

Linezolid pharmacokinetics and pharmacodynamics in clinical treatment

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Linezolid has been widely used in the treatment of Gram-positive infections for more than a decade. It is unique amongst antibiotics active against most multiply-resistant Gram-positive bacteria in that there is an oral preparation with 100% bioavailability and an extensive volume of distribution. This review examines pharmacokinetic data relating to linezolid use in different patient groups (obesity, enteral feeding, renal failure, neonates, and paediatrics) and in different clinical conditions (sepsis syndrome, skin and soft tissue infection, diabetic foot infection, pneumonia, bone and joint infection, infection of the central nervous system, eye infection, and neutropenic sepsis).

Keywords: oxazolidinones, concentrations, PK–PD

Introduction

Linezolid is the only licensed member of the new group of synthetic antimicrobials within the class oxazolidinones that have activity against most Gram-positive bacteria and mycobacteria. Linezolid has been in widespread use for 10 years, during which time a considerable body of clinical and pharmacokinetic data have been accumulated.

The pharmacokinetics of linezolid were extensively and thoroughly reviewed by MacGowan in 2003.¹ Most of the data available then were from studies of linezolid use in healthy volunteers. Since then, a considerable amount of data has been accumulated on linezolid pharmacokinetics in different patient groups. An online literature search was carried out through MEDLINE using the search terms 'linezolid', 'pharmacokinetics', 'pharmacodynamics' and 'concentrations'. Papers were selected that reported on linezolid pharmacokinetics and pharmacodynamics in clinical infection. This review summarizes the available data.

Preparations and dosing

Linezolid is available in an intravenous formulation, film-coated tablets and oral suspension. The dose is 600 mg every 12 h and no dose adjustment is needed when switching from the intravenous to oral formulations or when there is moderate renal or hepatic derangement.

In a major dosing study,² subjects were exposed to oral (375, 500 or 625 mg) or intravenous (500 or 625 mg) linezolid or placebo twice daily. Serial blood and urine samples were obtained after the first- and multiple-dose administrations for up to 18 days. Non-compartmental pharmacokinetic analyses were used to describe the disposition of linezolid. Plasma

linezolid concentrations and AUCs increased proportionally with dose, irrespective of the route of administration. Plasma linezolid concentrations remained above the MIC₉₀ for susceptible target pathogens (4.0 mg/L) for the majority of the 12 h dosing interval. Mean clearance, half-life and volume of distribution were similar, irrespective of dose for both the oral and intravenous routes. Oral and intravenous linezolid exhibit linear pharmacokinetics with the results supporting a twice-daily schedule for linezolid and demonstrating the feasibility of converting from intravenous to oral dosing without a dose adjustment.^{2–4}

General pharmacokinetics

Linezolid is well absorbed, with a bioavailability of approximately 100% in healthy volunteers.⁵ This characteristic is a major benefit, allowing this agent to be used early intravenously, then switching to oral, or indeed even to commence treatment of infection with oral therapy. After oral doses of 600 mg, steady-state peak serum concentrations (C_{max}) are 15–27 mg/L and are reached 0.5–2 h after administration.^{3–8}

The level of plasma protein binding is 31% and the volume of distribution approximates to the total body water content of 40–50 L. Plasma elimination half-life is 3.4–7.4 h. Linezolid is metabolized to two inactive metabolites, an aminoethoxyacetic acid (metabolite A) and a hydroxyethyl glycine (metabolite B). The clearance rate (\pm SD) is 80 ± 29 mL/min and by non-renal (65%) and renal mechanisms. Renal tubular reabsorption may occur. A proportion of the dose is excreted unchanged in the urine.⁹

Stalker *et al.*^{2,7,10} have carried out extensive work on the pharmacokinetics of linezolid at different doses and in different groups of patients. A small degree of non-linearity has been observed, with a 30% decrease in clearance after a 5-fold

increase in dose. The non-linearity is not relevant over the therapeutic dosage range. Plasma linezolid concentrations in elderly patients, patients with mild to moderate hepatic impairment or mild to severe renal impairment are similar to those achieved in young or healthy volunteers. Higher concentrations are observed in women as compared with men, but the difference is not sufficient to warrant an adjustment in dosage.

In patients with severe renal impairment requiring haemodialysis, the exposure to the two primary metabolites was 7- to 8-fold higher than in patients with normal renal function. Therefore it is recommended that linezolid be used with caution in patients with severe renal insufficiency. A higher clearance of linezolid was found in children as compared with adults, and therefore higher daily dosages per kilogram of body weight are required in children. There is no pharmacokinetic interaction when linezolid is co-administered with aztreonam, gentamicin or warfarin.

Linezolid is a mild, reversible, inhibitor of monoamine oxidases A and B. Co-administration of linezolid with the adrenergic agents pseudoephedrine and phenylpropranolamine resulted in increases in blood pressure relative to these agents alone or to placebo. The degree of the change in blood pressure was within that associated with normal daily activities. In the 10 years of clinical use of linezolid, these theoretical interactions with adrenergic agents have not been found to result in significant adverse clinical events. No interaction was observed when linezolid was co-administered with the serotonergic agent dextromethorphan.¹⁰

Linezolid reaches tissue concentrations sufficient to inhibit the growth of pathogens with MICs up to 4 mg/L throughout the dose interval (see Figure 1).^{10,11}

Food and absorption

When a high-fat meal is given with linezolid, the mean time to reach C_{max} is delayed 1.5–2.2 h and C_{max} is decreased by 15%–20%; however, AUC values are the same.^{5,9} Absorption of the oral suspension is similar to that of the film-coated tablets.⁹

Free concentrations of linezolid were determined at steady state in the interstitial space fluid (ISF) of skeletal muscle and subcutaneous adipose tissue under fasting and non-fasting conditions in healthy volunteers ($n=9$) by means of *in vivo* microdialysis. Ingestion of food led to a delay in the time to reach the peak concentration (T_{max}), whereas the AUC from 0–24 h (AUC_{0-24}) remained unchanged.¹² These data suggest that the rate of linezolid absorption is marginally decreased by food intake. However, the overall extent of linezolid absorption and the distribution of linezolid were not affected. Tissue levels of linezolid appeared sufficiently high to eradicate pathogens with MICs ≤ 4 mg/L.

