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Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections

Alasdair P. MacGowan*

Bristol Centre for Antimicrobial Research and Evaluation, University of Bristol and North Bristol NHS Trust, Department of Medical Microbiology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

The pharmacokinetics and pharmacodynamics of linezolid have been extensively investigated in laboratory models, healthy volunteers and patients. Three formulations exist: an intravenous (iv) form, film-coated tablets and an oral suspension. Linezolid can be assayed in serum and body fluids by HPLC and has good bioavailability with a C_{max} at 0.5–2 h. The protein binding is 31%, and the volume of distribution is 30–50 L with adequate to good tissue penetration into skin blister fluids, bone, muscle, fat, alveolar cells, lung extracellular lining fluid and CSF. There are two major metabolites of linezolid (PNU-142586 and PNU-142300). Non-enzymic formation of PNU-142586 is the rate-limiting step in the clearance of linezolid, and linezolid and its two main metabolites plus several minor ones are all excreted in the urine. Dose linearity is evident in the C_{max} and AUC across a wide range of doses. Gender and age have little effect on pharmacokinetics, but children have greater plasma clearance and volume of distribution and hence, have lower serum concentrations for equivalent doses in adults. No dose modification is needed in mild to moderate liver disease or any degree of renal impairment; however, both PNU-142586 and PNU-142300 accumulate in renal failure. Linezolid is bacteriostatic with a significant post-antibiotic effect against the key pathogens. In animal models of infection, the time the antibiotic concentration exceeds the MIC (t > MIC) helps to determine outcome, and a t > MIC of 40% is predictive of a bacteriostatic effect for both staphylococci and pneumococci. In man, t > MIC and AUC/MIC have been related to bacteriological and clinical outcomes. AUC and length of treatment are also related to the risk of thrombocytopenia.

Introduction

The pharmacokinetics and pharmacodynamics of linezolid have been extensively studied in healthy volunteers and patients. As the first licensed member of a new class of antibiotics, the oxazolidinones, there are no pre-existing data from other members of the class to help put the pharmacokinetic and pharmacodynamic findings for linezolid into a broader perspective. Given the robust nature of the studies performed on linezolid, however, this lack of class data is not a problem and means that the pharmacokinetic and pharmacodynamic findings are genuinely new. As additional oxazolidinones are developed and the details of the pharmacokinetic/pharmacodynamic relationships of linezolid are refined with clinical use and future studies, it can be anticipated that our understanding of this class of drugs will be considerably enhanced.

In this review, the basic pharmacokinetics of linezolid, the impact of special patient groups on drug disposition, drug interactions and the pharmacodynamic profile of linezolid will be summarized.

Pharmacokinetics

The pharmacokinetics of linezolid have been extensively studied as part of the clinical development of the agent. Therefore, abundant data have been generated in studies in healthy volunteers and patients with stable excretory organ failure. Fewer data are available on the pharmacokinetics of linezolid in patient groups, and data on tissue penetration continue to accumulate. Linezolid may be assayed in body fluids by HPLC.[1] Available formulations of the agent include an intravenous (iv) form, film-coated tablets and an oral suspension.

*Tel: +44-117-959-5652; Fax: +44-117-959-3154; E-mail: alasdair.macgowan@north-bristol.swest.nhs.uk

Absorption

Linezolid is well absorbed with a mean absolute bioavailability of ~100% in healthy volunteers.[2] Maximum serum concentrations (C_{max}) are reached 0.5–2 h after oral administration.[3–7] The mean time to reach C_{max} is delayed from 1.5 to 2.2 h and C_{max} is decreased by 15–20% when a high-fat meal is given with linezolid; however, $AUC_{0-\infty}$ values are the same.[2,8] Absorption of the oral suspension is similar to that of the film-coated tablets.[9] No detailed data are available on absorption in patients.

