Clinical audit of linezolid use in a large teaching hospital

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Objectives: Linezolid, the first available agent in the new class of oxazolidinone antibiotics, represents a significant advance in the management options available for combating methicillin-resistant Staphylococcus aureus (MRSA) infections. In the UK it was launched for clinical use in 2001. The aim of this study was to audit the clinical use of linezolid and compliance with the guidelines of the hospital antibiotic committee.

Methods: Our hospital antibiotic committee agreed clinical indications for linezolid use. We undertook an audit of compliance with these recommendations and also reviewed its use in terms of the source of infection, microbiology, duration of therapy, side-effects and choice of previous treatment.

Results: Seventy-seven inpatients prescribed linezolid in Ninewells Hospital in the 3 years between March 2001 and September 2003 were audited. Overall compliance with our local recommendations appears to be very good. The main justification for using linezolid is the presence of existing or worsening renal dysfunction or poor venous access (34%) or lack of tolerance or clinical failure following glycopeptide monotherapy or combination therapy (32%). Skin and soft tissue infections (26%) were the most frequently diagnosed infections, although an increasing number of patients appear to receive linezolid for the treatment of lower respiratory tract infections, primarily in the ICU for nosocomial or ventilator-associated pneumonia. MRSA organisms were the most common cause of microbiologically proven treated infections [n = 43 (56%)]. Disappointingly, only 34 out of 77 patients had case record documentation of prior approval by an infection specialist.

Conclusions: The use of linezolid in our hospital appears to follow local guidelines, but the quality of information recorded in the notes could be optimized. Consequently, a linezolid mandatory order form to be completed by the attending prescribing clinician has been introduced, and will be subject to future evaluation. We recommend such specific antibiotic utilization reviews or audits of new agents introduced into clinical infection practice.

Keywords: Staphylococcus aureus, antibiotic utilization, glycopeptides

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) infections represent a major therapeutic challenge. Linezolid, the first available agent in the new class of oxazolidinone antibiotics, represents a significant advance in the management options available for combating these infections. In the UK it was launched for clinical use in 2001. We published a set of recommendations in 2001 outlining the likely formulary positioning of this agent in our hospital. These recommendations were widely accepted as a reasonable and appropriate positioning for early use of linezolid in UK practice. Once these recommendations were accepted by our Antibiotic Committee, linezolid use was monitored by our Pharmacy Department-implemented ALERT antimicrobial programme. ALERT antibiotics are a number of primarily intravenous (iv) antibiotics that can only be prescribed for approved indications and are subject to ongoing surveillance by the clinical pharmacists. One of the key components of this surveillance is that linezolid would be used only for the above agreed indications and subject to prior approval by an infection specialist (clinical microbiologist or infectious disease physician). It is clear that since these recommendations were published, linezolid has been used successfully in a number of other therapeutic areas based on new published clinical trial data and evolving clinical experience.

The results of this surveillance for linezolid are presented here. The intention of this audit is: (i) to provide an analysis of 31 months...
of clinical experience with a new agent so that clinicians and our Antibiotic Committee can identify compliance with locally agreed guidance and appropriateness of its use; and (ii) to understand the challenges and demands on a new agent from clinicians so that the formulary committee is responsive to this information.

The key function of the audit was to review the adherence to our recommendations/guidelines, analyse linezolid’s clinical use and assess the degree of its use by various departments in the hospital (data not presented here).

Methods

During the time of the audit the surveillance system was rather basic. Each time linezolid was prescribed, the clinical pharmacist would complete a form (kept in pharmacy records) recording the patient’s hospital number, the ward, the date of the prescription and the attending consultant. Seventy-seven inpatients prescribed linezolid at Ninewells Hospital, Dundee, UK, between March 2001 and September 2003 were reviewed. The key recommendations (Table 1) were used as the audit standards.\(^3\) Data from inpatient notes and inpatient medicine charts were collected for a variety of parameters including clinical indications, isolated pathogen(s) and source of infection, as shown in Table 2. We also specifically looked at duration and choice of previous treatment and reviewed the incidence of linezolid-related adverse effects. If information was not documented in case notes or medical charts it was recorded as unavailable.

