The changing face of antibiotic therapy

Antimicrobial resistance is one of the biggest challenges facing the NHS. Part of the solution is education and improved prescribing by doctors. Janssen-Cilag sponsored a meeting in May 2009 in Glasgow focussing on doripenem, a new carbapenem. This report highlights the role of doripenem in health-care-associated infection control.

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A decline in the development of new antibiotic agents coupled with the ongoing challenge of antimicrobial resistance, as stated in the Chief Medical Officer's 2008 annual report (Department of Health, 2009), highlights the importance of optimizing the use of currently available agents. Hospital infection rates remain high, impacting not only on mortality but also on length of hospital stay and increased health-care costs (Plowman et al, 2001).

Dr David Livermore, Director of the Centre for Infection's Antibiotic Resistance Monitoring and Reference Laboratory in London, shared the good news that numbers of meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemias have been declining since 2003, but the specific reasons are difficult to pinpoint. He suggested that improved infection control, a natural decline in one of the two major MRSA strains responsible and the introduction of a number of newer antibiotics with anti-MRSA activity had probably all played a part. However, Dr Livermore cautioned that it was not all good news. 'We have seen a dramatic increase in fluoroquinolone and cephalosporin resistance in *Enterobacteriaceae* and a slow dissemination of a number of different carbapenemases in *Enterobacteriaceae* as well as *Acinetobacter baumannii*. *Pseudomonas aeruginosa* remains a problem organism too, mainly due to mutational resistance rather than acquired genes,' he said.

According to Professor Alistair Leanord, Consultant Medical Microbiologist at the Southern General Hospital in Glasgow, early appropriate and adequate use of antibiotic therapy has a significant impact on mortality and morbidity. Almost 30 years ago, Kreger et al (1980) showed that appropriate antibiotic therapy decreased mortality and the frequency of septic shock in gram-negative bloodstream infection. More recently, Kollef et al (1999) reported that inadequate treatment of infections was the most important independent determinant of hospital mortality.

The role of carbapenems in treating health-care-associated infections

Dr Anne Eastaway, Consultant Microbiologist at Health Protection Scotland, highlighted the important role of carbapenems in the treatment of severe infection: 'They should be used as empiric therapy in severe nosocomial infections in critically-ill patients in the intensive care unit, in late-onset nosocomial pneumonia and severe intra-abdominal infection as well as in chronic infections with multi-drug resistant *Pseudomonas* spp.' She cautioned that their use should not just be reserved for infections with known resistant organisms, but that empiric use should be based on local antimicrobial resistance data. Their use should be monitored against local policy within a broader antimicrobial stewardship programme.

Doripenem in health-care-associated infection control

Doripenem is the newest, broad-spectrum, intravenous carbapenem antibiotic indicated for the treatment of nosocomial pneumonia including ventilator-associated pneumonia, complicated intra-abdominal infection and complicated urinary tract infection. While all carbapenems share a core molecular structure, each agent has a slightly different side chain. Subtle differences in both the core and side chain components of the carbapenem molecule can confer different properties on the molecule: substituting a methyl group for a hydrogen at the C1 position significantly stabilizes the molecule from hydrolysis by the renal enzyme DHP-1. Alterations to the side chain can shift the relative balance between activity against gram-negative or gram-positive organisms, although no currently licensed carbapenem has clinically useful anti-MRSA activity.

Clinical data show that doripenem is comparable to both imipenem and meropenem in the treatment of ventilator-associated pneumonia and complicated intra-abdominal infection respectively (Chastre et al, 2008; Lucasti et al, 2008). In another ventilator-associated pneumonia study (Merchant et al, 2008), although overall efficacy was similar between the two carbapenems, patients receiving doripenem were both extubated and discharged from hospital a day earlier than those receiving imipenem. Similarly, when patients were stratified by APACHE score in a ventilator-associated pneumonia study, doripenem achieved a significantly better cure rate in patients with high APACHE scores (>24) when compared to imipenem (75% *vs* 17%, P=0.043) (Chastre et al, 2008).

