



ORIGINAL ARTICLE

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**Linezolid drug interactions: A retrospective study**

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**Abstract**

Linezolid is an antimicrobial drug which has good activity against clinically important gram-positive methicillin and vancomycin resistant microorganisms. However, linezolid is a lifesaving medicine for resistant infections, it can be responsible for severe drug interactions. Linezolid is a nonselective, weak, reversible inhibitor of monoamine oxidase A and B. That is why it can lead to increase activity of concomitant administered monoamine oxidase inhibitors, serotonergic and adrenergic agents. This study is a one-month retrospective chart review of inpatients at a university hospital. All charts in a 1368 bed university hospital were reviewed via electronic records. Charts, which include linezolid have evaluated by clinical pharmacists and were assessed for prevalence and severity of potential drug-drug interactions using the UpToDate drug reference database. Fifty-four patients included in this study. Total number of interactions with linezolid was 86, which was 28.2 percent of all interactions. Eight of these interactions were in X category (avoid combination), 59 were in D category (consider therapy modification) and 19 were in C category (monitor therapy). There wasn't any interaction classified as category B (no action needed). In our study, it was predicted that serotonergic toxicity and hypertension may develop in many patients due to concurrent administration of linezolid with serotonergic and/or adrenergic drugs. If the coadministration of these drugs is unavoidable, physicians should be alert to the symptoms and management of serotonergic toxicity and hypertension. The number of patients and its retrospective nature were limiting factors of our study. More comprehensive prospective studies are needed.

**Keywords:** Linezolid, drug interaction, clinical pharmacist

**Introduction**

Linezolid is a synthetic oxazolidinone derivative antimicrobial drug which has good activity against clinically important gram-positive methicillin and vancomycin resistant microorganisms. Linezolid was introduced as an ideal reserve drug for treatment of vancomycin-resistant *Enterococcus* spp. (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA) [1].

It is reasonable to use linezolid in the intensive care unit because of its advantages. Linezolid prevent the expression of virulence elements because it decreases Gram-positive pathogens toxins. Also, it has good cerebrospinal fluid penetration in central nerve system infections. Linezolid is effective in the treatment of ventilator-associated pneumonia and catheter related bacteremia [2].

However, linezolid is a lifesaving medicine for resistant infections, it can be responsible for severe drug interactions. Linezolid is a nonselective, weak, reversible inhibitor of monoamine oxidase A and B. That is why it can lead to increase activity of concomitant administered monoamine oxidase inhibitors, serotonergic and adrenergic agents [3].

**Materials and Methods**

This study is a one-month retrospective chart review of inpatients at İnönü University Turgut Özal Medical Center.

All charts in the 1368 bed hospital were reviewed for 30 days via electronic records. Patients, who have received linezolid included in the study. Charts between 01.03-31.03.2019, which include linezolid have evaluated by clinical pharmacists and were assessed for prevalence and severity of potential drug-drug interactions using the UpToDate drug reference database. Severity was classified as "avoid combination (X)", "consider therapy modification (D)", "monitor therapy (C)", "no action needed (B)".

**Results**

Fifty-four patients included in this study. Age range of patients was

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from 4 months to 93 years and sex ratio (male/ female) was 1,57.

Thirty-three male and 21 female patients had total 305 drug interactions. Thirteen of these interactions were in X category (avoid combination), 95 were in D category (consider therapy modification), 162 were in C category (monitor therapy), and 35 were in category B (no action needed).

Total number of interactions with linezolid was 86, which was 28.2 percent of all interactions. Eight (9.3%) of these interactions were in X category (avoid combination), 59 (68.6%) were in D category (consider therapy modification) and 19 (22.1%) were in C category (monitor therapy). There wasn't any interaction classified as category B (no action needed) (Figure 1).

