Clinical population pharmacokinetics and toxicodynamics of linezolid.


Abstract

Thrombocytopenia is a common side effect of linezolid, an oxazolidinone antibiotic often used to treat multidrug-resistant Gram-positive bacterial infections. Various risk factors have been suggested, including linezolid dose and duration of therapy, baseline platelet counts, and renal dysfunction; still, the mechanisms behind this potentially treatment-limiting toxicity are largely unknown. A clinical study was conducted to investigate the relationship between linezolid pharmacokinetics and toxicodynamics and inform strategies to prevent and manage linezolid-associated toxicity. Forty-one patients received 42 separate treatment courses of linezolid (600 mg every 12 h). A new mechanism-based, population pharmacokinetic/toxicodynamic model was developed to describe the time course of plasma linezolid concentrations and platelets. A linezolid concentration of 8.06 mg/liter (101% between-patient variability) inhibited the synthesis of platelet precursor cells by 50%. Simulations predicted treatment durations of 5 and 7 days to carry a substantially lower risk than 10- to 28-day therapy for platelet nadirs of <100 ×10(9)/liter. The risk for toxicity did not differ noticeably between 14 and 28 days of therapy and was significantly higher for patients with lower baseline platelet counts. Due to the increased risk of toxicity after longer durations of linezolid therapy and large between-patient variability, close monitoring of patients for development of toxicity is important. Dose individualization based on plasma linezolid concentration profiles and platelet counts should be considered to minimize linezolid-associated thrombocytopenia. Overall, oxazolidinone therapy over 5 to 7 days even at relatively high doses was predicted to be as safe as 10-day therapy of 600 mg linezolid every 12 h.

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