Antimicrobial Chemotherapy

doi:10.1093/jac/dkp236

Advance Access publication 30 June 2009

Killing with kindness? Drug reaction eosinophilia with systemic symptoms (DRESS) masquerading as acute severe sepsis

Philippa Horsfield¹, Sanjay Deshpande¹ and Richard Ellis^{2*}

¹Department of Intensive Care, South Tyneside District Hospital, South Shields, NE34 0PL, UK; ²Department of Microbiology, South Tyneside District Hospital, South Shields, NE34 0PL, UK

Keywords: β -lactams, hypersensitivity, antimicrobial reactions

*Corresponding author. Tel: +44-191-4041000;
Fax: +44-191-2024145; E-mail: richard.ellis@stft.nhs.uk

Sir,

A 37-year-old white UK-born male was admitted acutely unwell in late 2008 with a 2 h history of upper abdominal pain, vomiting, headache, pain between the shoulder blades and feeling feverish. Two hours prior to the onset of symptoms, the patient had taken the first dose of amoxicillin prescribed that day by his dental surgeon on the basis of an empirical diagnosis of possible periapical infection.

The patient had been previously fit and well and was on no regular medication. On examination, he was sweaty, hot and clammy. He had a diffuse erythematous macular rash on his back. He was febrile (39°C), hypotensive (88/60 mmHg), tachycardic and tachypnoeic with peripheral cyanosis. Initial fluid resuscitation failed to show an improvement in the patient's condition and he was transferred to the intensive therapy unit (ITU).

Blood results on admission showed a neutropenia of $1.08 \times 10^9/L$ (ref. $2.0\text{--}7.5 \times 10^9/L$); eosinophil levels were also low at $0.01 \times 10^9/L$ (ref. $0.04\text{--}0.40 \times 10^9/L$). Total white cell count was $1.7 \times 10^9/L$ (ref. $4.0\text{--}12 \times 10^9/L$). Initial chest X-ray was clear but one performed 12 h later showed a marked deterioration, with shadowing in both lower zones consistent with adult respiratory distress syndrome (ARDS)/pneumonitis.

A differential diagnosis of neutropenic sepsis was considered. The putative infection was treated empirically with piperacillin/tazobactam, metronidazole and gentamicin. This was subsequently rationalized by the microbiologist 18 h after admission to ciprofloxacin and clindamycin on the basis that this may have been an atypical drug reaction to β -lactams and that concurrent administration of piperacillin/tazobactam was therefore not in the patient's best interests. Oral prednisolone (30 mg) also given on the basis of a possible drug reaction made a marked improvement to the patient's respiratory function; however, his biochemical markers continued to show derangement.

Over the next 2 days, the patient developed liver and kidney failure. His urea and creatinine peaked at 14.7 mmol/L and 237 mmol/L, respectively, whilst bilirubin and alanine aminotransferase increased to 56 mmol/L (ref. range 0–21 mmol/L) and 151 $\mu\text{g/dL}$ (ref. range 3–35 $\mu\text{g/dL}$), respectively. His white cell counts began to rise (Table 1). A mild eosinophilia developed on the 7th day and at this point all antibiotic cover was stopped on the basis that the diagnosis was now that of drug reaction eosinophilia with systemic symptoms (DRESS) syndrome. Eosinophil levels increased markedly throughout the next 3 days (Table 1). Sepsis was excluded following negative

legionella antigen, sputum culture, urine culture, blood culture and atypical pneumonia screen. Treatment with steroids continued. Mast cell tryptase assay carried out retrospectively on one of the admission bloods was within the normal range, which effectively excluded an anaphylactic reaction. The patient was discharged fully recovered 10 days after initial admission. Post-discharge testing for other causes of eosinophilia were performed: the patient tested negative for intestinal helminths (faecal microscopy) and Schistosoma and Hydatid ELISA were both negative. Eosinophils were measured 4 months post-discharge and had returned to normal levels ($0.39 \times 10^9/L$, upper limit of normal $0.4 \times 10^9/L$).

DRESS syndrome is part of a group of conditions collectively known as drug hypersensitivity syndrome (DHS),^{1,2} which describes a severe systemic reaction to a drug, often with multi-organ involvement. There are no definitive criteria for the diagnosis of DRESS syndrome, but the diffuse maculopapular rash and multiorgan involvement exhibited by this patient have been described in previous case reports and studies on DRESS syndrome and DHS.^{3–5} The differential diagnoses included anaphylaxis, which was excluded by the negative mast cell tryptase result, and neutropenic sepsis, which was unlikely given the sudden onset of the condition in association with the amoxicillin prescribed, the initial lack of a clear source of infection and the failure to improve with antibiotics.

A key feature of DRESS syndrome is eosinophilia. This case is atypical in that the eosinophil and neutrophil count was initially low. It is hypothesized that this was due to initial toxic marrow suppression following massive degranulation of eosinophils in response to the administration of the amoxicillin and/or tissue sequestration of both cell lines secondary to the inflammatory reaction.