Distribution

The volume of distribution at steady state in healthy adults is 30–50 L[4,6,10,11] or 0.5–0.6 L/kg, which approximates to total body water. Protein binding is ~31% and is not concentration dependent.[11]

Tissue distribution has been determined in small numbers of patients or healthy volunteers. In a group of six healthy volunteers receiving five 600 mg oral doses of linezolid every 12 h, penetration into cantharidine-induced skin blisters was 104% ± 21% (range 80–130%) compared with serum.[3] Another group of 25 volunteers also received five doses of oral linezolid 600 mg every 12 h before undergoing bronchoalveolar lavage. Linezolid concentrations were measured in plasma, bronchoalveolar lavage fluid and alveolar cells. Concentrations in epithelial lining fluid were calculated using urea diffusion.[12] Four hours after the last dose, plasma and lung epithelial lining fluid concentrations were 15.5 ± 24.2 and 64.3 ± 33.1 mg/L, respectively; at 12 h, the concentrations were 10.2 ± 2.3 and 24.3 ± 13.3 mg/L, respectively. Concentrations in alveolar cells were much lower, with a mean C_{max} of 2.2 ± 0.6 mg/L at 4 h. The concentration ratios of epithelial lining fluid to plasma and alveolar cells to plasma were 4.5:1.0 and 0.15:1.0 when measured at steady-state C_{max}.[9]

The mean fluid to plasma ratios for sweat and saliva were 0.55:1 and 1.2:1, respectively.[8] In a study of 12 patients undergoing elective total hip replacement for reasons other than infection, patients were given linezolid 600 mg before surgery and 12 h later. Linezolid penetrated bone, fat and muscle rapidly, with 37% penetration into fat and 95% into muscle.[13] In a patient with vancomycin-resistant *Enterococcus faecium* infection, administration of iv linezolid 600 mg 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 μg/mL and 4.7 μg/mL, respectively; corresponding CSF levels were 5.36 μg/mL and 3.8 μg/mL, respectively.[14] In a limited study of CSF penetration in patients with ventricular–peritoneal shunts and non-inflamed meninges, the ratio of CSF:plasma concentration was 0.7:1.0 after multiple linezolid doses.[9] However, mean penetration was 18% or 38% in rabbit meningitis models.[15,16]

Metabolism

Linezolid has a relatively complex metabolism that produces two major metabolites and numerous minor ones. The metabolites have been characterized in healthy volunteers using HPLC–atmospheric pressure chemical ionization-mass spectrometry and ^{19}F nuclear magnetic resonance spectroscopy.[4]

The two primary metabolites are produced by oxidation of the morpholine ring, resulting in two inactive open-ring carboxylic acid derivatives—the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586). PNU-142586, the predominant human metabolite, is formed by a non-enzymic process and may therefore occur throughout the body (Figure 1).[17] Formation of PNU-142586 is the rate-limiting step in the clearance of linezolid. The steady-state pharmacokinetic parameters for linezolid, PNU-142586 and PNU-142300 are shown in Table 1. PNU-142586 circulates at much lower concentrations and has a later T_{max} than linezolid. There is an inverse relationship between linezolid and PNU-142586 concentrations. PNU-142300 concentrations are ~33% of PNU-142586 concentrations, and while PNU-142586 accounts for

