Linezolid audit: similarities and contrasts with published experience

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Sir,

Ziglam et al. 1 have recently reported an audit of linezolid use in a hospital in Scotland for the period March 2001–September 2003. We conducted a similar audit of linezolid use in a 504 bed teaching hospital, to assess the profile of patients prescribed linezolid, clinical and microbiological indications for treatment, adherence to the licensed indications and product specifications, and documented adverse events. The hospital provides a range of surgical and medical specialties with the exceptions of orthopaedics, neurosurgery and renal medicine. The audit was conducted between October 2004 and April 2005. The hospital drugs and therapeutics committee recommends that linezolid be used in consultation with the Departments of Infectious Diseases or Microbiology; however, consultation cannot be mandated within the hospital governance system.

Patients prescribed linezolid were identified through pharmacy, and the medical records for each case were reviewed. Fifty-three courses of linezolid were prescribed to 46 patients, and the clinical indications are listed in Table 1.

Methicillin-resistant Staphylococcus aureus (MRSA) was the microbiological indication for 49% of the courses; vancomycin-resistant enterococcus (VRE) in 4%, vancomycin-susceptible Enterococcus faecium (4%) and coagulase-negative staphylococcus were also targeted (2%). In 41% of the courses the prescription was empirical. In 55% of cases linezolid was prescribed as initial therapy for a vancomycin-susceptible organism. In 31% of cases this prescription was made without a recorded or apparent justification for favouring linezolid use over vancomycin.

Of the 53 courses prescribed, 20 were initiated by the Department of Microbiology or Infectious Diseases in the intensive therapy unit, and a further three courses were initiated following consultation with these departments. Thirty courses (57%) represented autonomous prescribing decisions. The median duration of therapy was 12 days (range 1–58 days). One course of linezolid was associated with a documented adverse effect, being a reversible pancytopenia which occurred in a 65-year-old lady.

Our findings present both similarities to and contrasts with those of Ziglam et al. 1. Our audit was conducted more than a year after the study by Ziglam et al. 1 was completed. By the time of this audit, evidence indicating that linezolid may have advantages for initial therapy for MRSA pneumonia 2,3 was widely disseminated, and there was greater familiarity with linezolid among clinicians. As with the previous study, we found that MRSA is the most common microbiological indication for linezolid prescription and that major prescribing was done without consultation with Microbiology or Infectious Disease. In contrast with Ziglam et al. 1, we found that linezolid was used in a high proportion of cases (42% compared with 6%) without apparent microbiological indication. Impaired renal function or poor venous access was an indication for linezolid use in 34% of cases in the Ziglam study 1 but only for 6% of the courses prescribed in this study. Thrombocytopenia was noted in 8% of the courses in the earlier study but in only 2% in this study.

Our audit indicates relatively frequent use of linezolid without microbiological justification and its use as first line therapy for organisms/infections that could be expected to respond to vancomycin. This pattern of use may reflect growing familiarity with linezolid among clinicians. Anecdotal experience suggests that the convenience of administration of linezolid and its low toxicity, together with persistent fears of glycopeptide toxicity, are major factors in driving linezolid prescription.

Linezolid is a valuable but expensive agent for treatment of resistant Gram-positive agents. Given that emergence of linezolid resistance during treatment has been described previously on a number of occasions, 4,5 efforts to limit the use of this agent are appropriate. Mandatory consultation with infection specialists with regard to linezolid prescription is not enforceable in many healthcare governance systems, and in such settings reliance must be placed on educational activities, including audits such as this and feedback of findings.

Table 1. Clinical indications for use of linezolid during a 6 month audit in a teaching hospital

<table>
<thead>
<tr>
<th>Clinical indications</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Pneumonia</td>
<td>17 (32)</td>
</tr>
<tr>
<td>SSTI</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Biliary sepsis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dental abscess</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Infected haematoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Intolerance to glycopeptides</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>1 (2)</td>
</tr>
<tr>
<td>No infection site noted</td>
<td>1 (2)</td>
</tr>
<tr>
<td>‘Chesty post-op.’</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

SSTI, skin and soft tissue infection.

n = 53.
Transparency declarations

None to declare.

References


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Sir,

Unprecedented advances have occurred in the treatment of chronic hepatitis B during the past 5 years. However, the introduction of orally active antiviral nucleoside/nucleotide analogue treatments has seen the emergence of drug resistance as the major factor limiting their efficacy.

The first of these agents to be used clinically was lamivudine, which effectively suppresses viral replication, reduces disease activity and improves liver histology. However, prolonged treatment with lamivudine results in the emergence of drug-resistant hepatitis B virus (HBV) in 24% of patients after 1 year of therapy and 70% of patients following 4 years of therapy. Viral resistance to lamivudine has been mapped to specific mutations in the tyrosine–methionine–aspartate–aspartate (YMDD) motif in the C domain of HBV polymerase, with compensatory mutations in the B domain at V173L and L180M.

Adefovir dipivoxil, an orally available prodrug of adefovir monophosphate, has potent antiviral activity against lamivudine-resistant strains of HBV. In contrast to lamivudine, the cumulative incidence of adefovir resistance is 0% at 48 weeks, 3% at year 2, 6% at year 3 and 15% at year 4, due to development of point mutations rtA181V/T or N236T in the B or D domains, respectively. The adefovir-associated mutation rtN236T in the HBV polymerase gene has been shown to maintain susceptibility to lamivudine in vivo. However, the other adefovir-associated mutation, rtA181V/T, confers partial resistance to lamivudine. Therefore, antiviral agents active against both adefovir- and lamivudine-resistant HBV strains are required.

In this report, molecular evidence of the emergence of adefovir resistance during antiviral therapy in two patients with e antigen-positive chronic HBV is presented. To our knowledge, these are the first cases reported in the Republic of Ireland of HBV polymerase gene mutations associated with resistance to adefovir.

Case 1 was a 36-year-old male of Asian ethnic origin who was found to have hepatitis B e antigen (HBeAg)-positive chronic HBV infection during a pre-employment check-up in 2003. He was referred to St James’ Hospital, Dublin, where investigations

Figure 1. Virological course before and after the emergence of adefovir resistance in Case 1 (a) and Case 2 (b). HBV polymerase gene mutations are shown above each graph. Antiviral therapy is indicated below each graph.