Linezolid: safety and efficacy in special populations

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Linezolid has been in general use in the UK since 2000. Although toxicity, particularly haematological and neurological, has been an issue, linezolid has proved to be an effective alternative to glycopeptides in the treatment of Gram-positive infections. Since its original licence for the treatment of skin and soft tissue infections and pneumonia, there have been reports of its successful use in the treatment of bone and joint infections, endocarditis, and other difficult-to-treat infections.

Keywords: oxazolidinone, toxicity, adverse events, Gram-positive infection

Introduction

Linezolid was first licensed in 2000 and is currently approved for use in the UK to treat documented complicated skin and soft tissue infections (SSTIs) and pneumonia caused by susceptible Gram-positive bacteria. In the years since it became available, the use of linezolid has been widened to include the treatment of other difficult infections. This article focuses on the safety and efficacy of linezolid in these clinical settings. In particular, this article will discuss the use of this agent in patients who have pre-existing conditions or who are at risk for some of the recognized adverse effects of linezolid.

As background for this paper, a literature search was conducted of all published articles in English over the past 10 years using ‘linezolid’ and ‘oxazolidinone’ as search criteria. This was combined with literature searches previously conducted using ‘MRSA’ and ‘bone and joint infections’. From these, meta-analyses of randomized controlled trials and other papers that specifically included mention of adverse effects were selected for inclusion.

Safety

Analysis of the initial Phase 3 clinical trials demonstrated that drug-related adverse events were significantly more common in patients receiving linezolid, but the incidence of serious adverse events was similar between linezolid and comparators.1 These data, together with those obtained from subsequent trials and patient adverse event reports, facilitated the categorization of linezolid-related adverse events into a number of broad headings. It has been postulated that the majority of the adverse reactions associated with linezolid can be attributed to mitochondrial toxicity.2,3

Haematological

Animal studies performed prior to human trials demonstrated reversible time and dose-dependent myelosuppression.5 Analysis of the early human clinical trials did not reveal any significant difference in the rates of haematological events between linezolid and the comparator.4 Nevertheless, when linezolid became clinically available, reports of thrombocytopenia, anaemia and pancytopenia began to emerge.5,6 Re-analysis of the data for patients treated for longer than 14 days revealed that the incidence of thrombocytopenia was greater with linezolid than with the comparator drug.4 As even more patient data emerged, the incidence of thrombocytopenia and anaemia appeared to be greater than that predicted from the clinical trials, although these conditions were reversible.7 Certain groups of patients, particularly those with renal impairment, appear to be more susceptible to haematological complications.8 Evidence is conflicting about the risk of thrombocytopenia and anaemia in patients with pre-existing haematological abnormalities, however, three studies evaluating linezolid use in cancer and bone marrow transplantation failed to show any increased risk of haematological adverse effects.9–11

Neuropathy

Serious neuropathy (both optical and peripheral) has been reported in patients receiving therapy for more than 28 days.7 The peripheral neuropathy usually presents as paresthesia of the extremities with preservation of motor function. Optical neuropathy presents with acute loss of central vision that progresses to loss of colour vision and visual acuity.12,13 Although symptoms improve once linezolid has been discontinued, case reports have described some permanent disability.13

Lactic acidosis

Increases in plasma lactate (>2 mmol/L) have been described with linezolid use, generally in patients with numerous co-morbidities, such as sepsis, thiamine deficiency and cirrhosis.9 It is largely asymptomatic and consequently probably under
diagnosed. Following discontinuation of therapy, lactate levels return to normal.\textsuperscript{14}

**Hepatic dysfunction**

Linezolid can induce hepatic transaminases and has been associated with cholestasis, but these abnormalities are infrequent, minor and rarely lead to therapy being truncated.\textsuperscript{4}

**Drug interactions**

Linezolid is a weak inhibitor of monoamine oxidase (MAO) and may potentially cause ‘serotonin syndrome’ in patients taking selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, MAO inhibitors, cocaine and other recreational drugs such as MDMA (3,4 methylenedioxyxymethamphetamine, more commonly known as ‘ecstasy’).\textsuperscript{1} Although the use of linezolid would normally be avoided in patients taking these drugs, Taylor et al.\textsuperscript{15} published their experience with concomitant use in 72 patients and concluded that it was safe so long as the patients were closely monitored. Discontinuation of therapy was necessary in only four patients.

**Paediatrics**

Linezolid has been widely used in paediatrics, however, patient numbers fall well below those of adults. From the data available, reports of the incidence and range of adverse reactions are very similar to those seen in adults.\textsuperscript{16} Further details can be found in a separate paper in this Supplement.\textsuperscript{17}

**Efficacy**

**Skin and soft tissue infection**

The efficacy of linezolid compared with other agents has been studied in a number of randomized clinical trials (RCTs) and this has been the subject of two recent meta-analyses.\textsuperscript{18,19} For all SSTIs, Beibei et al.\textsuperscript{19} analysed six RCTs and concluded that for empirical treatment linezolid was associated with high clinical response rates. For SSTIs caused by methicillin-resistant Staphylococcus aureus (MRSA), Bounthavong and Hsu\textsuperscript{18} analysed five studies comparing vancomycin and linezolid and concluded that although clinical outcomes were inconsistent, linezolid was more likely to achieve microbiological success. Logman et al. widened the analysis to include other antibiotics as comparators and demonstrated higher success rates for linezolid, dalbavancin and telavancin when compared with vancomycin and tigecycline.\textsuperscript{20} In 2004, Wilcox et al. compared linezolid with teicoplanin in 228 patients with SSTI and found no statistical difference in clinical outcome.\textsuperscript{21}

