Serum and sputum concentrations following the oral administration of linezolid in adult patients with cystic fibrosis

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Objectives: Linezolid is a new oxazolidinone antibiotic with efficacy against a broad range of Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). In this study, we have determined the serum and sputum linezolid concentrations in adults with cystic fibrosis (CF) following oral drug administration.

Methods: Eleven adult patients with CF were recruited. Subjects received 600 mg of linezolid orally every 12 h for a total of six doses. Serum and sputum levels were measured just before and at 2 h after the final dose of linezolid. A further serum level was measured at 4 h.

Results: Ten adult patients completed the study. Mean (s.d.) serum linezolid concentrations were 2.3 mg/L (1.5) at 12 h following the fifth dose. At 2 and 4 h following the sixth dose, concentrations were 13.5 (4.3) and 8.1 (3.3). Mean (s.d.) linezolid sputum concentrations were 3.6 (2.1) and 17.4 (7.2) mg/L at 0 and 2 h following drug administration.

Conclusions: The oral administration of linezolid results in good sputum penetration in patients with CF. Mean levels exceed the required MIC for the treatment of MRSA for >80% of the dosing period for serum and the majority of the dosing period for sputum.

Keywords: oxazolidinones, MRSA, serum levels, pancreatic insufficient

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) infects a wide range of vulnerable patients including those with cystic fibrosis (CF). Because of the innate resistance of this organism, treatment options are limited and usually involve the administration of intravenous vancomycin or teicoplanin. Recently, the new oxazolidinone antibiotic, linezolid, has been introduced as an alternative. It can be administered either intravenously or orally, has 100% oral bioavailability, excellent tissue penetration and minimal toxicity. Linezolid is approved for the treatment of nosocomial pneumonia caused by MRSA, but there is little information in the literature as to its absorption, sputum penetration and efficacy in patients with CF. However, one case report demonstrated equivalence of intravenous and oral dosing in an adult with cystic fibrosis. Past studies have demonstrated that higher doses of drugs are frequently required in patients with CF due to their increased volume of distribution, decreased plasma concentration and enhanced renal elimination.

Prior to starting clinical effectiveness trials, the aim of this study was to see whether adequate serum and sputum concentrations would be obtained following the oral administration of linezolid in pancreatic-insufficient patients with CF.

Materials and methods

Study design

This was a prospective study investigating serum concentrations and sputum penetration of oral linezolid in adult patients attending the Leeds Regional CF Unit. The study was approved by St James’s University Hospital ethics committee and written informed consent was obtained from all participants.
Subjects
Eleven randomly chosen subjects (five males) with a mean (range) age of 25.5 years (19–37) were entered into the study during January–March 2002. All patients were undergoing inpatient intravenous antibiotic therapy for chronic infection with *Pseudomonas aeruginosa* and were pancreatic insufficient. Exclusion criteria included an FEV₁ < 15%, age <16 years, significant liver disease, impaired renal function, MRSA infection, poor venous access and concomitant administration of drugs known to interact with linezolid. All patients had characteristic radiological and clinical features of CF and had been diagnosed based on two positive sweat tests and/or two CF mutations.

Patient assessment
Routine pre-assessments included height, weight, physical examination, pulmonary function tests, chest radiograph and sputum cultures. Blood taken routinely before and after the trial was used for a full blood count, and for urea, creatinine, electrolyte and liver function tests. A record of all other concomitant drugs, including intravenous antibiotics, was noted.

Drug administration
Oral linezolid was administered at a dose of 600 mg/12 h for six doses. All doses were given under nursing supervision. On day 3, peripheral blood samples were taken to measure the serum linezolid concentrations just before, and 2 and 4 h after the final dose. A sputum sample was taken by the physiotherapist before and 2 h after the final dose.

Linezolid assay
Peripheral blood was centrifuged and the serum separated. Sputum and serum samples were then stored at −20°C and transported on dry ice for analysis. Serum linezolid concentrations were measured by HPLC in the Department of Microbiology, Southmead Hospital (Bristol, UK), using established methodology as reported previously.10

Data analysis
Data were expressed as means and S.D. Haematological and biochemical parameters were compared using the paired *t*-test (Microsoft Corporation, Redmond, USA). A *P* value of <0.05 was regarded as significant.

Results
Ten adult patients completed the study. One was withdrawn after developing transient blurred vision. Mean (range) age, BMI and % predicted FEV₁ were 25.5 years (19–37), 20 (16.5–23.7) and 47.8% (22–90), respectively.