Results and discussion

The median age of the patients was 65 years (Table 2). Only 57 of 77 (71%) of patients had already received a glycopeptide (40 of 77 single and 17 of 77 combination), whilst a further 10 of 77 (13%) had received an oral agent such as rifampicin with either trimethoprim or minocycline according to the MRSA susceptibility result (Table 2). Therefore, 84% of patients in total had received prior treatment. The four patients who had meticillin-susceptible \textit{S. aureus} (MSSA) had received glycopeptide therapy as part of the outpatient and home parenteral iv therapy programme (OHPAT). Vancomycin-resistant enterococcus (VRE) was only isolated from eight (10%) patients treated with linezolid (Table 2). The mean duration of iv linezolid was 7.2 days and the mean duration of oral linezolid was 15.7 days. We had written evidence of approval from an infectious diseases physician or clinical microbiologist in only 34 of 77 (44%) patients. Only 10 of 77 patients experienced linezolid adverse effects; six of 10 had thrombocytopenia, two anaemia and two rash.

Our data indicate that infections due to VRE are infrequent in our hospital and were confined primarily to the renal unit. Overall compliance with our recommendations appears to be very good. The main justification for using linezolid appears to be due to the presence of existing or worsening renal dysfunction or poor venous access (34%), or lack of tolerance or clinical failure following glycopeptide monotherapy or combination therapy (32%). A significant number (71%) of these patients had received glycopeptide (single or combination) or other (14%) oral therapy prior to starting linezolid. This confirms that conventional therapy with glycopeptides remains the first-line treatment. Outpatient use of linezolid in our hospital remains minimal, presumably as a result of a large local ambulatory OHPAT programme,\(^2\) although conversion from iv to oral therapy followed by early hospital discharge has remained an option in a small percentage of patients (13/88; 15%).

Table 1. Formulary positioning of linezolid\(^3\)

<table>
<thead>
<tr>
<th>Source of infection</th>
<th>Number of sources of infection (%)</th>
<th>Clinical indications according to guidelines</th>
<th>Number of patients (%)(^a)</th>
<th>Isolated pathogen</th>
<th>Number of patients (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BJI</td>
<td>19/78 (25)</td>
<td>deteriorating or severely impaired renal function or poor venous/iv access</td>
<td>30/88 (34)</td>
<td>MRSA</td>
<td>43 (56)</td>
</tr>
<tr>
<td>cSSTI</td>
<td>20/78 (26)</td>
<td>glycopeptide clinical failure or intolerance</td>
<td>28/88 (32)</td>
<td>MRSE</td>
<td>11 (14)</td>
</tr>
<tr>
<td>PDI</td>
<td>6/78 (8)</td>
<td>intravenous to oral switch</td>
<td>13/88 (15)</td>
<td>enterococci</td>
<td>4 (6)</td>
</tr>
<tr>
<td>SBP</td>
<td>5/78 (6.5)</td>
<td>proven VRE</td>
<td>8/88 (9)</td>
<td>others(^c)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>VAP/NP</td>
<td>16/78 (21)</td>
<td>outpatient therapy</td>
<td>5/88 (6)</td>
<td>no organisms identified</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Line bacteraemia</td>
<td>9/78 (12)</td>
<td></td>
<td>4/88 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3/78 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BJI, bone and joint infections including prosthesis and osteomyelitis; cSSTI, complicated skin and soft tissue infection; PDI, peritoneal dialysis infection; SBP, spontaneous bacterial peritonitis; VAP/NP, ventilator-associated pneumonia/nosocomial pneumonia; MRSE, meticillin-resistant \textit{Staphylococcus epidermidis}.\(^d\)

\(^{a}\)Eleven patients had more than one indication.

\(^{b}\)Three patients had both MRSE and MRSA, one patient had MSSA and VRE, and one patient had MRSA and VRE.

\(^{c}\)One patient with nephrostomy site infection, isolation of MRSA; three patients who were on trimethoprim/rifampicin got hepatitis with rifampicin.

