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Oxazolidinones:

A New Class of Antibiotics

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Linezolid Pharmacokinetics

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The pharmacokinetics of linezolid have been described in healthy male and female volunteers participating in the phase I safety tolerance trials following both oral and intravenous (IV) dosing. Pharmacokinetic studies have been conducted to assess dose proportionality, absolute bioavailability, and the effect of food and formulation variables on bioavailability. The following doses have been studied: single oral doses (bulk drug in capsule) of 50 mg to 500 mg;[1] multiple oral doses of 100 mg to 750 mg every 8 hours for up to 10 days;[1] multiple oral doses of 375 mg to 625 mg every 12 hours for 14 days;[2] single IV doses (30-minute infusion) of 250 mg to 750 mg;[1] multiple IV doses of 250 mg to 500 mg every 8 hours for up to 7 days;[1] and multiple IV doses of 500 mg and 625 mg every 12 hours for 7 days.[3]

After single or multiple IV doses, the total systemic elimination clearance (CL) averaged about 125 mL/min. About 30% of the dose is eliminated unchanged in the urine. Renal clearance (CL_r) averaged about 40 mL/min. Linezolid exhibits low binding to plasma proteins (about 31% bound), and CL_r for free drug (about 59 mL/min) suggests net tubular reabsorption. The nonrenal clearance (CL_{nr}), calculated as the difference between CL and CL_r, averaged about 100 mL/min and was more variable than CL_r. The distribution of linezolid appears to be limited to the volume of total body water (steady-state volume of distribution, V_{ss}, averaged about 50 L). The elimination half-life averaged about 5 to 7 hours.[1-3] Neither CL nor V_{ss}, estimated from single-dose data in parallel groups, appears to differ significantly with increasing dose.[1-3]

Linezolid is rapidly and extensively absorbed after oral dosing.[1] Maximum concentrations (C_{max}) are reached within two hours of dosing,[1-3] and the average absolute bioavailability is 103%. Therefore, linezolid may be given orally without dose adjustment in patients who are able to receive oral medication. There was no significant difference in the AUC values when linezolid was administered while fasting or after a high-fat breakfast. The average C_{max} value for linezolid administered under the fasting condition was 23% higher than for the fed condition. This difference does not influence the efficacy of linezolid and therefore linezolid may be administered without regard to meals. Systemic clearance after oral dosing (CL_{po}) was similar to CL following IV administration, and CL_r and CL_{nr} following oral administration were similar to those following IV administration.[1-3]

The dose proportionality of orally administered linezolid was assessed for single-dose and steady-state administration of 125 mg, 375 mg, and 625 mg doses in a crossover study. The results of this study indicate that there is a small degree of nonlinearity with higher doses of linezolid. The total clearance for the 625 mg dose is about 30% lower than would be predicted from the 125 mg dose. The decrease in CL was accounted for by decreases in both CL_r and CL_{nr}. This dose dependency was observed after single and multiple doses. The percent of the dose that appeared in the urine as linezolid remained constant at about 35% across all dose levels for both single- and multiple-dose administration. Although the pharmacokinetics of linezolid have been shown to be statistically dependent upon dose, the degree of nonlinearity is small relative to the overall variability among subjects, such that dose adjustments in the clinical use of linezolid are not considered necessary.

The average minimum concentration (C_{min}) values for oral administration of 200 mg or 400 mg of linezolid every 8 hours for 10 days were 3.57 µ/mL and 7.62 µ/mL, respectively, and the corresponding average C_{max} values were 8.28 µ/mL and 15.37 µ/mL, respectively.[1] The average C_{min} values for oral administration of 375 mg or 625 mg of linezolid every 12 hours for 14.5 days were 3.90 µ/mL and 8.01 µ/mL, respectively, and the corresponding average C_{max} values were 13.1 µ/mL and 18.8 µ/mL, respectively.[2] Together, the results of these two studies indicate that for these dose regimens the C_{min} values are near or above the highest MIC_{90} (4 µ/mL) for the most resistant susceptible target pathogens, and bid dosing provides average plasma linezolid concentrations comparable to tid dosing. Therefore, twice daily and three times daily dosing should provide comparable efficacy for the same total daily dose.[1,2]

Linezolid has little or no coverage for gram-negative bacteria; therefore, a companion antimicrobial agent may be used in infections with a mixture of gram-positive and gram-negative organisms. Aztreonam and gentamicin are two probable companion drugs to provide gram-negative coverage. Drug interaction studies have been conducted for linezolid administered with aztreonam and with gentamicin.[4] There is no change in the plasma concentration profiles of linezolid or aztreonam when administered alone or together.[4] Similarly, there was no difference in the plasma concentration profiles of linezolid or gentamicin when given separately or together.[4] Therefore, either aztreonam or gentamicin may be given concurrently with linezolid with no change in dosage for either drug.