Antacids

Several antibiotics show significant pharmacokinetic interactions when they are given orally concomitantly with antacids. A study has evaluated the effects of antacid (containing magnesium) on the pharmacokinetics of linezolid.¹³ A single dose of 600 mg linezolid was given orally alone and 10 min after administration of the antacid Maalox 70mVal, which contains 600 mg magnesium hydroxide and 900 mg aluminium hydroxide, to nine healthy males and nine healthy females in a crossover and randomized study. Linezolid plasma concentrations were determined by HPLC and pharmacokinetic parameters were calculated for both treatments. Co-administration with antacids did not

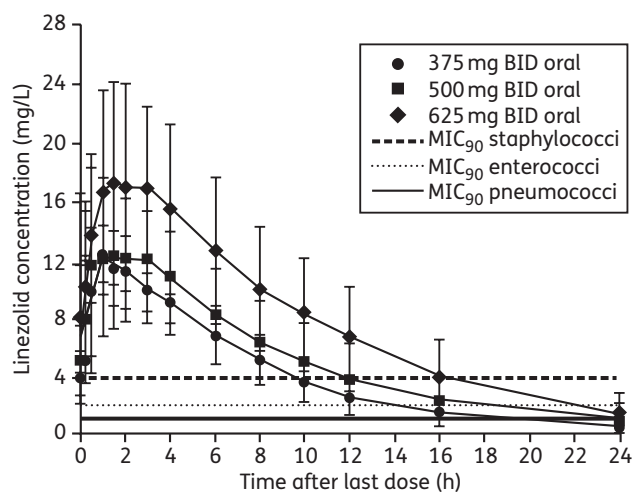


Figure 1. Area under the curve for different doses of linezolid in relation to MICs of Gram-positive pathogens (reproduced from Stalker DJ *et al.* *J Antimicrob Chemother* 2003; **51**: 1239–46).² BID, twice daily.

change the pharmacokinetics of linezolid. The ratios [90% confidence intervals (CI)] of the individual values of the AUC and the plasma C_{max} (linezolid plus antacid versus linezolid alone) were 1.01 (0.99–1.02) and 0.99 (0.96–1.02), respectively.

In addition there was no significant difference in any of the other pharmacokinetic parameters observed between the treatment groups [T_{max} , lag time, volume of distribution (V/F), and clearance (CL/F)]. However, a significant sex difference was observed for AUC, C_{max} , V/F , and CL/F ; these differences could be almost completely explained by the differences in body weight between males and females. No clinically relevant adverse effects were detected under either condition. The co-administration of antacids had no effect on the pharmacokinetics of linezolid. This demonstrated that the oral absorption of linezolid was not affected by the presence of antacids containing magnesium hydroxide and aluminium hydroxide, and antacids can be safely administered together with linezolid.

Enteral feeding

Patients requiring supportive nutrition via the intravenous or enteral routes can prove challenging for drug administration. Bioavailability studies of linezolid administered enterally in the presence of enteral feeding in hospitalized patients showed that the oral suspension was rapidly and completely absorbed by either the oral or enteral route of administration.¹⁴ Bioavailability was unaltered in the presence of enteral feeding. This is important in view of the increasing insertion rates of percutaneous endoscopic gastrostomy.¹⁵

Obesity

Serum concentrations of orally administered linezolid have been measured in obese patients (>50% over their calculated ideal body weight) being treated for cellulitis.¹⁶ Serum concentrations of oral linezolid in this patient population were diminished compared with those of healthy volunteers, but still provided prolonged serum inhibitory activity against common pathogens

associated with skin and soft tissue infections. This may be related to the increased volume of distribution in this group of patients.

Following a minimum of three doses, samples collected prior to (trough) and 1 and 6 h after a dose demonstrated mean linezolid serum concentrations of 4.2, 12.3 and 7.2 mg/L at these timepoints. These samples were then tested for inhibitory and cidal activity against a variety of clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA; linezolid MICs of 1.0, 2.0 or 4.0 mg/L) and one strain each of vancomycin-resistant *Enterococcus faecium* (VREF; MIC 2.0 mg/L), *Bacteroides fragilis* (MIC 2.0 mg/L) and *Peptostreptococcus magnus* (MIC 1.0 mg/L). Inhibitory concentrations were observed for 12 h (100% of the dosing interval) against each organism with the exception of the least-susceptible strain of MRSA (MIC 4.0 mg/L). Serum inhibitory activity was observed only at the 1 h timepoint against this isolate. Prolonged (≥ 6 h) bactericidal titres were observed against one isolate of MRSA (MIC 1.0 mg/L) as well as the strains of VREF and *P. magnus*.

Sepsis

The pharmacokinetics and pharmacodynamics of many drugs may be significantly altered in critically ill septic patients. With antibiotics in such patients there is a risk of prolonged periods with concentrations below the MIC and of low AUC:MIC ratios. Some studies have demonstrated that there needs to be no dosage adjustment in the critically ill.^{17,18} Whitehouse *et al.*¹⁷ reported that plasma concentrations of linezolid exceed MIC breakpoints for approximately 11 h of the 12 h dosing intervals in patients with sepsis. Thallinger *et al.*¹⁸ looked at whether differences in the severity of sepsis translated to differences in the pharmacokinetic profile of linezolid in plasma and the interstitium of target tissues after a single intravenous dose of 600 mg by means of the microdialysis technique. They concluded that the severity of sepsis had no impact on the pharmacodynamic parameters of linezolid and that extrapolated AUC measurements were satisfactory at the standard dose of 600 mg and a 12 h dosing interval.

Other studies have suggested an advantage for more frequent or continuous administration.^{19,20} The pharmacokinetic–pharmacodynamic (PK/PD) profile of linezolid administered by intermittent or continuous infusion in critically ill septic patients has been compared. Serum levels were monitored for 72 h and the clinical outcome in both groups was monitored. In the intermittent dosing group, linezolid trough serum levels (C_{\min}) varied widely and were below the susceptibility breakpoint (4 mg/L) during the study period; in 50% of patients C_{\min} was < 1 mg/L. In the continuous infusion group, mean linezolid serum levels were more stable and, starting from 6 h, were significantly higher than C_{\min} levels observed in the intermittent dosing group and were always above the susceptibility breakpoint. The time that the free drug concentration was above the MIC ($T_{>MIC}$) was greater in the continuous group than in the intermittently dosed group ($P < 0.05$). Finally, with continuous infusion it was possible to achieve AUC/MIC values of 80–120 more frequently than with intermittent infusion ($P < 0.05$). According to PK/PD parameters, continuous infusion has theoretical advantages over intermittent dosing in this population of patients.¹⁹

One study measured unbound linezolid concentrations in ISF of subcutaneous adipose tissue and skeletal muscle in patients in septic shock by microdialysis and HPLC.²⁰ Linezolid showed good distribution into ISF, but with high interindividual variability. This study suggested that a scheme of more-frequent daily dosing of linezolid for some critically ill patients might be taken into consideration to avoid subinhibitory unbound concentrations in the infected tissue. Neither this nor the previous study reported any increase in adverse events with continuous infusion of linezolid.