Discussion
Given the uncertainty surrounding the significance of MRSA isolated from the sputum of CF patients, it is not always clear when and
Linezolid in cystic fibrosis

which antibiotics should be prescribed. Many units would now advocate instituting prompt therapy after the first isolation of MRSA from the sputum in an attempt to eradicate the organism, as colonization is associated with social isolation and impacts directly on the individual’s eligibility for transplantation.2

Currently, the most commonly used agents for both treatment and eradication of MRSA are intravenous vancomycin or teicoplanin. Whereas vancomycin is more active in vitro against MRSA than teicoplanin, it is more toxic, and can potentiate nephrotoxicity, especially in the presence of other drugs such as aminoglycosides. Vancomycin is usually given twice daily and monitoring serum levels is mandatory. For these reasons, teicoplanin is sometimes the preferred agent as it has the advantages of fewer side effects, once-daily dosing and rapid infusion over a few minutes, all of which make it much more suitable for home intravenous administration. Other antibiotics, such as rifampicin or fusidic acid, can be given in addition during the early stages of colonization or infection. Some units have also used aerosolized vancomycin.1

In contrast to vancomycin and teicoplanin, the newer antibiotic, linezolid, has several advantages. It possesses excellent activity against a number of Gram-positive organisms and can be administered orally.5 Linezolid is metabolized by oxidation and mainly excreted in the urine. Dosing adjustment is not necessary in renal or hepatic insufficiency, and drug monitoring is not required, which makes it suitable for home therapy and it does not potentiate nephrotoxicity. This is particularly important, as many patients with CF require concurrent courses of aminoglycosides and polymyxin antibiotics.

Linezolid has a unique mode of action in that it inhibits protein synthesis during early translation.6 It inhibits MRSA strains at concentrations of 0.1–4 mg/L, has an MIC90 in the range 2–4 mg/L, and has similar in vitro and in vivo activity to vancomycin.6,14,15 Whereas the potential emergence of cross-resistance with other antibiotics is thought to be unlikely, in vitro resistance to MRSA has been reported.16

Linezolid has been licensed for the treatment of hospital- and community-acquired pneumonia, including that caused by MRSA. There have been no formal trials of its use in CF, although a few case reports have shown a positive outcome.8,17 Linezolid is expensive and clinical efficacy studies need to be carried out in patients with CF using the most effective dose. A study by Li et al.15 has shown that in patients with MRSA, the use of linezolid was associated with a significant reduction in intravenous and hospital days as compared with vancomycin recipients.

The present study was small and short in duration, but oral linezolid appeared to be well tolerated by this group of patients, with only one adverse event being reported—in the form of an episode of mild blurring of vision. This was transient and may have been related to other antibiotic therapy prescribed concurrently.

Comparisons with previous studies carried out with healthy volunteers suggest that serum linezolid levels in patients with CF are slightly lower at 0, 2 and 4 h.5–7 Most of these studies have measured plasma rather than serum drug levels, but both measurements appear to be similar in healthy volunteers.5–7,14 The presence of lower drug levels suggests that the absorption of linezolid may be affected by either the presence of pancreatic dysfunction, impaired gut motility or CF-related alterations in drug clearance (increased clearance).5,6 Whereas the effect of food on the bioavailability of linezolid appears to be minimal, it can reduce peak levels by causing a small change in the rate of absorption. In the present study, we found that there was no significant reduction in the 2 h serum linezolid levels in four patients undergoing overnight gastrostomy feeding, although feeding had been discontinued several hours before they took their medication.19

There was intra-subject variability in serum levels at both 2 and 4 h. However, the S.D. in our group appears to be similar to that previously reported in healthy controls.5,11,12

Pharmacokinetic studies suggest that peak concentrations of linezolid are reached at 1–2 h following oral administration, but unlike antibiotics such as the aminoglycosides, the clinical efficacy of linezolid appears to be related to the duration at which plasma levels exceed the MIC for any given bacterium.3 With MRSA infection, concentrations remaining above 2–4 mg/L for at least 40% of the dosing schedule should be adequate for effective treatment. In the present study, this was achieved in all but one patient, who had a 4 h serum concentration of 1.8 mg/L. Adequate sputum concentrations were achieved with a mean sputum:plasma ratio of 1.4 at 2 h. Interestingly, the patient with the lowest sputum linezolid levels had a relatively high serum concentration. This discrepancy may have occurred as a result of the quality of the sputum sample obtained. Lung concentrations may be more important than serum concentrations in these patients as the time above the MIC at the site of infection is probably the pharmacodynamic parameter best associated with outcomes. It must also be appreciated that sputum linezolid levels may not reflect lung concentrations because of sputum pooling and contamination with saliva. Whereas bronchoalveolar lavage and endobronchial biopsies may have produced more accurate results, these tests are invasive and carry the risk of complications.

The oral administration of 600 mg of twice-daily linezolid results in good sputum penetration in patients with cystic fibrosis. Concentrations exceeded the MIC90 for MRSA for nearly the whole dosing period for sputum and for 80% of the dosing period for serum. However, mean serum concentrations appear to be lower that previously reported in non-CF individuals and correlations to efficacy need to be investigated.

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References

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