



Stop Sweltering over Linezolid and Serotonin Syndrome

Linezolid is an antibiotic with broad activity against gram-positive organisms, including MRSA and VRE. It plays an increasing role as oral stepdown therapy for *S. aureus* bacteremia and in empiric therapy for necrotizing skin and soft tissue infections.¹⁻³ Linezolid possesses weak monoamine-oxidase inhibitor properties, therefore risk exists for serotonin syndrome when administered with other serotonergic medications.⁴ With a potentially expanding role in therapy, how should this drug interaction be managed?

What is serotonin syndrome and how does it present?

Serotonin syndrome is caused by overstimulation of central and peripheral serotonin receptors. It can be mild or life threatening. Serotonin syndrome is characterized by the triad of mental status changes (e.g. agitation, anxiety, restlessness), autonomic hyperactivity (e.g. increased heart rate, high blood pressure, increased respiratory rate, elevated temperature, sweating), and neuromuscular activity (e.g. tremors, muscle rigidity, rhythmic muscle contractions).

What is the risk of serotonin syndrome when linezolid is given with another serotonergic medication?

In a meta-analysis of phase 3 and phase 4 linezolid clinical trials (20 studies with ~10,000 patients), 41% of patients received at least one serotonergic agent. Among those, 303 (5.6%) received an SSRI. Twelve (0.54%) in linezolid group vs 4 (0.19%) in comparator group had symptoms meeting serotonin toxicity criteria.⁴

In a large observational study of 1135 outpatients who received linezolid, 215 patients received a concomitant antidepressant. In the overall cohort, less than 6 cases of serotonin syndrome were reported, with fewer cases of serotonin syndrome occurring in the antidepressant group. Additionally, 166 patients that received concomitant linezolid and an antidepressant were matched using propensity scores to patients that received linezolid alone. When comparing propensity scored matched groups, the risk for developing serotonin syndrome was numerically lower in the antidepressant group with an adjusted risk difference of -1.2% (95% CI, -2.9% to 0.5%; p=0.50). Notably, no patients in this study were receiving monoamine-oxidase inhibitors, which may be higher risk for serotonin syndrome compared to other serotonergic medications.⁵

How should serotonergic medications be managed in patients needing linezolid?

The FDA recommends a minimum 2-week washout of serotonergic drugs prior to linezolid initiation, however this caution is primarily based on passive surveillance and case reports.⁶ The risk of serotonin syndrome with linezolid in patients receiving most antidepressants is low and should not deter the administration of linezolid in patients who need treatment.

Key takeaway: Risk for serotonin syndrome with linezolid in a patient receiving concomitant serotonergic medication is low. Risks versus benefits should be weighed when considering the use of linezolid.

References:

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