It is difficult to draw firm conclusions from these studies. All of them were performed on small patient groups with varying degrees of severity of sepsis. For most critically ill patients, it would appear that the standard dose and dosing interval is satisfactory and appropriate. Continuous infusion of linezolid may be an advantage for a small number of patients, particularly with regard to ensuring high levels of unbound antibiotic in infected tissue.

In burns, serum concentrations may fall to below the MICs of infecting pathogens, suggesting a requirement for increased or more frequent dosing of linezolid.²¹ There is therefore a potential for patients who are critically ill with sepsis or burns to have subinhibitory serum concentrations of linezolid with standard dosing regimens. Further data are required to establish how significant these findings are and whether continuous infusion dosing or more frequent daily dosing is likely to be beneficial in this group of patients.

Skin and soft tissue infection and diabetic foot infection

Animal and healthy volunteer skin blister studies have demonstrated excellent and prolonged soft tissue penetration of linezolid.¹ Linezolid penetration through the skin was found to be 104%.³ The mean fluid:plasma ratios for sweat and saliva were 0.55:1 and 1.2:1, respectively.⁹ A number of studies have shown better clearance of staphylococci from skin sites with linezolid as opposed to a comparator (vancomycin and teicoplanin), at least in the short term, suggesting good soft tissue drug penetration.^{22,23} In patients with diabetic foot infections, penetration of linezolid at the standard dose and frequency into inflamed areas of tissue gave tissue:plasma ratios of just over 100% with a mean concentration of 9.6 $\mu\text{g/g}$, greater than those predicted to be effective against most strains of methicillin-resistant staphylococci and other Gram-positive pathogens.²⁴

The microdialysis technique has been used to collect serial samples of ISF from inflamed subcutaneous adipose tissue and metatarsal bone 0–8 h post-dose in diabetic patients.²⁵ In a recent study, mean peak concentrations of free linezolid in plasma, healthy subcutis, inflamed subcutis and cancellous bone were found to be 16.6 ± 3.0 , 15.5 ± 2.5 , 15.8 ± 2.8 and 15.1 ± 4.1 mg/L, respectively. These concentrations are 4–30 times the MIC of potential Gram-positive pathogens. The degree of tissue penetration as expressed by the ratio of the AUC of free linezolid from 0–12 h (fAUC_{0-12}) in tissue to the fAUC_{0-12} in plasma was 1.32 ± 0.09 , 1.12 ± 0.22 and 1.09 ± 0.11 for healthy subcutis, inflamed subcutis and bone, respectively. This demonstrates the excellent antibiotic

penetration of infected soft tissue and bone and little difference in drug concentrations between healthy and inflamed tissue.

Even in patients with severe peripheral vascular disease and complex diabetic foot infections requiring surgery, another study found linezolid was effective at penetrating affected tissue in sufficient concentrations to be microbiologically active.²⁶ In these patients, linezolid concentrations in tissue were found to be 51% (range 18–78%) of simultaneous serum concentrations. Rapid (1 h) and prolonged (12 h) inhibitory activity (titres 1:2) was observed for linezolid against a range of MRSA strains, including those with reduced vancomycin susceptibility. Furthermore, bactericidal activity (titres 1:2) was observed for at least 6 h (50% of the dosing interval) against all but one of the strains.

The high oral bioavailability of linezolid permits either early intravenous to oral switch or outpatient oral therapy in its entirety, a highly attractive option for patients with complex soft tissue infections who are not critically ill and for reducing healthcare costs.

Bone and joint infection

Linezolid is being widely used to treat bone and joint infections^{27,28} and it penetrates osteoarticular tissue well.^{29–31} Linezolid is theoretically an attractive therapeutic option for these infections because it is active against their predominantly Gram-positive microbial causes, particularly methicillin-resistant staphylococci and glycopeptide-resistant enterococci. Again, its oral bioavailability permits convenient and tolerable administration for durations that may be prolonged. The cost of the drug and its potential for haematological adverse effects and peripheral neuropathy with prolonged courses are disadvantages that need weighing against the benefits. If such an assessment falls in favour of administering a prolonged course of linezolid, then haematological parameters and symptoms of optic and peripheral neuropathy should be monitored weekly.

One study has shown that linezolid exhibits rapid penetration into bone, fat and muscle of patients undergoing hip arthroplasty, rapidly achieving levels in excess of its MIC for susceptible organisms (4 mg/L).³² Therapeutic concentrations were maintained in the haematoma fluid that surrounds the operation site for more than 16 h. Mean concentrations of linezolid in bone of 9.1 mg/L (95% CI 7.7–10.6 mg/L) were achieved at 10 min after an infusion of 600 mg, decreasing to 6.3 mg/L (95% CI 3.9–8.6 mg/L) at 30 min. Correction for the simultaneous blood concentrations gave mean values for bone penetration of 51% at 10 min, 60% at 20 min and 47% at 30 min.

Although the penetration of linezolid into fat was also rapid, mean concentrations and the degree of penetration were approximately 60% of those in bone: at 10 min, 4.5 mg/L (95% CI 3.0–6.1 mg/L; penetration 27%); at 20 min, 5.2 mg/L (95% CI 4.0–6.4 mg/L; penetration 37%); and at 30 min, 4.1 mg/L (95% CI 3.3–4.8 mg/L; penetration 31%). For muscle, the corresponding values were 10.4 mg/L (95% CI 8.1–12.7 mg/L; penetration 58%) at 10 min, 13.4 mg/L (95% CI 10.2–16.5 mg/L; penetration 94%) at 20 min and 12.0 mg/L (95% CI 9.2–14.8 mg/L; penetration 93%) at 30 min. Mean concentrations of linezolid in the haematoma fluid drained from around the operation site were 8.2 mg/L at 6–8 h and 5.6 mg/L at 10–

12 h after the infusion and 7.0 mg/L at 2–4 h following a second 600 mg infusion given 12 h post-operatively.

Penetration of linezolid into bone and joint tissues was studied by HPLC in another study of 13 patients suffering from implant-associated infections with methicillin-resistant staphylococci. Mean concentrations of linezolid in infected tissues around the prosthesis were >10 mg/L in a sampling time range of 35–124 min after administration of the preoperative dose, except in bone specimens, where they reached 3.9 ± 2.0 mg/L.³⁰

Eradication of bacteria by linezolid in bone infection appears to be directly proportional to local concentration of antibiotic, which itself is closely related to the AUC.³³ Higher success rates for linezolid may occur at AUC:MIC values of 80–120 and when concentrations remain above the MIC for the entire dosing interval.

