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

1. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol* 2001; **137**: 357–64.

2. Volpe A, Marchetta A, Caramaschi P *et al.* Hydroxychloroquine-induced DRESS syndrome. *Clin Rheumatol* 2008; **27**: 537–9.

3. 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.

4. Bankar RN, Kohnke A, Palani SB. Drug rash with eosinophilia and systemic symptoms syndrome due to quinine. *J Postgrad Med* 2007; **53**: 272–3.

5. 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.

6. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* 2003; **206**: 353–6.

7. 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.

8. 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.

9. Descloux 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.

10. 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 Lamoth[1], Thierry Buclin[2], Andres Pascual[1], Thierry Calandra[1] 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

renal function (median 2 g/day, range 1–4; divided in four infusions over 30 min every 6 h). Results of imipenem plasma trough concentrations measured during persistent fever by a validated HPLC-UV method were obtained at a median of 6 days after start of therapy (range 3–11). Imipenem trough concentrations above 1 mg/L [MIC_{90} for the most frequent pathogens of febrile neutropenia according to the susceptibility data from the European Committee on Antimicrobial Susceptibility Testing (EUCAST); http://www.eucast.org] were targeted.

Median imipenem trough concentrations were 0.9 mg/L (range 0.25–5). A cause of persistent fever was documented in 16/29 (55%) episodes (6 resistant bacteria, 8 probable/possible mycoses and 2 non-infectious aetiologies). In 13/29 (45%) episodes (4 MDIs, 5 CDIs and 4 FUO) the cause of persistent fever (median duration 6 days, range 3–16) remained unknown. Imipenem concentrations were interpreted as low according to the above criteria in eight (62%) of them (median 0.6 mg/L, range 0.25–1). Imipenem underdosing was considered the probable cause of failure in three cases (no documented alternative cause and clinical improvement within 3 days after imipenem dose adjustment in the absence of any concomitant intervention): the clinical characteristics are summarized in Table 1. In the five remaining cases, the role of imipenem underdosing in the unexplained persistence of fever could not be assessed because of concomitant interventions in addition to imipenem dose adjustment (empirical antifungal therapy and/or vancomycin therapy, three cases), change of antibacterial therapy (one case) or spontaneous resolution of fever in the absence of any intervention (one case).

In febrile neutropenic patients, variations in the pharmacokinetics of β-lactam antibiotics, such as an increase in the volume of distribution and/or renal clearance, have been frequently reported. These modifications result in lower plasma concentrations when compared with healthy subjects.[6,7] We observed a high proportion of insufficient imipenem plasma concentrations in febrile neutropenic patients with persistent fever receiving the recommended 2 g daily dose. The analysis of clinical data suggests that imipenem underdosing was the probable cause of failure in a subgroup of patients not responding to therapy.

The persistence of fever despite broad-spectrum antibacterial therapy is observed in one-third of febrile neutropenic episodes. According to the Infectious Diseases Society of America guidelines, reassessment of empirical antibacterial therapy is recommended after 3–5 days of persistent fever; as resistant bacterial infections or invasive mycoses are suspected, an extensive diagnostic work-up, empirical modifications of antibacterial therapy and/or addition of antifungal therapy have to be considered.[2] In the majority of cases the cause of persistent fever cannot be identified and the utility of such interventions remains unknown. Although changes in pharmacokinetic parameters are frequently observed in these patients, inappropriate antibiotic dosing is usually not considered among the possible causes of failure. The measurement of antibiotic plasma concentrations by HPLC (or bioassay, as a simple alternative in hospitals without a clinical pharmacology service) is non-invasive and inexpensive, and might be easily added to the clinical, microbiological and radiological reassessment of response to empirical antibacterial therapy recommended during the time window including 3–5 days of persistent neutropenic fever. Documentation of low antibiotic blood levels in the absence of another cause of failure may contribute to optimizing individual management by avoiding

Table 1. Clinical characteristics of neutropenic patients with persistent fever attributed to imipenem underdosing

Sex (M/F)/age (years)/weight (kg)/creatinine clearance (mL/min)	Aetiology of febrile neutropenia	Imipenem dosing schedule	Imipenem trough blood concentration[a]	Assessment of response to imipenem therapy at time of obtention of trough concentrations: duration of fever/clinical course	Modification of imipenem dosing schedule	Days to resolution of fever after imipenem dose adjustment
M/48/61/92	CDI (neutropenic enterocolitis)	0.5 g qid	1 mg/L	3 days/persistent fever and enterocolitis	increase infusion time from 30 to 120 min	1
M/51/67/75	FUO	0.5 g qid	<0.25 mg/L	4 days/persistent fever	100% increase: 1 g qid	3
M/69/99/51	FUO	0.5 g tid	0.7 mg/L	6 days/persistent fever	33% increase: 0.5 g qid	1

M, male; F, female; qid, four times a day; tid, three times a day.
[a]HPLC-UV method validated according to international guidelines (analytical range 0.25–200 mg/L, intra-/inter-assay accuracy and precision >95% and <5%, respectively).[8]

JAC antiviral

unnecessary and expensive investigations and empirical modifications of therapy. Prospective pharmacodynamic investigations are needed to confirm the utility of measuring antibiotic plasma concentrations in persistent febrile neutropenia, which would justify its implementation in clinical management.