Dr Tony Donovan, of Janssen-Cilag, highlighted that doripenem has a lower in-vitro propensity to select carbapenem-resistant *P. aeruginosa* than either imipenem and meropenem (Sakyo et al, 2006). Clinical trials showed doripenem to be well tolerated, with rates of adverse effects

similar to comparator agents, and to have a low seizure potential compared with piperacillin/tazobactam and imipenem (Chastre et al, 2008; Réa-Neto et al, 2008).

Professor Alistair Leanord evaluated the cost-effectiveness of doripenem in the treatment of nosocomial pneumonia, complicated intra-abdominal infection and ventilator-associated pneumonia in the Greater Glasgow and Clyde region. He concluded that, based on list price, doripenem offers savings on the basis of drug acquisition cost alone in all three indications. It also offers cost savings associated with length of hospital stay, particularly in the intensive care unit, and on the ward for ventilator-associated pneumonia when compared with imipenem. He went on to calculate the potential cost savings to the Greater Glasgow and Clyde region if patients were switched from meropenem 1 g three times daily to doripenem 500 mg three times daily. 'Switching only 10% of patients from meropenem would equate to an annual cost saving of approximately £6000, and a 50% conversion could save £30 000', advised Professor Leanord.

Optimizing carbapenem use in health-care-associated infection

Dr Robert Masterton, Executive Medical Director and Consultant Microbiologist at NHS Ayrshire and Arran, reiterated the importance of maximizing the potential of available agents, especially in the treatment of severe sepsis. He outlined the concept of target attainment, which uses microbiological data, pharmacokinetic data and dosing regimens to help clinicians select the most appropriate empiric therapy. It is increasingly accepted that a target attainment rate of >90% is required when treating severe infection. With carbapenem antibiotics, as with all β-lactams, the fraction of the dosing interval that the plasma (or other tissue) concentration exceeds the organism minimum inhibitory concentration (fT>MIC) is the best criterion for assessing effective antimicrobial activity. This is particularly relevant when treating organisms, such as *Pseudomonas*, that are frequently inherently less susceptible to β-lactam antibiotics.

Using prolonged antibiotic infusions can help to achieve an increase in the fT>MIC without increasing the antibiotic dose, facilitating microbiological and clinical cure rates. This requires that the antibiotic is sufficiently stable so as not to breakdown during this increased administration period. Doripenem is unique among the anti-pseudomonal carbapenems to have received a license for 4-hour administration. Other carbapenems are either not sufficiently stable to use this method at all or special precautions are required for an extended infusion (Viaene et al, 2002; Kuti et al, 2004).

'Infusion means that patients are more likely to receive a dose that is adequate, timed and consistent,' highlighted Dr Masterton. He emphasized that there was definite evidence of cost savings with extended infusion of carbapenems before highlighting data from Chastre et al (2008) on the use of doripenem where the authors reported a trend towards a clinical benefit with extended infusion of doripenem in older patients and in those with higher APACHE II scores as well as a trend towards a benefit in terms of the generation of less resistance with doripenem. **BJHM**

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KEY POINTS

- Although levels of meticillin-resistant *Staphylococcus aureus* infection are decreasing, developing resistance trends need to be closely monitored.
- The rate of new antibiotics being licensed and the pipeline of new antibiotics in development are both reducing.
- Until new antibiotics are available the use of existing agents must be optimized. For carbapenems, as with all β-lactam antibiotics, the proportion of the dosing interval that the blood concentration is over the pathogen minimum inhibitory concentration is the crucial parameter.
- Where the antibiotic is sufficiently stable extended infusion can be a cost-effective way of using carbapenems to maximize target attainment without incurring additional costs by increasing the dose.
- Doripenem may offer additional benefits by limiting the selection of resistant organisms, a potential issue with carbapenem therapy.