Bone and joint infections are often treated with combination therapy on theoretical grounds relating to a perceived improvement in antibiotic bone penetration, antibiotic synergy and a possible reduction in the development of resistance. Prolonged linezolid given in combination with rifampicin has been shown to have a further advantage. This combination is associated with fewer adverse haematological events, especially anaemia, but not an improvement or a reduction in efficacy when compared with other linezolid-containing regimens in patients with bone and joint infections.^{34,35} One possible reason for this may be that rifampicin could increase extrarenal linezolid metabolism. Resultant lower serum concentrations, but not tissue levels, could be responsible for the lower frequency of haematological adverse events.³⁵ Although thrombocytopenia occurred in patients on this regimen, it was not necessary to discontinue linezolid in any case. In this study, chronic renal failure was not associated with the development of anaemia or thrombocytopenia, whereas a similar study did find an association between chronic renal failure and an increased risk of thrombocytopenia.³⁴

Pulmonary infection

An early study examined the steady-state intrapulmonary concentrations and pharmacokinetic parameters of orally administered linezolid in healthy volunteers.³⁶ Linezolid (600 mg every 12 h for a total of five doses) was administered orally to 25 healthy adult male subjects. Each subgroup contained five subjects who underwent bronchoscopy and bronchoalveolar lavage (BAL) 4, 8, 12, 24, or 48 h after administration of the last dose. Blood was obtained for drug assay prior to administration of the first dose and fifth dose and at the completion of bronchoscopy and BAL. Standardized bronchoscopy was performed without systemic sedation. The volume of epithelial lining fluid (ELF) recovered was calculated by the urea dilution method, and the total number of alveolar cells (AC) was counted in a haemocytometer after cytocentrifugation. Linezolid was measured in plasma by HPLC and in BAL specimens and AC it was measured by a combined HPLC–mass spectrometry technique. AUCs for linezolid in plasma, ELF and AC were derived by non-compartmental analysis.

Half-lives for linezolid in plasma, ELF and AC were calculated from the elimination rate constants derived from a monoexponential fit of the means of the observed concentrations at

each timepoint. Concentrations (means \pm SD) in plasma, ELF and AC were, respectively, 7.3 ± 4.9 , 64.3 ± 33.1 and 2.2 ± 0.6 mg/L at the 4 h BAL timepoint and 7.6 ± 1.7 , 24.3 ± 13.3 , and 1.4 ± 1.3 mg/L at the 12 h BAL timepoint.

Linezolid concentrations in plasma, ELF and AC declined exponentially with half-lives of 6.9, 7.0 and 5.7 h, respectively. For an MIC of 4, the 12 h plasma AUC:MIC and C_{max} :MIC ratios were 34.6 and 3.9, respectively, and the percentage of time the drug remained above the MIC over the 12 h dosing interval was 100%; the corresponding ratios in ELF were 120 and 16.1, respectively, and the percentage of time the drug remained above the MIC was 100%. The long plasma and intrapulmonary linezolid half-lives and the percentage of time above the MIC of 100% of the dosing interval strongly supported a 12 h dosing regimen. This early study supported linezolid as a likely agent for the treatment of pulmonary infections.

In a later study that has come to support linezolid as the agent of choice in the treatment of multiresistant Gram-positive pulmonary infections, Bosselli *et al.*³⁷ examined the steady-state plasma pharmacokinetic variables and ELF concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. This was a prospective, open-label study in an intensive care unit and research ward in a university hospital. The number of patients was small; 16 critically ill adult patients with ventilator-associated pneumonia were included. All subjects received 1 h intravenous infusions of linezolid 600 mg twice daily. After 2 days of therapy, the steady-state plasma pharmacokinetic variables and ELF concentrations of linezolid were determined by HPLC. The mean linezolid peak and trough concentrations were 17.7 ± 4.0 mg/L and 2.4 ± 1.2 mg/L in plasma and 14.4 ± 5.6 mg/L and 2.6 ± 1.7 mg/L in ELF, respectively, showing a mean linezolid percentage penetration in ELF of approximately 100%. The mean AUC₀₋₁₂ was 77.3 (± 23.7) mg/L/h, corresponding to a mean AUC₀₋₂₄ of 154.6 mg/L/h (Figure 2). This study showed linezolid concentrations exceeding the susceptibility breakpoint for Gram-positive bacteria in both plasma and ELF for most of the dose duration.

The excellent pharmacokinetics of linezolid in the lung confirm its role in staphylococcal pneumonia.^{38,39} *In vitro* studies suggest that linezolid is effective in switching off bacterial toxin production, which may be involved in the pathogenesis of pneumonia.⁴⁰

Cystic fibrosis

The pharmacokinetics of many drugs are altered in patients with cystic fibrosis (CF), often necessitating different dosage requirements than those used in non-CF patients. A study specifically examining CF patients determined the pharmacokinetics of linezolid so that dosage requirements could be established.⁴¹ Twelve adult patients (six male) ranging in age from 22–39 years were studied. A single 600 mg dose was administered intravenously over 0.5 h and plasma samples were collected at 0 (pre-dose), 0.5, 0.75, 1, 2, 4, 8, and 24 h. Linezolid concentrations were determined by HPLC. Pharmacokinetic parameters were estimated using standard non-compartmental methods. The pharmacokinetic parameters, while variable, with half-lives varying from 1.76–8.36 h, were similar to those previously described in other populations. Mean values for pharmacokinetic parameters

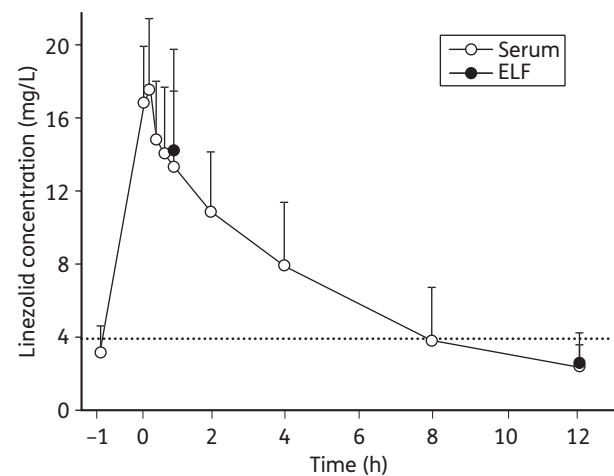


Figure 2. Concentrations of linezolid in serum and epithelial lining fluid in critically ill patients with ventilator-associated pneumonia (reproduced with permission from Bosselli E *et al.* *Crit Care Med* 2005; **33**: 1529–33).³⁷

of interest were as follows: elimination rate constant, 0.21 ± 0.11 /h; half-life, 4.41 ± 2.43 h; volume of distribution at steady state, 0.87 ± 0.19 L/kg of body weight; and total body clearance, 0.12 ± 0.06 L/h/kg. In this small group, no patient would have achieved the pharmacodynamic target of an AUC:MIC ratio of 83 h for pathogens for which the MIC was 4 mg/L. There may be a case in CF patients for considering more frequent dosing or even continuous infusion for severely ill patients. Clearly further pharmacokinetic data are required in this group to enable definitive recommendations to be made.