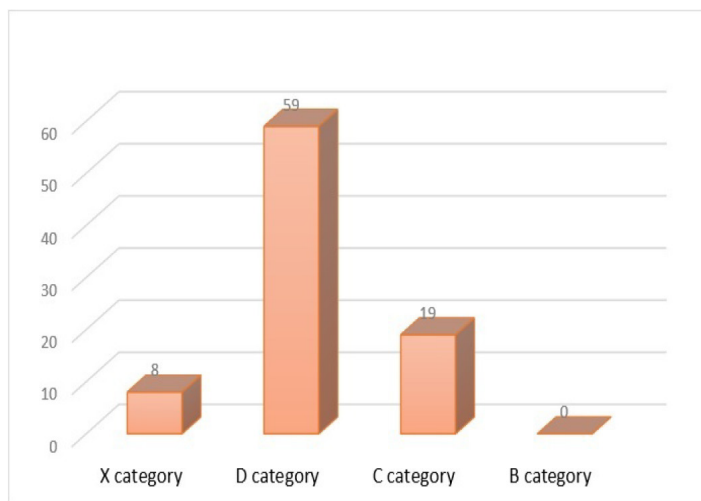


Figure 1. Total number of interactions with linezolid (n:86)

Linezolid-fentanyl and linezolid-pethidine interactions were belonging to the risk category X (Figure 2).

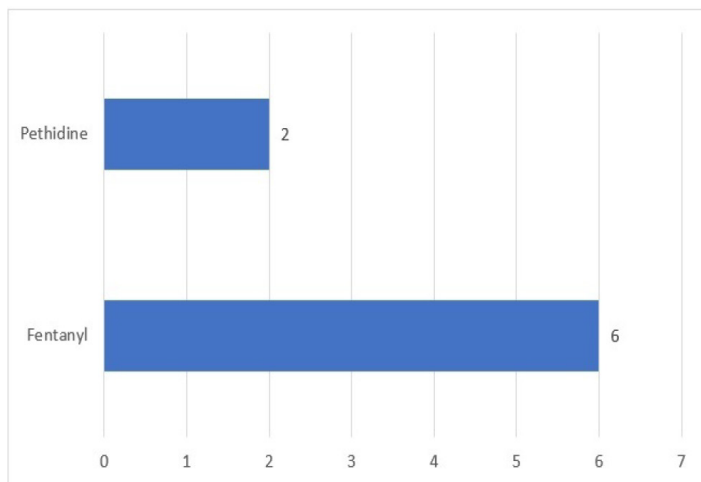


Figure 1. Total X category drug interactions of linezolid (n:8)

Ten (16,95%) of total 59 D category drug interactions were adrenaline, 12 (20.34%) were salbutamol, 13 (22.03%) were tramadol, 9 (15.25%) were dopamine, 5 (8.47%) were theophylline, 5 (8.47%) were escitalopram and 5 (8.47%) were noradrenaline (Figure 3).

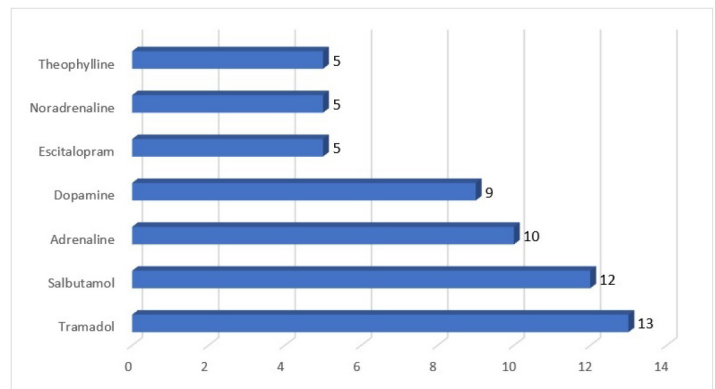


Figure 3. Total D category drug interactions of linezolid (n:59)

Five (26.32%) of total 19 C category drug interactions were metoclopramide, 4 (21.05%) were quetiapine, 4 (21.05%) were trimethoprim and sulfamethoxazole, 2 (10.53%) were granisetron, 1 (5.26%) was aripiprazole, 1 (5.26%) was haloperidol, 1 (5.26%) was risperidone and 1 (5.26%) was metformin (Figure 4).