Linezolid is neither a substrate nor an inhibitor of the major human cytochrome P-450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, it is anticipated that the metabolism of linezolid will be unaffected by inhibitors or inducers of cytochrome P-450 and linezolid will not inhibit the metabolism of compounds cleared by cytochrome P-450 enzymes. Induction studies of cytochrome P-450 enzymes CYP1A2, CYP2B, CYP2C, CYP2E, CYP3A, and CYP4A in rats indicate that linezolid does not induce any of these isoforms.

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4. Jungbluth GL, Lasher-Sisson T, Hopkins NK, Knechtel TJ, Burton NK, Donaldson KM. Linezolid and gentamicin or aztreonam: a pharmacokinetic evaluation of intravenous coadministration in healthy volunteers. In: Program and abstracts of the 35th annual meeting of the Infectious Diseases Society of America; September 13-September 16, 1997; San Francisco, Ca. Abstract.

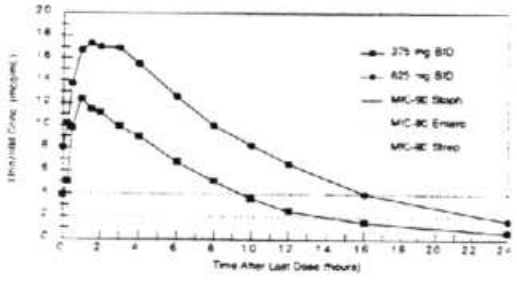
Pharmacokinetic Characteristics

Oral bioavailability	100%
Food effect	Slight decrease in rate, but no effect on extent of absorption
Volume of distribution	40 to 50 L
Protein binding	31%
Elimination half-life	5 to 7 hours

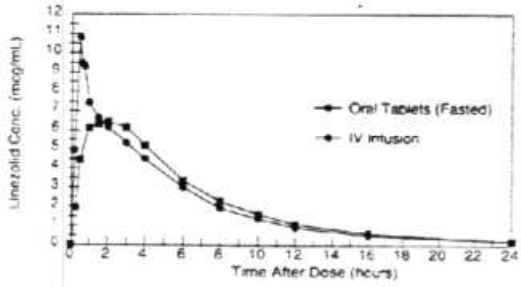
Pharmacokinetic Characteristics

Metabolism	- Not metabolized by CYP-450 - No inhibition of major CYP-450 isoforms - Metabolites do not contribute antibacterial activity
Clearance	
. Total	100 to 200 mL/min
. Renal	30 to 50 mL/min
Nonrenal	70 to 150 mL/min
Percent of drug dose excreted in urine as parent compound	30% to 35%

Average Steady-State Plasma Linezolid Concentrations After Oral Administration of 375 or 625 mg Given Two Times a Day for 14 Days

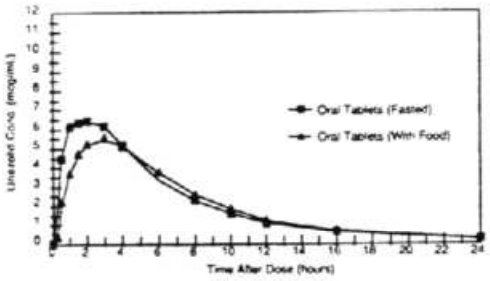


Average Steady-State Plasma Linezolid Concentration After Administration of a Single 375 mg Dose Given as Oral Tablets or IV Infusion



Linezolid Pharmacokinetics

Average Steady-State Plasma Linezolid Concentrations After Administration of a Single 375 mg Dose Given as Oral Tablets With or Without Food



Linezolid Metabolism

- Not metabolized by cytochrome P450 enzymes
- Morpholine ring susceptible to chemical oxidation
- Does not inhibit the catalytic activity of the major human P450 drug metabolizing enzymes
- Does not induce P450 enzymes in the rat

Monoamine Oxidase Inhibition

- Inhibition of catecholamine metabolism
  - Tyramine or sympathomimetic effect
  - MAO-A inhibition associated with elevation of blood pressure
- Inhibition of serotonin metabolism
  - Serotonin syndrome
  - MAO-B inhibition associated with hyperthermia, CNS alteration

Drug Interactions

In Phase I studies, mild to moderate changes in diastolic and systolic blood pressure were seen in normal healthy volunteers given concomitant

- Phenylpropanolamine
- Pseudoephedrine
- Tyramine

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