Serotonin Syndrome and Linezolid

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We present a case of serotonin syndrome in a patient who initiated linezolid therapy shortly after discontinuation of therapy with a selective serotonin reuptake inhibitor (paroxetine).

Linezolid is the first oxazolidinone available for clinical use. The advantages of this agent include its clinically significant activity against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. As such, linezolid is a welcome addition to the antibiotic armamentarium. Concerns regarding the use of linezolid have largely focused on the potential emergence of resistance and the occurrence of thrombocytopenia and suppression of all cell lines in the bone marrow in patients who receive longer courses of therapy [1–5]. Although linezolid is known to inhibit monoamine oxidase (MAO) activity, there are limited data regarding the occurrence of clinically significant interactions [1, 6]. Herein, we describe a case of serotonin syndrome caused by combined use of linezolid and paroxetine.

Case report. A 56-year-old woman with a history of depression, chronic hepatitis C infection, hypertension, diabetes, and cervical stenoses (at C4–C7) was admitted for elective laminectomy. Of note, an abdominal CT scan revealed evidence of hepatic cirrhosis. Preoperative medications included paroxetine, IFN-α, felodipine, terazosin, lisinopril, insulin, methocarbamol, morphine sulfate, and ibuprofen. The patient’s postoperative course was uneventful until postoperative day 11, when she became oversedated. Administration of morphine sulfate and methocarbamol was discontinued, and administration of paroxetine was tapered for 3 days. The last dose of paroxetine administered on postoperative day 14, at which time the patient’s mental status had significantly improved (figure 1). However, it was then discovered that the patient had a grossly infected surgical wound; surgical incision and drainage of a deep abscess were performed at the surgical site. Because of an unspecified β-lactam allergy, empiric therapy with vancomycin was initiated (figure 1). Cultures of intraoperative specimens grew methicillin-sensitive S. aureus.

Despite appropriate antimicrobial therapy and the absence of other foci of infection, the patient remained febrile (temperature, 39.5°C [103°F]). Because drug fever was suspected, on postoperative day 17, intravenous linezolid was substituted for vancomycin (figure 1). Within 24 h, the patient developed delirium, hypertension, hostility, anger, and tremors. A psychiatric consultant attributed these symptoms to the serotonin syndrome; linezolid therapy was discontinued and vancomycin therapy was restarted. Within 48 h, the patient had returned to her baseline mental status and had defervesced. Her subsequent course was unremarkable.

Discussion. This case indicates that linezolid may provoke the serotonin syndrome in persons who have recently received selective serotonin reuptake inhibitors (SSRIs). Our patient met the Sternbach criteria for serotonin syndrome: she had fever, agitation, mental status changes, and tremors [7]. With the exception of persistent fever, metabolic abnormalities were excluded as causes for these signs and symptoms. Linezolid was the only new drug started before the onset of the symptoms that could potentially interact with paroxetine. Such reactions may be due to the inhibitory effect of linezolid on MAO, as demonstrated by the ability of linezolid to potentiate hypertensive responses to pseudoephedrine or phenylpropanolamine [9]. However, no such effect was observed in a study that evaluated interactions between dextromethorphan and linezolid in healthy volunteers [9].

Serotonin is removed from the synapse by active transport (or reuptake) or degradation by MAO. Therefore, because the serum half-life of paroxetine is 21 h, it is likely that the inhibitory effect of linezolid combined with residual paroxetine activity to produce the serotonin syndrome in our patient. Although this reaction has not been noted in previous reports of concomitant use of SSRIs and linezolid, the patient we describe may have been at increased risk for this syndrome because of her receipt of other medications and a decreased hepatic clearance of paroxetine [1].

Previous information on the interactions of linezolid with SSRIs is largely limited to an analysis of patients who received SSRIs and either linezolid (n = 52) or other antimicrobials (n = 67) [10]. In that study, adverse effects were grouped into
3 categories: group I included diaphoresis, hyperthermia, and flushing; group II included confusion, sedation, delirium, or CNS depression; and group III included restlessness, tremor, and myoclonus. Among patients who received linezolid, the incidences of reactions were as follows: group I, 3.8% of patients; group II, 3.8%; and group III, 0%; among patients who received other antimicrobials, the corresponding incidences were 4.5%, 1.5%, and 0% [10]. A single previous article briefly described another case in which the serotonin syndrome occurred after linezolid was administered to a patient receiving an SSRI (paroxetine) [6].

In summary, we report the occurrence of serotonin syndrome in a patient who received linezolid shortly after discontinuation of therapy with an SSRI (paroxetine). Although withdrawal of opiate treatment and use of other pharmaceutical agents may have contributed to the occurrence of the serotonin syndrome, we recommend caution when prescribing linezolid along with an SSRI, especially in persons receiving multiple pharmacological agents. More studies or case reports may be helpful in delineating the risks and safety of linezolid. In high-risk persons, it may prove to be prudent to observe a 2-week “washout” period between the discontinuation of SSRIs and the initiation of linezolid, as has been recommended for the use of MAO inhibitors [7, 8].

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References