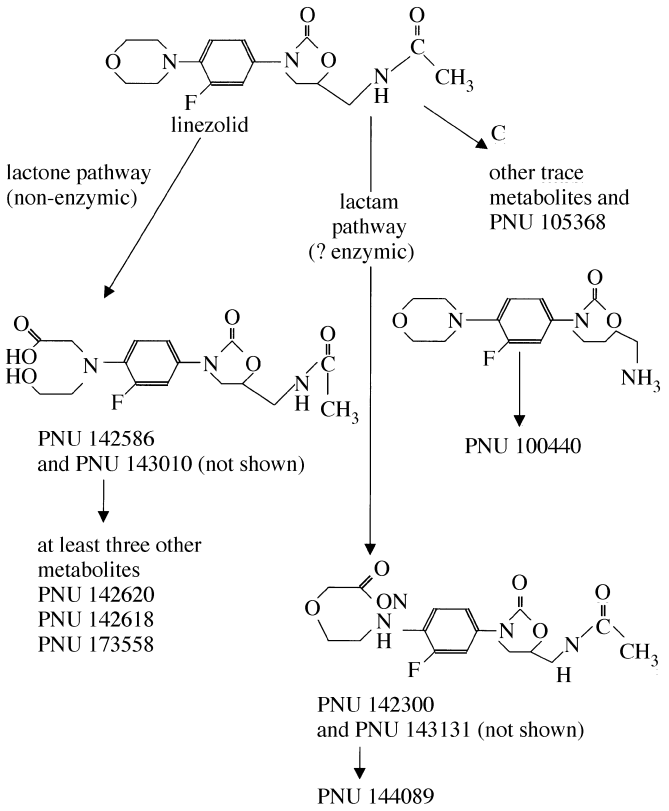

Figure 1. Metabolic pathways of linezolid, based on data from mice, dogs and humans. Adapted from figure 1, Stetter *et al.*[4]

Table 1. Steady-state dose pharmacokinetic parameters for linezolid and its metabolites PNU-142586 and PNU-142300[a]

Parameter	Linezolid	PNU-142586	PNU-142300
$AUC_{0–12}$ (mg·h/L)	99.5 ± 47.5	35.7 ± 17.4	11.5 ± 6.4
C_{max} (mg/L)	17.8 ± 6.03	3.98 ± 1.78	1.61 ± 0.78
T_{max} (h)	0.87 ± 0.35	3.25 ± 0.46	2.00 ± 0.46
$t_{½}$ (h)	3.54 ± 1.37	6.38 ± 3.04	4.09 ± 1.12
V_{ss} (L)	29.8 ± 9.42	–	–
C_{min} (mg/L)	2.43 ± 2.15	1.61 ± 0.91	0.36 ± 0.24

$AUC_{0–12}$, area under the concentration–time curve from 0 to 12 h; C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; $t_{½}$, half-life; V_{ss}, volume of distribution at steady state; C_{min}, minimum concentration of drug in serum.
[a]Adapted from table 6, Stetter *et al*.[4]

~25% of the dose, PNU-142300 contributes ~10%. Neither PNU-142300 nor PNU-142586 have any antibacterial activity.

Elimination

Urine is the major route of excretion for linezolid. As the metabolites of linezolid are formed, they are excreted into the urine. At steady state, 30% of the dose appears in the urine as linezolid, 40% as PNU-142586 and 10% as PNU-142300. No parent drug is found in the faeces while ~6% of the dose appears in faeces as PNU-142586 and 3% as PNU-142300. Overall, non-renal clearance is ~65% of the total clearance of linezolid and the plasma half-life is in the range 3.5–6 h.[3,4,6,7,18]

In dose-escalation studies, non-linearity of clearance was observed with increasing doses, which may be due to lower renal and non-renal clearance at higher concentrations. However, these differences are small and are not reflected in the serum half-life.[9]

Serum concentration and pharmacokinetic profile

Oral administration of doses of 375, 500 and 625 mg linezolid every 12 h for 14.5 days indicated generally linear increases in C_{max} and AUC values with dose.[6] Intravenous administration of linezolid 500 or 625 mg every 12 h for 7.5 days also indicated that AUC values were generally proportional to dose with C_{min} values of 3.5 mg/L and 3.8 mg/L for the 500 mg and 600 mg regimens, respectively.[18] Mean C_{max} values after oral administration of linezolid 600 mg at steady state have varied from 16.3 to 21 mg/L and the mean $AUC_{0–12}$ values have ranged from 107 to 138 mg·h/L.[3,5,9] Mean C_{min} values at steady state were 6.2 mg/L following twice-daily oral dosing of linezolid 600 mg and 3.7 mg/L for linezolid 600 mg iv[19] (Table 2).