Acknowledgements

We would like to thank Merck, Sharp & Dohme-Chibret.

Funding

Merck, Sharp & Dohme-Chibret provided unrestricted grant support for development of the HPLC-UV analytical method, data collection and analysis.

Transparency declarations

No conflicts of interests (all authors).

References

1. Klastersky JA. Use of imipenem as empirical treatment of febrile neutropenia. *Int J Antimicrob Agents* 2003; **21**: 393–402.

2. Hughes WT, Armstrong D, Bodey GP *et al.* 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; **34**: 730–51.

3. Mouton JW, Touzw DJ, Horrevorts AM *et al.* Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet* 2000; **39**: 185–201.

4. Ariano RE, Nyhlen A, Donnelly JP *et al.* Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39**: 32–8.

5. Lortholary O, Lefort A, Tod M *et al.* Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia. *Lancet Infect Dis* 2008; **8**: 612–20.

6. Lamoth F, Buclin T, Csajka C *et al.* Reassessment of recommended imipenem doses in febrile neutropenic patients with hematological malignancies. *Antimicrob Agents Chemother* 2009; **53**: 785–7.

7. Navas D, Caillon J, Batard E *et al.* Trough serum concentrations of β-lactam antibiotics in cancer patients: inappropriateness of conventional schedules to pharmacokinetic/pharmacodynamic properties of β-lactams. *Int J Antimicrob Agents* 2006; **27**: 102–7.

8. Giannoni E, Moreillon P, Cotting J *et al.* Prospective determination of plasma imipenem concentrations in critically ill children. *Antimicrob Agents Chemother* 2006; **50**: 2563–8.

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkp216
Advance Access publication 23 June 2009

Inadvertent non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy in dual HIV-1/2 and HIV-2 seropositive West Africans: a retrospective study

Fred S. Sarfo[1], David F. Bibby[2], Uli Schwab[1], Lambert T. Appiah[1], Duncan A. Clark[2], Paul Collini[1], Richard Phillips[1], Ingrid Green[2], Matthias T. Dittmar[3] and David R. Chadwick[4]*

[1]*Department of Medicine, Komfo Anokye Teaching Hospital, PO Box 1934, Kumasi, Ghana;* [2]*Department of Virology, Barts and The London NHS Trust, London, UK;* [3]*Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, Queen Mary University, London, UK;* [4]*Department of Infection and Travel Medicine, The James Cook University Hospital, Middlesbrough, UK*

Keywords: Ghana, HIV, viral load

*Corresponding author. Tel: +44-1642-854429;
Fax: +44-1642-854017; E-mail: davidr.chadwick@stees.nhs.uk

Sir,

HIV-2 or dual HIV-1/2 infection makes up between 4% and 24% of all HIV infections in West Africa, and dual infection ~12% of all infections in Ghana.[1] HIV-2 infection progresses to AIDS more slowly than HIV-1; however, dual infection appears to progress at a rate similar to that of HIV-1.[2] Antiretroviral therapy (ART) has been widely available in Ghana since 2003, with good initial results.[3] Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART is first-line therapy. In many centres HIV testing has not routinely been type-specific, so patients infected with HIV-2 have started ART including NNRTIs that are ineffective against HIV-2.

To analyse the impact of NNRTI-based ART in dual HIV-1/2 or HIV-2 seropositive individuals in terms of clinical outcomes, surrogate markers or resistance mutations, we conducted a retrospective study of patients attending a large HIV clinic in Ghana where type-specific HIV testing was not routine. The study was approved by the Committee on Human Research Publications and Ethics at KNUST, Kumasi. Patients were tested for HIV-2 seropositivity using the Immunocomb HIV-1&2 Biospot test (Orgenics, Yavne, Israel). Response to NNRTI-based ART, efavirenz/nevirapine with two nucleoside reverse transcriptase inhibitors (NRTIs), was compared in 57 dual HIV-1/2 seropositive, 16 HIV-2 seropositive and 197 HIV-1 seropositive patients who had completed at least 12 months of ART. Clinical and laboratory data were collected retrospectively at 6 monthly intervals. Changes in patient weight, total CD4 count and HIV viral load a minimum of 3 months after starting ART were compared. Mean values for (normally distributed) laboratory data were compared using *t*-tests and χ^2 tests for categorical data.

Baseline characteristics (pre-ART) and responses to ART are shown in Table 1. There were significantly more females in the HIV-2-infected groups. Increases in mean CD4 count at 6 and/or 12 months after starting ART were significantly lower in HIV-2 seropositive compared with HIV-1 and dual seropositive patients, despite starting from higher CD4 counts. Weight gain was also lower in this group. Samples were available to quantify HIV-2 and/or HIV-1 viral loads in a proportion of patients (HIV-2, 63%; dual seropositive, 56%; HIV-1, 22%) after a median of 14 months of ART. Whilst in the majority of dual seropositive and HIV-1 seropositive patients HIV-1 ± HIV-2 viral loads were suppressed on ART, only 19% of the HIV-2 seropositive patients achieved undetectable HIV-2 viral loads. There was little difference in the rates of AIDS-defining pathology between groups. Only one death was recorded, in a HIV-2 seropositive patient; however, a number of patients were lost to follow-up after the first year of ART. In samples from seven