Urinary tract infection and renal dysfunction

At steady state, 30% of a linezolid dose is excreted unchanged in the urine, the remaining renal excretion being the two inactive metabolites of linezolid. Thus there are good concentrations of the active drug present in urine, well above the MICs of potential Gram-positive pathogens.¹

Complicated urinary tract and prostatic infections (UTIs) are frequent nosocomial infections. The bacterial spectrum encompasses Gram-negative as well as Gram-positive pathogens in up to 30–40% of cases, and in such complex infections the latter may be multiply resistant. The existing treatment for Gram-positive pathogens is not always optimal. Antimicrobials for the treatment of Gram-positive uropathogens comprise older agents, such as aminopenicillins with or without β -lactamase inhibitors and vancomycin, as well as newer fluoroquinolones. However, resistant bacteria such as vancomycin-resistant enterococci (VRE) or MRSA are generally not susceptible to fluoroquinolones. The pharmacokinetics and the mode of action of linezolid suit its use in patients with complicated UTIs caused by multiply-resistant Gram-positive bacteria.⁴²

Several studies have examined the clearance of linezolid in subjects with renal dysfunction. Twenty-four subjects with renal function that ranged from normal to severe chronic impairment were studied, including patients with end-stage renal disease who were maintained on haemodialysis.⁴³ Haemodialysis subjects were studied while they were both on and off

dialysis. Linezolid was administered as a single oral 600 mg dose, and plasma and urine samples were assayed for linezolid and metabolites for 48 h for all subjects and for up to 96 h for those subjects with impaired renal function not on dialysis. The total apparent renal clearance of linezolid did not change with renal function and ranged from 92.5–109.6 mL/min for subjects not requiring dialysis.

For subjects on dialysis, the total apparent renal clearance increased from 76.6 mL/min on their off-dialysis day to 130.0 mL/min on their on-dialysis day. Approximately one-third of the dose was removed by dialysis. However, those subjects with severe renal insufficiency (creatinine clearance <40 mL/min) and those with end-stage renal disease maintained on haemodialysis had higher concentrations of both metabolites. This study concluded that no adjustment of the linezolid dosage was needed in subjects with renal dysfunction or subjects on haemodialysis.

A further question arose in relation to critically ill patients with renal failure on intermittent haemodialysis and whether this removal adversely affected serum antibiotic concentrations.⁴⁴ Five male critically ill patients with a mean age of 75 years (range 68–82 years) and a mean APACHE II score of 26.4 (range 23–29), with sepsis and renal failure on haemodialysis, were administered intravenous linezolid 600 mg every 12 h. Serum antibiotic levels were measured by HPLC/mass spectrometry. Trough concentrations were determined with and without a haemodialysis session performed after linezolid infusion.

A total of 222 serum linezolid concentrations were available over 36 days of antibiotic therapy, during which patients underwent 31 haemodialysis sessions. Trough serum linezolid levels averaged 5.83 mg/L (range 1.48–15.84 mg/L), exceeding 4.0 mg/L in 68.9% of the samples. Not surprisingly, the trough levels with haemodialysis [4.68 mg/L (range 1.48–9.07 mg/L)] were significantly lower than those without haemodialysis [6.74 mg/L (range 2.04–15.84 mg/L)]. Clearance and half-life were 6.0 L/h and 4.0 h, respectively, while patients were on dialysis, and 4.4 L/h and 7.3 h, respectively, when they were off dialysis. Haemodialysis does significantly reduce serum linezolid levels in critically ill patients with renal failure, but not, it would seem, much below the MIC required for most pathogens.

Intra-abdominal infection

Linezolid is used relatively infrequently in intra-abdominal infections because it has no activity against Gram-negative pathogens. However, it has been shown to penetrate intra-abdominal abscesses in experimental animal models.⁴⁵ Although there are few pharmacokinetic data relating to peritonitis, cholangitis and intra-abdominal abscesses, Gram-positive organisms are frequent co-pathogens at these sites. Indeed, multiply-resistant enterococci are not infrequently isolated. Clinical experience has suggested a useful role for linezolid in these circumstances.⁴⁶

Where concentrations of linezolid have been measured in peritoneal dialysate in patients on continuous ambulatory peritoneal dialysis (CAPD) treated orally, concentrations >4 mg/L have been achieved after the first dose of linezolid and maintained after repeated doses.⁴⁷ CAPD peritonitis is most frequently

caused by Gram-positive pathogens, coagulase-negative staphylococci and enterococci. During the course of therapy for CAPD peritonitis in these patients, mean linezolid concentrations in peritoneal dialysis fluid tended to increase (mean 7.60 mg/L, range 3.54–16.2 mg/L). All assayed peritoneal dialysis samples demonstrated linezolid concentrations >4 mg/L at the end of 4 or 8 h dwell times. The duration of dwell times did not appear to correlate with linezolid concentrations. Linezolid therapy has a role in CAPD peritonitis based on its antimicrobial activity, pharmacokinetic properties, ease of administration and tolerability.⁴⁷

CNS infection

After somewhat discouraging results for linezolid penetration in rabbit experimental meningitis models where linezolid concentrations were 18%–38% of plasma concentrations,^{48,49} the pharmacokinetics of linezolid in the human CNS have proved much more promising. Concentrations of linezolid within the CSF have been sufficient to eradicate multiresistant *E. faecium* causing meningitis.^{50,51} In a patient with VREF infection, administration of linezolid 600 mg iv every 12 h produced adequate CSF penetration, with a CSF:plasma ratio of 0.8. Plasma levels collected at 5 and 12 h after infusion on day 5 of treatment were 6.66 mg/L and 4.7 mg/L, respectively; corresponding CSF levels were 5.36 mg/L and 3.8 mg/L, respectively. In a limited study of CSF penetration in patients with ventricular-peritoneal shunts and non-inflamed meninges, the CSF:plasma concentration ratio was 0.7:1.0 after multiple linezolid doses.⁹

The pharmacokinetic profile of linezolid in CSF in five neurology intensive care patients with staphylococcal ventriculitis was studied.⁵² The mean AUC was 63 ± 18.9 mg/L/h, with a CSF:plasma ratio of 0.8 ± 0.3 . Times above the MIC in CSF were 99.8% and 57.2% for pathogens with MICs of 2 mg/L and 4 mg/L, respectively, for the duration of the dosing interval. These results suggest that for pathogens with MICs of 4 mg/L, combination therapy may be required for timely control of infection and pathogen eradication, but data to support this are not available.