Table 2. Mean linezolid pharmacokinetic parameters after single or multiple doses of oral or intravenous linezolid

Dose	*N*	Single dose or multiple doses	C_{max} (mg/L)	C_{min} (mg/L)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0–12}$ (mg·h/L)	$AUC_{0–8}$ (mg·h/L)	V_{SS} (L)	CL (mL/min)	Reference
600 mg po[a]	–	single	12.7	–	1.3	4.3	91.4	–	–	127	19
600 mg iv[a]	–	single	12.9	–	0.5	4.4	80.2	–	–	138	19
400 mg po[a]	431	multiple	11.0 ± 4.4	3.1 ± 2.2	1.1	4.7	73.4 ± 33.5	–	–	–	19
500 mg po	16	multiple	17.8 ± 6.0	–	0.9 ± 0.4	3.5 ± 1.4	99.5 ± 47.5	–	29.8 ± 9.4	109 ± 54	4
600 mg po	6	multiple	18.3 ± 6.0	–	0.7 ± 0.3	4.9 ± 1.8	107 ± 41	140 ± 73	–	–	3
600 mg po	14	multiple	16.3 ± 3.8	–	1.4 ± 0.5	–	–	173 ± 118	–	–	5
600 mg po[a]	431	multiple	21.0 ± 5.8	6.2 ± 2.9	1.0	5.4	138 ± 42	–	–	80	19
375 mg iv	12	single	10.3 ± 1.9	–	–	4.4	–	56.0 ± 17.9	42.3 ± 6.7	121 ± 34	10
600 mg iv[a]	431	multiple	15.1 ± 2.5	3.7 ± 2.4	0.5	4.8	89.7 ± 31.0	–	–	123	9

C_{max}, maximum concentration of drug in serum; C_{min}, minimum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; $t_{1/2}$, half-life; $AUC_{0–12}$, area under the concentration–time curve from 0 to 12 h; $AUC_{0–8}$, area under the concentration–time curve from 0 to 8 h; V_{ss}, volume of distribution at steady state; CL, clearance; po, oral; iv, intravenous.
[a]Data presented are normalized from 375 mg po and 625 mg iv infusion data.

Considerable variability in the AUC values in these studies was demonstrated when standard deviations were taken into account. When a population pharmacokinetic model was developed for linezolid based on Phase I data, a total of 1937 concentrations in 31 subjects were included. Linezolid doses administered were 125, 375 or 625 mg. The median volume of distribution (V_D) was 0.67 L/kg, and steady state was achieved within 3 days with twice-daily dosing.[20]

Special groups

Age

Linezolid has been studied in single 1.5 mg/kg (n = 44) and 10 mg/kg (n = 14) doses in children. A correlation between age and total body clearance was noted, with clearance being greater in the younger children, especially those younger than 20 months. The half-life was 3.0 ± 2.2 h, generally shorter than in adults, and the V_D of 0.73 ± 0.18 L/kg was significantly larger than in adults.[21] The pharmacokinetic data are shown in Table 3. The linezolid concentration after the 10 mg/kg dose at 12 h was only 0.33 ± 0.07 mg/L, and the dose-normalized AUC was ~35% lower than that reported in adults.

The pharmacokinetics of linezolid are age dependent, with infants and children having greater plasma clearance, larger volumes of distribution and corresponding lower serum concentrations and serum AUC.[21] At present, no clinical efficacy data are available in children, but administration of linezolid 10 mg/kg three times daily may be effective.

No differences were noted in C_{max}, T_{max}, total clearance, renal clearance and serum half-life between groups of men and women with mean ages of 30 ± 7 years (n = 15) and 70 ± 3 years (n = 14).[10] Pharmacokinetic studies have not been performed to date in patients of extreme old age, but dose adjustment in old age is not recommended.

Table 3. Paediatric pharmacokinetic data[a]

	Dose	
Parameter	1.5 mg/kg	10 mg/kg
N	40	14
Age (years)	5.4 ± 4.9	7.9 ± 4.4
Weight (kg)	21.8 ± 15.7	30.1 ± 16.1
C_{max} (mg/L)	2.5 ± 0.8	15.3 ± 4.7
T_{max} (h)	0.6 ± 0.1	0.5 ± 0.1
AUC_{0-8} (mg·h/L)	5.2 ± 3.2	44.2 ± 17.0
$t_{½}$ (h)	3.1 ± 1.1	2.7 ± 0.9
CL (mL/min/kg)	6	43
V_{SS} (L/kg)	0.75 ± 0.2	0.66 ± 0.2