There is no clear consensus of the treatment of DRESS syndrome beyond stopping the causative agent. There is no definitive evidence that the administration of steroids benefits patients with the syndrome.⁶

The pathogenesis of DRESS syndrome is also unclear but is understood to be multifactorial, incorporating both constitutional and acquired components.¹ It is currently hypothesized that reactive drug metabolites play a key part in the development of this condition along with coexisting viral infections and coadministration of other drugs.^{4,7,8}

DRESS syndrome has been commonly linked to anticonvulsants such as carbamazepine, phenytoin and, more recently, lamotrigine, but is also associated with a variety of other drugs including the antimicrobials sulfasalazine, other sulphonamides and trimethoprim.^{1,3,5,9,10} To the best of our knowledge this is the first time that DRESS syndrome has resulted from the use of amoxicillin and with so rapid a response including toxic marrow

Table 1. Evolution of total peripheral leucocyte, neutrophil and eosinophil counts during admission

	Day of admission									
	1	2	3	4	5	6	7	8	9	10
Leucocytes ($\times 10^9/L$)	1.7	4.3	14.4	16.4	14.3	12.1	7.7	8.0	7.4	11.5
Neutrophils ($\times 10^9/L$)	1.08	4.19	13.98	15.69	13.49	11.17	5.18	4.26	3.45	6.41
Eosinophils ($\times 10^9/L$)	0.01	0.01	0.16	0.25	0.26	0.17	0.85	1.29	1.43	1.62

suppression and/or tissue cell sequestration, which somewhat delayed the diagnosis. Studies have shown that the syndrome takes between 1 and 8 weeks to develop; in this case the patient became unwell within a matter of hours. The rapidity of the onset of the patient's symptoms mimics the IgE-mediated reaction seen in anaphylaxis; however, the negative mast cell tryptase result precludes this diagnosis.

In summary, we describe a novel, acute severe manifestation of DRESS syndrome caused by administration of a β -lactam antibiotic. The further administration of a β -lactam antibiotic to treat a presumptive neutropenic sepsis may have exacerbated the patient's condition and, had the early recognition of a possible DRESS syndrome not been made, could easily have resulted in a case report with a less favourable outcome. A case, nearly, of 'killing with kindness' through protocol-driven antimicrobial prescribing, in this case for presumed neutropenic sepsis. This case may question in part perhaps the broad philosophy of protocol-driven prescribing and emphasizes the need for better education regarding the presentation of acute sepsis and its medical mimics, and the existence of non-anaphylactic acute, severe drug reactions.

The patient has been told to avoid all β -lactam drugs in the future and that the condition may recur in conjunction with administration of other classes of drugs.

The patient's consent for publication of this case report has been obtained.

Acknowledgements

We thank Mr David Edwardson BDS, MFDS for providing the dental history.

Funding

None received.

Transparency declarations

None to declare.

References

- Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol* 2001; **137**: 357–64.
- Volpe A, Marchetta A, Caramaschi P *et al.* Hydroxychloroquine-induced DRESS syndrome. *Clin Rheumatol* 2008; **27**: 537–9.
- Ganeva M, Gancheva T, Lazarova R *et al.* Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review. *Int J Dermatol* 2008; **47**: 853–60.
- Bankar RN, Kohnke A, Palani SB. Drug rash with eosinophilia and systemic symptoms syndrome due to quinine. *J Postgrad Med* 2007; **53**: 272–3.
- Michel F, Navellou J-C, Ferraud D *et al.* DRESS syndrome in a patient on sulfasalazine for rheumatoid arthritis. *Joint Bone Spine* 2005; **72**: 82–5.
- Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* 2003; **206**: 353–6.
- Descamps V, Valence A, Edlinger C *et al.* Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001; **137**: 301–4.
- Uetrecht J. New concepts in immunology relevant to idiosyncratic drug reactions: the 'danger hypothesis' and innate immune system. *Chem Res Toxicol* 1999; **12**: 387–95.
- Descoux E, Argaud L, Dumortier J *et al.* Favourable issue of a fulminant hepatitis associated with sulfasalazine DRESS syndrome without liver transplantation. *Intensive Care Med* 2005; **31**: 1727–8.
- Schlienger RG, Knowles S, Shear N. Lamotrigine-associated anticonvulsant hypersensitivity syndrome. *Neurology* 1998; **51**: 1172–5.

Journal of Antimicrobial Chemotherapy

doi:10.1093/jac/dkp233

Advance Access publication 7 July 2009

Imipenem underdosing as a cause of persistent neutropenic fever?

Frédéric Lamoth¹, Thierry Buclin², Andres Pascual¹,
Thierry Calandra¹ and Oscar Marchetti^{1*}

¹*Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland;*

²*Division of Clinical Pharmacology and Toxicology, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland*

Keywords: blood concentrations, febrile neutropenia, persistent fever

*Corresponding author. Tel: +41 21 314 10 10 or 26;
Fax: +41 21 314 10 18; E-mail: Oscar.Marchetti@chuv.ch

Sir,

Clinical trials with the recommended 2 g daily dose (500 mg four times a day) of imipenem in febrile neutropenia have reported success rates of 60–80%.¹ Causes of persistent neutropenic fever often remain unexplained, which results in multiple investigations and empirical modifications of antimicrobial therapy.² The pharmacodynamic parameter predicting the *in vivo* antibacterial efficacy of β -lactam antibiotics is the proportion of the dosing interval during which plasma concentrations are above the MIC for the causative pathogen ($T_{>MIC}$). For carbapenems, $T_{>MIC}$ during 50–60% of the dosing interval is required to achieve bactericidal activity in neutropenic experimental animal models.³ In life-threatening infections, such as febrile neutropenia, success rates were significantly higher with $T_{>MIC}$ during 75–100% of the dosing interval.⁴ Based on these observations, some experts have recommended maintaining the trough antibiotic concentrations above the MIC, e.g. by extending the drug infusion time or by administering the drug with a continuous infusion.^{3,5}

We retrospectively assessed the association between imipenem plasma concentrations and response to antibacterial therapy in 29 neutropenic patients (79% acute leukaemias; 86% males; median age 58 years, range 27–78) with persistent fever for ≥ 3 days: 14 microbiologically documented infections (MDIs; 48%); 9 clinically documented infections (CDIs; 31%); and 6 fever of unknown origin (FUO; 21%). Imipenem was prescribed at the recommended dose for febrile neutropenia adjusted to the