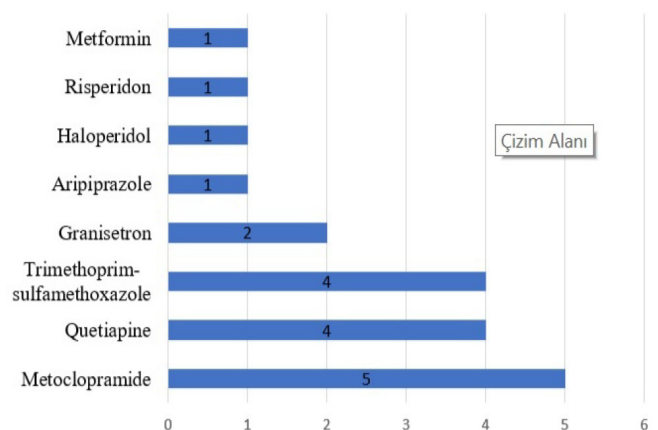


Figure 4. Total C category drug interactions of linezolid (n:19)

## Discussion

The mechanism of pethidine and fentanyl interactions with linezolid are likely related to additive effects on serotonin, with monoamine oxidase inhibitor reducing serotonin metabolism, and pethidine or fentanyl possibly blocking neuronal uptake [4].

For the management of this interactions should be avoided pethidine or fentanyl use in patients who are receiving, or have received within 14 days, monoamine oxidase inhibitors. Concomitant use of these agents is contraindicated [4].

Management for the salbutamol, adrenaline, theophylline and noradrenalin interactions are the same. Initial doses of sympathomimetic agents should be reduced, and closely monitored for enhanced blood pressure elevations, in patients receiving linezolid [4].

For the management of linezolid and dopamine interactions, dopamine initial dose should be maximum one-tenth (1/10) of the usual dose in patients who are receiving (or have received within the last 2 to 3 weeks) monoamine oxidase inhibitors. Patients

should be monitored for an exaggerated hypertensive response to dopamine [4].

Management for tramadol and escitalopram interactions are the same. Because of serotonin toxicity risk, serotonergic agents should be discontinued at least 14 days before the administration of linezolid. If immediate initiation of linezolid is needed, the availability of alternative agents and interventions should be considered. If the benefit of linezolid under such circumstances outweighs the risk of serotonin toxicity, discontinue the serotonin modulator immediately and monitor closely for signs of serotonin toxicity for 14 days after the last serotonin modulator dose, or 24 hours after the last linezolid dose, whichever comes first. Serotonin modulator treatment may be resumed 24 hours after the last dose of linezolid [4].

Management for metoclopramide, aripiprazol, risperidone, haloperidol and quetiapine interactions are the same. Concurrent use of any serotonin modulator with linezolid should be used with caution. Patients should be monitored extra closely for evidence of serotonin toxicity (e.g., mental status changes, autonomic instability, and neuromuscular hyperactivity) or neuroleptic malignant syndrome (e.g., hyperthermia, muscle rigidity, autonomic dysfunction) [4].

For the management of linezolid and granisetron interaction patients should be monitored due to the risk of serotonin syndrome [4].

Management for metformin and trimethoprim sulfamethoxazole interactions are the same. Patients should be monitored for excessive pharmacologic effects (e.g., hypoglycemia) [4].

There are many case reports in the literature regarding the serotonin syndrome seen as a result of coadministration of linezolid and serotonergic drugs.

A review, which published in 2009 discusses 17 case reports of serotonin syndrome associated with linezolid-SSRI interaction [5] and another review published in 2013 discusses 32 cases of serotonin syndrome from case reports and retrospective studies, including all case reports discussed in the previous review [6].

A retrospective cohort study which include forty-two freestanding children's hospitals throughout the United States shows that 30 percent of the all contraindicated interactions were with linezolid [7].

In a multicentered study from our country has been found that linezolid is the most often contraindicated drug in all drug interactions. In this study also has been shown that physicians were not aware of the risk of coadministration of linezolid and other medications [8].

The number of patients and its retrospective nature were limiting factors of our study. More comprehensive prospective studies are needed.

In our study, it was predicted that serotonergic toxicity and hypertension may develop in many patients due to concurrent administration of linezolid with serotonergic and/or adrenergic drugs. If the coadministration of these drugs is unavoidable, physicians should be alert to the symptoms and management of serotonergic toxicity and hypertension.

Multidisciplinary teamwork is effective to both the patients and the health professionals. Clinical pharmacists and clinicians should collaborate to optimize linezolid use, especially in the detection of drug interactions and appropriate prescriptions of linezolid.

#### Competing interests

*The authors declare that they have no competing interest.*

#### Financial Disclosure

*The authors received no financial support for the research.*

#### Ethical approval

*Ethically approved by İnönü University Ethics Committee (Approval number: 2019/279)*

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