C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; AUC_{0-8}, area under the concentration–time curve from 0 to 8 h; $t_{1/2}$, half-life; CL, clearance; V_{ss}, volume of distribution at steady state.
[a]Adapted from Kears *et al.*[21]

Gender

The total clearance of linezolid is 20% lower in females than males.[10] However, renal clearance and the serum half-life are the same in both sexes. Females also have a slightly lower V_D than males, and plasma concentrations are higher in females, in part due to lower body weight. It is not expected that serum concentrations in females will rise above those known to be well tolerated; therefore, dose adjustment is not needed.[9,10]

Pregnancy

There are no pharmacokinetic data available on the use of linezolid in pregnant females.

Obesity/low body weight

No studies have been performed on subjects whose weights are significantly above or below ideal body weight.

Concurrent disease and infection

No studies have been performed on the effects of concurrent disease on the pharmacokinetics of linezolid, with the exception of those in patients with excretory organ failure (see below). However, population pharmacokinetic studies have been performed in patients with community-acquired pneumonia, patients with skin and soft tissue infections, and seriously ill adults with significant Gram-positive infections.[22,23]

For patients with community-acquired pneumonia, and skin and soft tissue infections recruited into three linezolid trials, 3238 concentrations from 655 patients receiving linezolid 750 mg/day or 1125–1250 mg/day were available. A one-compartment model with linear/non-linear elimination adequately described linezolid pharmacokinetics. Men had a higher V_D than women, and V_D increased with body weight and decreased with age. Co-variate effects were small and not sufficient to require dose adjustment.[22]

Another study in 277 seriously ill adults in a compassionate-use protocol demonstrated different findings. All patients had significant Gram-positive infection and were treated with linezolid 600 mg every 12 h, usually iv but sometimes orally. Linezolid disposition was well described by a two-compartment model with parallel first order and Michaelis–Menten pathways of elimination. Substantial variations in AUC were noted compared with a group of volunteers analysed in parallel. These variations could not be explained by liver function, creatinine clearance, locality of care or ideal body weight. In addition, the AUC was 34% smaller in

patients than in volunteers, which was not related to poor absorption because 85% of the data was from iv doses. In a subset of patients, there was slow accumulation of drug and by day 5 of treatment, 14% of patients remained at <90% of steady state.[23]

The pharmacokinetics of linezolid in 24 critically ill patients in an intensive care unit was also studied. Following iv doses of linezolid 600 mg every 12 h in patients with known or suspected Gram-positive infection, mean peak concentration on day 4 of treatment was 12.8 ± 5.0 mg/L and mean trough concentration on day 4 was 4.7 ± 4.3 mg/L. Initial calculations suggested a first-dose half-life of 3.5 h.[24]

Table 4. Linezolid pharmacokinetics in liver disease[a]

Parameter	Subjects with liver disease	Healthy subjects	*t*-test
C_{max} (mg/L)	11.5 ± 2.0	11.9 ± 1.8	0.67
T_{max} (h)	1.4 ± 0.9	1.4 ± 0.9	0.99
$t_{½}$ (h)	6.8 ± 3.1	5.4 ± 1.6	0.30
$AUC_{0-\infty}$ (mg·h/L)	128 ± 60	97 ± 31	0.21
CL_R (mL/min/kg)	0.26 ± 0.18	0.37 ± 0.25	0.33
CL_{NR} (mL/min/kg)	0.86 ± 0.44	1.01 ± 0.38	0.49
CL_P (mL/min/kg)	1.12 ± 0.46	1.39 ± 0.35	0.22

C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; $t_{½}$, half-life; $AUC_{0-\infty}$, area under the concentration–time curve; CL_R, renal clearance; CL_{NR}, non-renal clearance; CL_P, total plasma clearance.
[a]Adapted from Hendershot *et al.*[25]