In 2010, Itani et al. compared linezolid with vancomycin in 1052 patients with documented cSSTI. Clinical success rates were high and similar in the two treatment groups.\textsuperscript{21a}

**Bacteraemia**

Data are more limited for the evaluation of efficacy in bacteraemia. Beibei found only three RCTs, these demonstrated treatment success in 76% of the patients receiving linezolid and 78% for vancomycin. This difference was not statistically significant. However, there were only 271 evaluable patients.\textsuperscript{19} When compared with teicoplanin in a study in which 56 patients were evaluated, linezolid was highly effective.\textsuperscript{20} It is interesting to note that the majority of teicoplanin failures occurred in patients with bacteraemia caused by S. aureus (9/18 for teicoplanin, 2/13 for linezolid).

In a Phase III study published in 2009, in comparing linezolid with vancomycin in patients with cSSSIs and catheter-related bloodstream infections (CRBSIs), non-inferiority criteria were met for the primary endpoints and the frequency and severity of adverse events were similar between groups. Mortality rates were 10.4% for linezolid recipients and 10.1% for control subjects in the modified intent-to-treat population (all patients with Gram-positive baseline culture) through test of cure, and they were 21.5% for linezolid recipients and 16.0% for the control group for all treated patients through post-study treatment day 84.

The authors concluded that linezolid demonstrated microbiological success rates non-inferior to those for vancomycin in patients with cSSSIs and CRBSIs caused by Gram-positive organisms and that patients with catheter-related infections must be carefully investigated for the heterogeneous underlying causes of high morbidity and mortality, particularly for infections with Gram-negative organisms.\textsuperscript{21b}

**Pneumonia**

There are a range of clinical trials that have evaluated the use of linezolid in the treatment of pneumonia. For community-acquired pneumonia (CAP), linezolid was compared with ceftriaxone.\textsuperscript{22} A total of 747 patients were studied and no difference in outcome was demonstrated in either group. These data suggest that linezolid should not be used as first-line therapy for CAP.\textsuperscript{23} For nosocomial pneumonia, a large meta-analysis of trials comparing glycopeptides and linezolid was recently published.\textsuperscript{24} That study reviewed eight trials with a total of 1641 evaluable patients. Their meta-analysis did not support the superiority of linezolid over glycopeptides in either all the patients studied or in a subgroup analysis of only those known to be MRSA positive. Another meta-analysis came to a similar conclusion, but went on to comment that the risk of thrombocytopenia doubled in the linezolid group.\textsuperscript{25} These results complement existing guidelines for the treatment of ventilator-associated pneumonia\textsuperscript{26} and MRSA.\textsuperscript{27}

**Bone and joint infections**

Linezolid has good bone penetration, is active in biofilms and has been used with mixed success both as monotherapy and in combination with other agents for the treatment of bone and joint infection, including prosthesis-related disease.\textsuperscript{28} In a series of 20 patients with prosthetic infection treated with monotherapy, four failures were reported, but owing to prolonged treatment courses there were a significant number of adverse effects.\textsuperscript{29} These findings were echoed by other studies that evaluated the use of linezolid in a range of orthopaedic infections.\textsuperscript{30} Good clinical data on the outcomes of combination therapy are lacking, but in vitro\textsuperscript{31} and animal model data\textsuperscript{32} are available. These experiments demonstrated that linezolid could protect...
against the emergence of rifampicin resistance. The combination of linezolid and gentamicin has been noted to be antagonistic in time–kill studies.

Endocarditis

The early animal models of endocarditis demonstrated that antibiotic therapy must be bactericidal to ensure success in the treatment of endocarditis. These experiments were nearly all based on cell wall active antibiotics, particularly benzylpenicillin. These experiments have been repeated with linezolid and rifampicin, producing a significant reduction in bacterial burden for MRSA infection. There have been a number of case series demonstrating the successful use of linezolid to treat endocarditis (both native and prosthetic), and even in patients with enterococcal endocarditis, which is notoriously difficult to eradicate.34

Central nervous system

Linezolid has good penetration into the brain and particularly CSF35 and is now widely used as empirical therapy for a range of neurological and neurosurgical infections36,37 and the treatment outcomes are scarce, and in most cases linezolid was used in combination with other antibiotics such as vancomycin and aminoglycosides administered via the intra-ocular route.

Endophthalmitis

Achieving active concentrations of antibiotics in the eye following systemic administration is a challenge. Studies have demonstrated that concentrations in excess of the MICs of common pathogens have been achieved with linezolid in both the aqueous and vitreous humours.38,39 Good clinical data on treatment outcomes are scarce, and in most cases linezolid was used in combination with other antibiotics such as vancomycin and aminoglycosides administered via the intra-ocular route.

Conclusions

Linezolid has proved to be successful in the treatment of a wide range of Gram-positive infections.40 Despite it being a bacteriostatic agent, there are reports of good outcomes in patients with difficult infections treated with monotherapy.

Haematological toxicity, particularly thrombocytopenia, remains an important issue, but studies evaluating the use of linezolid in high-risk recipients and those with pre-existing platelet dyscrasias do not seem to suggest any added toxicity.

The risk of haematological and neurological adverse effects has limited the recommended duration of linezolid therapy to a maximum of 28 days. This could potentially limit its use for patients with complicated bone and joint infections or for endocarditis, however, if patients can be monitored closely, therapy can be extended in exceptional circumstances.23

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References