Eye infection

Gram-positive bacteria are the most frequent cause of post-operative endophthalmitis, therefore a drug such as linezolid, which is oral, bioavailable and has a wide spectrum of distribution would seem a promising agent. One study described the ocular pharmacokinetics of linezolid in patients undergoing routine cataract surgery.⁵³ Patients were given a single oral 600 mg dose of linezolid at a variable time before surgery. Aqueous and serum levels of linezolid were assayed by HPLC and a pharmacokinetic curve was constructed from the pooled results. Orally administered linezolid rapidly achieves levels in the aqueous of non-inflamed eyes that exceed the concentration required to kill Gram-positive bacteria, with a maximum mean concentration of 6.8 ± 1.2 mg/L at 2–4 h post-dose. An effective concentration is maintained for at least 12 h. Linezolid offers the possibility of a potential rapid, oral approach to effective treatment of most cases of post-operative endophthalmitis, with the potential of improving visual outcome.

Endocarditis

There are few pharmacodynamic data for linezolid in relation to endocarditis, largely because there have been no randomized clinical trials in this condition. Plasma concentrations of linezolid support its use; however, it is regarded as being bacteriostatic rather than bactericidal and it is microbiological dogma that bactericidal drugs should be used to treat endocarditis.

Falagas *et al.*⁵⁴ reviewed cases and series in the literature and concluded that linezolid could be an option for endocarditis treatment caused by multiresistant Gram-positive bacteria or where other drugs have failed or are not tolerated. Failures of endocarditis treatment with linezolid have also been reported.

Paediatric and neonatal infection

There are a number of physiological and developmental differences between children and adults that can influence the absorption, distribution, metabolism and elimination of a drug. Thus it is important to determine the specific pharmacokinetic characteristics for individual drugs in paediatric patients so that appropriate age-specific dosage regimens can be developed and evaluated in clinical trials.

Linezolid pharmacodynamics during the first few months of life have been investigated in a study of infants of various gestational ages and in the first 3 months of life.⁵⁵ A single 10 mg/kg iv dose was given to 42 infants stratified as follows: group 1 ($n=9$), gestational age <34 weeks and post-natal age <8 days; group 2 ($n=7$), gestational age <34 weeks and post-natal age 8 days–12 weeks; group 3 ($n=11$), gestational age ≥ 34 weeks and post-natal age <8 days; group 4 ($n=15$), gestational age ≥ 34 weeks and post-natal age 8 days–12 weeks.

Linezolid serum concentrations were determined from repeated blood samples ($n=7$, 0.3 mL each) obtained over a 12 h period. Pharmacokinetic parameters were determined by standard model-dependent techniques. The mean values for total body clearance (CL) were 0.25 ± 0.12 L/h/kg, apparent volume of distribution 0.75 ± 0.19 L/kg, and elimination half-life 2.8 ± 2.1 h for the entire study cohort. These were similar to values reported previously for children and adolescents. Examination of the linezolid pharmacokinetics as a function of age revealed that CL increased rapidly during the first week of life and as a function of post-natal age. Age stratification revealed lower values for CL in those infants <8 days of age (group 1, 0.12 ± 0.06 L/h/kg; group 3, 0.23 ± 0.12 L/h/kg) as compared with those 8 days–12 weeks of age (group 2, 0.31 ± 0.07 L/h/kg; group 4, 0.31 ± 0.10 L/h/kg). In contrast to the results for CL, gestational age served to be the most useful predictor of volume of distribution. Evaluation of the pharmacokinetic data would appear to support the use of linezolid dosing regimens currently approved for infants and young children with a post-natal age >7 days.

In a broader meta-analysis, the pharmacokinetic parameters of linezolid in paediatric patients and the rationale for the approved dosing recommendations for this population were evaluated from data in four clinical trials, including >180 patients ranging in age from pre-term newborn infants up to 18 years of age.⁵⁶ In all of these studies, patients received a single intravenous dose of linezolid. Plasma linezolid concentrations were determined by validated HPLC (adult studies) or

liquid chromatography/mass spectrometry/mass spectrometry (paediatric studies) methods.

The pharmacokinetics of linezolid, especially clearance, is age dependent. Children younger than 12 years of age have a smaller AUC, a faster clearance and a shorter elimination half-life than adults.⁵⁶ Although clearance rates in newborn infants are similar to those in adults, clearance increases rapidly during the first week of life, becoming 2- to 3-fold higher than in adults by the seventh day of life.⁵⁵ The clearance of linezolid decreases gradually among young children, becoming similar to adult values by adolescence. The pharmacokinetics of linezolid in children aged 12 years and older is not significantly different from that of adults. Because of the higher clearance and lower AUC, a shorter dosing interval for linezolid is likely to be required for children younger than 12 years of age in order to produce adequate drug exposure against target Gram-positive pathogens. The pharmacokinetics of linezolid in older children are similar to those in adult populations.

A further study evaluated the efficacy of linezolid in 13 critically ill children with VRE infections.⁵⁷ Although pharmacokinetic parameters were not calculated, linezolid was clinically effective in 9 of 13 children at the test of cure visit, with microbiological eradication in 9 of 12 children.

Neutropenic sepsis

The clinical efficacy of antibiotics in immunosuppressed patients may be very different from the efficacy in immunocompetent patients even though the pharmacodynamics are similar. The efficacy of linezolid therapy in neutropenic cancer patients with Gram-positive bacterial infections from a compassionate-use programme has been evaluated in a prospective, multicentre, open-label, non-comparative, non-randomized programme in patients with serious Gram-positive infections.⁵⁸ To qualify for enrolment, patients were required to have an infection resistant to available antimicrobial agents, where available agents had failed, or to which they were intolerant. Patients with absolute neutrophil counts <500 cells/mm³ or <1000 cells/mm³ and expected to decrease to <500 cells/mm³, and who received linezolid 600 mg twice daily were included. Plasma samples for population pharmacokinetic analysis were collected. Clinical and microbiological assessments of outcomes were made at the end of therapy and at short-term follow-up.