Excretory organ failure

Hepatic failure. Linezolid pharmacokinetics have been studied in seven patients with mild to moderate liver disease and in healthy volunteers matched for gender, weight and age. Patients received a single 600 mg dose of linezolid.[25] The pharmacokinetic parameters are presented in Table 4. No statistically significant differences were observed compared with healthy volunteers, but numbers are small. No dose modification is recommended in mild to moderate hepatic insufficiency. Pharmacokinetics have not been studied in severe hepatic failure (i.e. Child–Pugh Class C), but as linezolid is metabolized predominantly by a non-enzymic process, impairment of hepatic function would not be expected to alter the pharmacokinetics significantly.[9,25]

Renal failure. Linezolid pharmacokinetics in patients with varying degrees of renal insufficiency have been studied. A single 600 mg dose was administered to 24 adults in four groups: group 1, healthy volunteers with no renal impairment (CL_{CR} > 80 mL/min); group 2, non-dialysis patients with moderate renal impairment (CL_{CR} 40–80 mL/min); group 3, non-dialysis patients with severe renal impairment (CL_{CR} 10–39 mL/min); and group 4, end-stage renal disease patients maintained on haemodialysis. The patient demographics and pharmacokinetic parameters are shown in Table 5. Values for $AUC_{0-\infty}$, C_{max}, T_{max}, V and CL_{TOTAL} did not change with

Table 5. Patient demographics and linezolid pharmacokinetic parameters[a]

	Group			
Parameter	1[b]	2[c]	3[d]	4 (off dialysis)[e]
Age (years)	34 ± 10	45 ± 7	48 ± 14	43 ± 5
Weight (kg)	75 ± 10	75 ± 25	79 ± 12	78 ± 26
C_{max} (mg/L)	12.7 ± 2.6	15.5 ± 7.1	10.8 ± 3.1	15.4 ± 5.0
T_{max} (h)	1.3 ± 0.8	0.8 ± 0.4	1.7 ± 1.1	0.9 ± 0.6
$t_{½}$ (h)	6.4 ± 2.2	6.1 ± 1.7	7.1 ± 3.7	8.4 ± 2.7
$AUC_{0-\infty}$ (mg·h/L)	110 ± 22	128 ± 53	127 ± 66	141 ± 45
CL_R (mL/min)	28 ± 6	21 ± 6	7.4 ± 2.2	–
CL_{NR} (mL/min)	67 ± 26	71 ± 48	100 ± 78	–
CL_{TOTAL} (mL/min)	95 ± 22	93 ± 44	110 ± 78	77 ± 21
V_D (L)	52 ± 17	46 ± 21	50 ± 14	57 ± 26

C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; $t_{1/2}$, half-life; AUC_{0-8}, area under the concentration–time curve from 0 to 8 h; CL_R, renal clearance; CL_{NR}, non-renal clearance; CL_{TOTAL}, total clearance; V_D, volume of distribution.
[a]Adapted from Brier *et al.*[26]
[b]Group 1 included healthy volunteers with no renal impairment (CL_{CR} > 80 mL/min).
[c]Group 2 included non-dialysis patients with moderate renal impairment (CL_{CR} 40–80 mL/min).
[d]Group 3 included non-dialysis patients with severe renal impairment (CL_{CR} 10–39 mL/min).
[e]Group 4 included end-stage renal disease patients maintained on haemodialysis.

decreased renal function. CL_R of linezolid was reduced as renal function decreased, but CL_{NR} increased.[26] Haemodialysis removed ~30% of the linezolid dose. Thus, administration of the standard dosage of linezolid, 600 mg every 12 h, is recommended and should be scheduled after haemodialysis.

The linezolid metabolites PNU-142300 and PNU-142586 accumulate to a significant degree depending on the degree of renal impairment. In severe renal insufficiency (CL_{CR} < 30 mL/min), for example, a seven- to eight-fold increase in exposure to both metabolites occurs. Although some of the metabolites are removed by dialysis, the $AUC_{0–48}$ values of PNU-142300 and PNU-142586 are still higher than those observed in patients with moderate renal insufficiency and healthy volunteers. The clinical significance of this accumulation is as yet unclear.

No data are available on the pharmacokinetics of linezolid in peritoneal dialysis or continuous veno-venous haemofiltration but as far as is known, no dose modification is required in renal insufficiency. Caution is advisable, however, given the likely accumulation of metabolites.

