In the Literature

Can Linezolid be Safely Used in Patients Receiving Serotonergic Drugs?


Linezolid is a nonselective weak reversible inhibitor of monoamine oxidase (MAO) with greater affinity for MAO-B (Kᵢ 0.71 µM) than for MAO-A (Kᵢ 561 µM). The former is mostly responsible for oxidation of benzylamine, dopamine, and β-phenylethylamine, whereas the latter primarily oxidizes epinephrine, noradrenaline, and serotonin. Tyramine is metabolized by both. As a consequence of its inhibitory activity, linezolid has the potential for causing serotonin toxicity in patients also receiving potentially interacting drugs.

Lawrence et al reviewed spontaneous reports to the US Food and Drug Administration (FDA) from 1997 through 2005 of serotonin toxicity in linezolid recipients [1]. They identified 20 cases that met their case definition, the majority of which were being treated with serotonin reuptake inhibitors (SSRIs). Only 3 of these, however, met a standardized set of criteria (modified Hunter Serotonin Toxicity Criteria). Most other reports of serotonin toxicity in patients receiving linezolid consist only of case reports or small case series that allow neither a determination of the incidence of this complication, nor comparison to a control group.
Butterfield et al have attempted to address this deficiency by examining the locked databases of 20 phase II and IV comparator-controlled clinical trials evaluating the relative efficacy of linezolid in the treatment of a variety of infections. The comparators were all β-lactam or glycopeptide antibiotics. Of the 10,488 patients enrolled in these trials, 4,265 (40.7%) were receiving at least 1 serotoninergic drug and are the subject of the analysis.

There were no investigator-initiated reports of serotonin toxicity. The presence of serotonin toxicity was also determined by the investigators in a treatment-blinded review, using standardized criteria (Steinhatch Criteria and the Hunter Serotonin Toxicity Criteria). Of the 2,188 patients receiving linezolid who also received at least 1 serotoninergic medication, 9 (0.41%) met the Steinhatch criteria, and among comparator recipients, 3 (0.15%) of the 2,075 met them (risk ratio, 2.79; 95% confidence interval: 0.76–10.31). Among patients also receiving serotoninergic agents, the Hunter Serotonin Toxicity Criteria were met by 3 (0.14%) linezolid recipients and 1 (0.05%) of recipient of a comparator (risk ratio, 2.79; 95% confidence interval, 9.29–28.85). No patient met both sets of criteria.

Thus, the incidence of apparent serotonin toxicity among patients also receiving serotoninergic agents, although numerically greater, did not significantly differ between patients receiving linezolid and those receiving a comparator antibacterial agent. Nonetheless, some degree of risk does exist and must be considered by the clinician. The FDA has, over the years, published cautions such as: "Unless patients are carefully observed for signs and symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: SSRIs, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, and bepridil.

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It should be further noted that discontinuing these agents at the time of initiating linezolid therapy does not solve the problem, at least with regard to SSRIs. Rapo discontinuation of an SSRI may lead to severe withdrawal symptoms. In addition, members of this class of drugs have prolonged elimination half-lives and complete elimination may take weeks.

Thus, the use of linezolid with serotoninergic agents comes down to a careful analysis of the available data and expert clinical judgment. The clinician must balance the benefits of treatment with linezolid relative to treatment with alternative antibiotics.

References