Of the patients in the compassionate-use trial, 103 were neutropenic. The mean age was 50.1 ± 17.5 years, 47% were female and 47.6% had a baseline neutrophil count of ≤ 100 cells/mm³. The mean duration of linezolid therapy was 14.6 ± 11.4 days. The most common site of infection was the bloodstream (90.3%), and the most commonly identified pathogen was VREF (83%).

Clinical and microbiological cure rates in the evaluable patients were 79% and 86%, respectively. Linezolid was well-tolerated in this patient population, with an overall adverse event rate of 17.5%; 5% of patients required discontinuation of the drug due to side effects. The pharmacokinetics of linezolid in patients with neutropenia did not differ from the overall compassionate-use population. Linezolid was safe and effective in treating resistant Gram-positive infections in neutropenic cancer patients.

Conclusions

Linezolid is an agent with remarkable properties. It is the only antibiotic active against multiresistant Gram-positive bacteria that has excellent oral bioavailability and effective penetration at therapeutic concentrations to almost every organ in the body. It is therefore a suitable agent for a wide range of infections caused by susceptible bacteria. The pharmacokinetic properties of this agent challenge the requirement for intravenous therapy for serious infection.

Transparency declaration

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References

- MacGowan A. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003; **51** Suppl S2: ii17–25.
- Stalker DJ, Jungbluth GL, Hopkins NK *et al.* Pharmacokinetics and tolerance of single- and multiple-dose oral or intravenous linezolid, an oxazolidinone antibiotic, in healthy volunteers. *J Antimicrob Chemother* 2003; **51**: 1239–46.
- Gee T, Ellis R, Marshall G *et al.* Pharmacokinetics and tissue penetration of linezolid following multiple oral doses. *Antimicrob Agents Chemother* 2001; **45**: 1843–5.
- Slatter JG, Stalker DJ, Feenstra KL *et al.* Pharmacokinetics, metabolism and excretion of linezolid following an oral dose of ¹⁴C linezolid to healthy human subjects. *Drug Metab Dispos* 2001; **29**: 1136–45.
- Welshman IR, Stalker DJ, Wajszczuk CP. Assessment of absolute bioavailability and evaluation of the effect of food on oral bioavailability of linezolid. *Anti-Infect Drugs Chemother* 1998; **16** Suppl 1: 54.
- Hendershot PE, Antal EJ, Welshman IR *et al.* Linezolid: pharmacokinetic and pharmacodynamic evaluation of co-administration with pseudoephedrine HCl, phenylpropanolamine HCl, and dextromethorphan HBr. *J Clin Pharmacol* 2001; **41**: 563–72.
- Stalker DJ, Wajszczuk CP, Batts DH. Linezolid safety, tolerance and pharmacokinetics following oral dosing twice daily for 14.5 days. In: *Abstracts of the Thirty-Seventh Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, 1997*. Abstract A-115, p. 23. American Society for Microbiology, Washington, DC, USA.
- Sisson TL, Jungbluth GL, Hopkins NK. A pharmacokinetic evaluation of concomitant administration of linezolid and aztreonam. *J Clin Pharmacol* 1999; **39**: 1277–82.
- Pharmacia Zyvox (linezolid) Clinical Information Pack (Jan. 2001). Pharmacia, Peapack, NJ, USA.
- Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. *Clin Pharmacokinet* 2003; **42**: 1129–40.
- Dehghanyar P, Bürger C, Zeitlinger M *et al.* Penetration of linezolid into soft tissues of healthy volunteers after single and multiple doses. *Antimicrob Agents Chemother* 2005; **49**: 2367–71.
- Islinger F, Dehghanyar P, Sauermann R *et al.* The effect of food on plasma and tissue concentrations of linezolid after multiple doses. *Int J Antimicrob Agents* 2006; **27**: 108–12.
- Grunder G, Zysset-Aschmann Y, Vollenweider F *et al.* Lack of pharmacokinetic interaction between linezolid and antacid in healthy volunteers. *Antimicrob Agents Chemother* 2006; **50**: 68–72.
- Beringer P, Nguyen M, Hoem N *et al.* Absolute bioavailability and pharmacokinetics of linezolid in hospitalized patients given enteral feedings. *Antimicrob Agents Chemother* 2005; **49**: 3676–81.
- Kurien M, Sanders DS. Antibiotic prophylaxis after percutaneous endoscopic gastrostomy. *BMJ* 2010; **341**: 55–6.
- Stein GE, Schooley SL, Peloquin CA *et al.* Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. *Ann Pharmacother* 2005; **39**: 427–32.
- Whitehouse T, Cepeda JA, Shulman R *et al.* Pharmacokinetic studies of linezolid and teicoplanin in the critically ill. *J Antimicrob Chemother* 2005; **55**: 333–40.
- Thallinger C, Buerger C, Plock N *et al.* Effect of severity of sepsis on tissue concentrations of linezolid. *J Antimicrob Chemother* 2008; **61**: 173–6.
- Adembri C, Fallani S, Cassetta MI *et al.* Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion. *Int J Antimicrob Agents* 2008; **31**: 122–9.
- Buerger C, Plock N, Dehghanyar P *et al.* Pharmacokinetics of unbound linezolid in plasma and tissue interstitium of critically ill patients after multiple dosing using microdialysis. *Antimicrob Agents Chemother* 2006; **50**: 2455–63.
- Hallam MJ, Allen JM, James SE *et al.* Potential subtherapeutic linezolid and meropenem antibiotic concentrations in a patient with severe burns and sepsis. *J Burn Care Res* 2010; **31**: 207–9.
- Cepeda JA, Whitehouse T, Cooper B *et al.* Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. *J Antimicrob Chemother* 2004; **53**: 345–55.
- Itani K, Dryden MS, Bhattacharyya H *et al.* Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be due to methicillin-resistant *Staphylococcus aureus*. *Am J Surg* 2010; **199**: 806–14.
- Majcher-Peszynska J, Haase G, Sass M *et al.* Pharmacokinetics and penetration of linezolid into inflamed soft tissue in diabetic foot infections. *Eur J Clin Pharmacol* 2008; **64**: 1093–100.
- Traunmüller F, Schintler MV, Spende S *et al.* Linezolid concentrations in infected soft tissue and bone following repetitive doses in diabetic patients with bacterial foot infections. *Int J Antimicrob Agents* 2010; **36**: 84–6.
- Stein GE, Schooley S, Peloquin CA *et al.* Linezolid tissue penetration and serum activity against strains of methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility in diabetic patients with foot infections. *J Antimicrob Chemother* 2007; **60**: 819–23.
- Bassetti M, Righi E, Di Biagio A *et al.* Role of linezolid in the treatment of orthopedic infections. *Expert Rev Anti Infect Ther* 2005; **3**: 343–52.
- Falagas ME, Siempos II, Papagelopoulos PJ *et al.* Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents* 2007; **29**: 233–9.
- Metallidis S, Nikolaidis J, Lazaraki G *et al.* Penetration of linezolid into sternal bone of patients undergoing cardiopulmonary bypass surgery. *Int J Antimicrob Agents* 2007; **29**: 742–4.
- Kutscha-Lissberg F, Hebler U, Muhr G *et al.* Linezolid penetration into bone and joint tissues infected with methicillin-resistant staphylococci. *Antimicrob Agents Chemother* 2003; **47**: 3964–6.
- Rana B, Butcher I, Grigoris P *et al.* Linezolid penetration into osteo-articular tissues. *J Antimicrob Chemother* 2002; **50**: 747–50.