Drug interactions

Cytochrome P450 enzyme system

Linezolid does not inhibit cloned human cytochrome P450s, CYPIA2, 2C9, 2C19, 2D6, 2E1 or 3A4. In addition, linezolid does not induce hepatic microsomal CYP1A, CYP3A or CYP4A. Levels of CYPP2B and CYP2E were increased 1.5-fold in male rats by linezolid; these increases were markedly less than those observed in animals that received phenobarbital or isoniazid.[17] When healthy volunteers received warfarin after a 5 day course of linezolid, a 10% reduction occurred in the mean maximum international normalized ratio (INR), a 5% reduction in the area under the INR versus time curve. Until data are accumulated from patients receiving warfarin plus linezolid, the clinical significance of these observations is unclear.[9,27]

Monoamine oxidase

Linezolid is a reversible non-selective inhibitor of monoamine oxidase and therefore, has the potential to interact with adrenergic and serotonergic agents. Patients receiving linezolid may experience a reversible enhancement of the pressor response to indirectly acting sympathomimetic agents, vasopressor or dopaminergic agents.

In normotensive healthy volunteers, linezolid enhanced the increase in blood pressure caused by the sympathomimetic agents pseudoephedrine and phenylpropanolamine.[5] Linezolid plus dextromethorphan (as a serotonin reuptake inhibitor) showed no serotonin effects such as confusion, delirium, restlessness, tremor, blushing or hyperpyrexia.[5] Furthermore, data from seven comparator-controlled Phase III trials were analysed to detect serotonin effects among patients receiving either linezolid (n = 52) or a comparator (n = 67) in combination with a selective serotonin reuptake inhibitor.[28] Reports of hyperthermia, diaphoresis or flushing occurred in 3.8% of linezolid-treated patients compared with 4.5% of comparator-treated patients; reports of confusion, sedation, delirium or CNS depression occurred in 3.8% and 1.5% of the treatment groups, respectively; and no reports of restlessness, tremor or myoclonus were recorded in either treatment arm. None of the reported adverse events was attributed to the combination of linezolid and a selective serotonin reuptake inhibitor.[28]

No significant pressor response was observed with subjects receiving both linezolid and <100 mg tyramine orally.[29] However, given the potential interactions, it is recommended that linezolid should only be administered to patients receiving serotonin reuptake inhibitors, tricyclic antidepressants, sympathomimetic agents, vasopressor agents, dopaminergic agents, pethidine or buspirone if there are facilities to monitor blood pressure. In addition, patients being treated with linezolid should avoid foods with a high tyramine content such as mature cheese, yeast extracts, undistilled alcoholic drinks and fermented soya bean products such as soya sauce.

Pharmacodynamics

The pharmacodynamics of linezolid have been studied in terms of *in vitro* systems, animal models and human trials.

Pattern of bacterial killing

Linezolid has a predominantly bacteriostatic action in time–kill experiments. This activity is most notable against staphylococci and enterococci[30–33] at concentrations of 2 ×, 4 × and 10 × MIC. These concentrations equate approximately to free drug concentrations achieved in human plasma. Much higher concentrations, i.e. 100 mg/L, are also bacteriostatic against staphylococci and enterococci.[34] Linezolid modelled at 600 mg every 12 h in an *in vitro* model was shown to be bacteriostatic against *Staphylococcus aureus* and enterococci.[35] Furthermore, modest bactericidal activity has been reported for linezolid in time–kill experiments against *Streptococcus pneumoniae* and *Streptococcus pyogenes*.[30,31]

Data from animals support the *in vitro* findings. For example, increasing the dose of linezolid produced minimal concentration-dependent killing against *S. aureus* and *S. pneumoniae* in a mouse thigh infection model.[36] In addition, linezolid was found to be bacteriostatic in a rabbit endocarditis model when human pharmacokinetics of 10 mg/kg/12 h were modelled.[37]