\(^{d}\)Other organisms included diptheroids, corynebacterium and anaerobes.
The main indication for changing from iv to oral linezolid is in complicated skin and soft tissue infections (cSSTIs), line-related infections with bacteraemia, and in a small group of patients with bacterial peritonitis with renal dysfunction where iv access was difficult or unable to be achieved and a rifampicin-containing regimen was deemed inappropriate by the attending liver team. We note that oral fusidic acid is not commonly used in our hospital.

A range of sources of infection was identified; only 26% were due to cSSTI. These patients were those who had refused OHPAT treatment or insisted on oral therapy. An increasing number of patients appear to receive linezolid for the treatment of lower respiratory tract infections, primarily in the ICU for nosocomial or ventilator-associated pneumonia (VAP). Use in the ICU for lower respiratory tract infections has continued to increase since this audit (D. Nathwani, personal observation). The main reasons responsible for increasing use of linezolid in the ICU are clinical failure or renal dysfunction, but our impression from talking to intensivists and others is that there are concerns about glycopeptide efficacy in severe MRSA-VAP. Emerging data may support some of these concerns.6 The greater flexibility offered by linezolid oral therapy and the high oral bioavailability is also often quoted by clinicians as a significant factor in choosing this option.

Linezolid use in bone and joint infections (BJIs) is primarily owing to clinical failure with existing options, the need for an oral agent as the patients were not deemed suitable for OHPAT or where patients had failed OHPAT. Despite traditional use of oral options such as tetracycline, trimethoprim or ciprofloxacin with rifampicin, we have noticed an increasing demand from orthopaedics for linezolid based on its good bone penetration and reports of success in some patients with osteomyelitis or BJIs.7 Whilst early data may appear encouraging for use in this group, particularly for protracted periods, linezolid should be approved with caution in light of safety concerns,8 the emergence of resistance9 and the lack of good quality clinical trials in this clinical setting.

Linezolid was generally well tolerated amongst our patient group, with a median duration of therapy of 22 days.

It is disappointing that only 34 of 77 patients had received prior approval by an infection specialist. Our experience and those of pharmacists suggests that more prescriptions had approval, but that this had not been recorded in the notes. In line with our previous experience,10 the quality of information in case notes is suboptimal. To facilitate this and ensure that prescribing clinicians actively consider good record keeping, which helps to protect the welfare of patients and clients and promote high standards of clinical care, we have developed and introduced a linezolid mandatory order form (Figure 1). This had been adapted from a similar scheme introduced by the Antibiotic Steering Group in Hammersmith Hospitals NHS Trust, London, UK, in 2002. The form will be required to be completed by the prescribing clinician and will only be valid for 21 days. If the treatment is to be continued further authorization will be required and a second form will need to be completed. Completion of the form will also be an educational tool for the prescribing clinician. This form will collect much of the information in this audit and will be placed in the patient’s case

**Figure 1.** Linezolid mandatory order form. This form is valid for a maximum of 21 days treatment, after which treatment must be reviewed with microbiology/infectious diseases and a new form written if treatment is to be continued. Platelet counts must be monitored weekly as linezolid can cause thrombocytopenia.
notes, as well as a copy being kept in the hospital pharmacy. We aim to ensure that future prescribers of linezolid are compliant with guidelines through this mechanism, with the hope that time-consuming case record audit with poor information will not be necessary. Ideally, in the future, such information will be recorded and available through an electronic prescribing recording system.

Linezolid use in our hospital appears to follow local guidelines. The majority of patients appeared to receive a glycopeptide as first-line treatment. New or worsening renal dysfunction and clinical glycopeptide failure or intolerance appear to be common justifications for changing to linezolid, whilst poor venous access and iv to oral switch are less common but important reasons for its use. In centres where an OHPAT programme is not available this may be an attractive option. The recording of approval of linezolid use by infection specialists was disappointingly low. It remains to be seen whether introducing a mandatory linezolid order form results in better quality of information to undertake a follow-up audit. We recommend such specific antibiotic utilization reviews or audits of new agents introduced into clinical infection practice.

References