- 32** Lovering AM, Zhang J, Bannister GC *et al.* Penetration of linezolid into bone, fat, muscle and haematoma of patients undergoing routine hip replacement. *J Antimicrob Chemother* 2002; **50**: 73–7.
- 33** Rayner CR, Forrest A, Meagher AK *et al.* Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. *Clin Pharmacokinet* 2003; **42**: 1411–23.
- 34** Legout L, Valette M, Dezeque H *et al.* Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia? *J Antimicrob Chemother* 2010; **65**: 2224–30.
- 35** Soriano A, Ortega M, Garcia S *et al.* Comparative study of the effects of pyridoxine, rifampin, and renal function on hematological adverse events induced by linezolid. *Antimicrob Agents Chemother* 2007; **51**: 2559–63.
- 36** Conte JE Jr, Golden JA, Kipps J *et al.* Intrapulmonary pharmacokinetics of linezolid. *Antimicrob Agents Chemother* 2002; **46**: 1475–80.
- 37** Boselli E, Breilh D, Rimmele T *et al.* Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med* 2005; **33**: 1529–33.
- 38** Nathwani D, Morgan M, Masterton RG *et al.* Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. *J Antimicrob Chemother* 2008; **61**: 976–94.
- 39** Dryden M, Andrasevic AT, Bassetti M *et al.* A European survey of antibiotic management of methicillin-resistant *Staphylococcus aureus* infection: current clinical opinion and practice. *Clin Microbiol Infect* 2010; **16** Suppl 1: 3–30.
- 40** Dumitrescu O, Badiou C, Bes M *et al.* Effect of antibiotics, alone and in combination, on Panton-Valentine leukocidin production by a *Staphylococcus aureus* reference strain. *Clin Microbiol Infect* 2008; **14**: 384–8.
- 41** Bosso JA, Flume PA, Gray SL. Linezolid pharmacokinetics in adult patients with cystic fibrosis. *Antimicrob Agents Chemother* 2004; **48**: 281–4.
- 42** Wagenlehner FM, Naber KG. New drugs for Gram-positive uropathogens. *Int J Antimicrob Agents* 2004; **24** Suppl 1: S39–43.
- 43** Brier ME, Stalker DJ, Aronoff GR *et al.* Pharmacokinetics of linezolid in subjects with renal dysfunction. *Antimicrob Agents Chemother* 2003; **47**: 2775–80.
- 44** Fiaccadori E, Maggiore U, Rotelli C *et al.* Does haemodialysis significantly affect serum linezolid concentrations in critically ill patients with renal failure? A pilot investigation. *Nephrol Dial Transplant* 2006; **21**: 1402–6.
- 45** Schülin T, Thauvin-Eliopoulos C, Moellering RC *et al.* Activities of the oxazolidinones linezolid and eperezolid in experimental intra-abdominal abscess due to *Enterococcus faecalis* or vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother* 1999; **43**: 2873–6.
- 46** Paterson DL. Clinical experience with recently approved antibiotics. *Curr Opin Pharmacol* 2006; **6**: 486–90.
- 47** DePestel DD, Peloquin CA, Carver PL. Peritoneal dialysis fluid concentrations of linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* peritonitis. *Pharmacotherapy* 2003; **23**: 1322–6.
- 48** Cottagnoud P, Gerber CM, Acosta F *et al.* Linezolid against penicillin-sensitive and -resistant pneumococci in the rabbit meningitis model. *J Antimicrob Chemother* 2000; **46**: 981–5.
- 49** Gerber CM, Acosta F, Cottagnoud M *et al.* Evaluation of linezolid against penicillin sensitive and resistant pneumococci in the experimental meningitis model. In: *Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 1787, p. 81. American Society for Microbiology, Washington, DC, USA.
- 50** Mizell KN, Carter JE. Vancomycin-resistant *Enterococcus faecium* meningitis successfully treated with linezolid. *South Med J* 2008; **101**: 569–70.
- 51** Hachem R, Afif C, Gokaslan Z *et al.* Successful treatment of vancomycin-resistant *Enterococcus meningitis* with linezolid. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 432–4.
- 52** Beer R, Engelhardt KW, Pfausler B *et al.* Pharmacokinetics of intravenous linezolid in cerebrospinal fluid and plasma in neurointensive care patients with staphylococcal ventriculitis associated with external ventricular drains. *Antimicrob Agents Chemother* 2007; **51**: 379–82.
- 53** Prydal JI, Jenkins DR, Lovering A *et al.* The pharmacokinetics of linezolid in the non-inflamed human eye. *Br J Ophthalmol* 2005; **89**: 1418–9.
- 54** Falagas ME, Manta KG, Ntziora F *et al.* Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother* 2006; **58**: 273–80.
- 55** Kearns GL, Jungbluth GL, Abdel-Rahman SM *et al.* Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther* 2003; **74**: 413–22.
- 56** Jungbluth GL, Welshman IR, Hopkins NK. Linezolid pharmacokinetics in pediatric patients: an overview. *Pediatr Infect Dis J* 2003; **22** Suppl 9: S153–7.
- 57** Deville JG, Goldfarb J, Kaplan SL *et al.* The use of linezolid in the treatment of paediatric patients with infections caused by enterococci including strains resistant to vancomycin. *J Antimicrob Chemother* 2010; **65**: 2267–70.
- 58** Smith PF, Birmingham MC, Noskin GA *et al.* Safety, efficacy and pharmacokinetics of linezolid for treatment of resistant Gram-positive infections in cancer patients with neutropenia. *Ann Oncol* 2003; **14**: 795–801.