Post-antibiotic effect

The post-antibiotic effect (PAE) of linezolid against *S. aureus* is 1.8–2.3 h[30] but depends on the concentration of exposure being longer for *S. aureus*, *E. faecalis* and *E. faecium* if 4 × MIC is compared with 1 × MIC.[32] The PAE for *S. pneumoniae* tends to be longer than that for *S. aureus* but for both species, the duration of the PAE continues to increase up to concentrations over 10 × to 100 × MIC.[38] PAEs of 3.6–3.9 h with *S. pneumoniae* and 3.7–3.9 h with *S. aureus* were reported in a murine thigh infection model.[36]

Animal models

The time interval over which drug concentration exceeds the MIC (t > MIC) was the major predictor of efficacy with *S. pneumoniae* in a murine thigh infection model where dose escalation and fractionation were employed to differentiate t > MIC, AUC/MIC and C_{max}/MIC. A t > MIC of 33–49% (mean 40%) for *S. pneumoniae* and a t > MIC of 33–59% (mean 41%) for *S. aureus* were required to produce a net bacteriostatic effect over 24 h.[36]

These data were confirmed in a rat pneumonia model in which high and low doses of linezolid were used to treat *S. pneumoniae* infection. Results demonstrated that a t > MIC of ≥45% was the best predictor of outcome.[39] A t > MIC of ≥40% in plasma was also shown to be associated with successful outcome in a gerbil model of *S. pneumoniae* acute otitis media; however, a t > MIC of 60% in the middle ear fluid was required.[40] The reason for this difference is unclear but may be related to the time course of tissue penetration for linezolid.

As may be expected with a drug in which t > MIC determines outcome, continuous infusion regimens have been modelled. Continuous infusion linezolid to a concentration of 20 × MIC was recently noted to be bactericidal against *S. aureus* in a rabbit endocarditis model.[41] It remains to be shown in other animal models whether a t > MIC of >40% will bring additional benefit in terms of bactericidal activity. However, linezolid is bacteriostatic in *in vitro* experiments against *S. aureus* and enterococci, even at relatively high concentrations.

Human studies

Three human studies on pharmacodynamics have been reported. Two assessed the efficacy of linezolid, and the third study was undertaken to develop correlates with adverse events. In the efficacy studies, fixed dosing regimens were used; hence, it is difficult to differentiate easily between t > MIC, C_{max}/MIC and AUC/MIC. Using a group of 231 patients with community-acquired pneumonia, skin and soft tissue infections or bacteraemia, t > MIC and AUC_{24}/MIC were evaluated in correlation with clinical and microbiological failure. As t > MIC was 100% of the dosing interval for most patients, this analysis was uninformative; however, a low AUC_{24}/MIC was related to a disproportionate number of failures. In patients with bacteraemia, age and AUC_{24}/MIC were shown to be significant predictors of failure in a logistic regression analysis. Unfortunately, the magnitude of the AUC_{24}/MIC associated with cure was not reported.[42] In a further study of 241 seriously ill adults with Gram-positive infection, time to pathogen eradication, pathogen eradication and clinical cure were predicted by AUC/MIC or t > MIC. Efficacy was maximal with a percentage t > MIC of ≥85% or an AUC/MIC of >100.[43]

Therefore, although the animal pharmacodynamic data support a breakpoint of <4 mg/L based on a t > MIC target of ≥40%, the above data in seriously ill humans support a breakpoint for susceptibility of ≤2 mg/L, as recommended in the European Summary of Product Characteristics.[9] The British Society for Antimicrobial Chemotherapy (BSAC) recommends a breakpoint of ≤4 mg/L based on limited clinical data that staphylococcal and enterococcal species for which the MIC is 4 mg/L can be successfully treated.[44]

In addition to these efficacy analyses, the degree of thrombocytopenia observed in debilitated, seriously ill patients with multiple, concurrent diseases and treatments in a compassionate-use programme was highly associated with AUC and length of linezolid therapy.[45]

In conclusion, the pharmacokinetics and pharmacodynamics of linezolid have been extensively studied in laboratory models, healthy volunteers and patients. Because linezolid is used in clinical practice, additional data will be forthcoming and the importance of the existing database to therapy in clinical practice will be further defined.

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