Effect of a serum lactate monitoring recommendation policy on patients treated with linezolid

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Abstract
Lactic acidosis is one of the most fatal adverse effects of linezolid, an antibiotic used to treat serious infections caused by antibiotic-resistant bacteria. However, the measures to prevent lactic acidosis have not been well established.

We performed a retrospective study to analyze the impact of applying a serum lactate monitoring recommendation policy in patients treated with linezolid.

Since September 2011, we have recommended inpatient monitoring of serum lactate levels in patients treated with linezolid at our hospital. Patients were divided into two groups according to whether they were seen during the non-recommendation or recommendation periods. The frequency of serum lactate monitoring, linezolid-induced lactatemia, lactic acidosis, critical illness, and death were compared between the two periods.

After September 2011, adherence to the recommendation to monitor serum lactate increased from 6.1% to 60.1%. No difference was observed in the incidence of linezolid-induced lactatemia and lactic acidosis between the two periods. However, there was a significant difference in the incidence of linezolid-induced critical illness between the non-recommendation and recommendation periods (3 vs 0 cases, \( P = .044 \)).

In patients treated with linezolid, serum lactate monitoring led to early detection of lactatemia, thus enabling rapid rescue. We recommend regular monitoring of serum lactate in all patients treated with linezolid.

Keywords: acidosis, lactate, lactic acidosis, linezolid, mortality

1. Introduction
Linezolid is an oxazolidinone class antibiotic that has exceptional activity against most clinically-important gram-positive bacteria and mycobacteria.\textsuperscript{[1]} The use of linezolid is increasing due to emerging multidrug-resistant organisms, such as vancomycin-intermediate resistant staphylococci, vancomycin-resistant enterococci, and multidrug-resistant tuberculosis, and an increased need for alternative drugs to glycopeptides.\textsuperscript{[2]} The increasing use of linezolid has highlighted the development of frequent adverse effects, such as bone marrow suppression, neuropathy, and lactic acidosis,\textsuperscript{[3]} which can be fatal as their early symptoms are not obvious and they are difficult to treat.\textsuperscript{[4]}

In our previous study, we reported the risk of linezolid-induced lactic acidosis through comparison with a teicoplanin group, and recommended monitoring of serum lactate in patients treated with linezolid.\textsuperscript{[5]} However, the impact of such generalized recommendations on patient outcomes has not yet been studied. Thus, we conducted a retrospective cohort study to investigate the incidence of linezolid-induced lactic acidosis and patient outcomes after recommending (from September 2011) serum lactate monitoring.

2. Methods
2.1. Overall design and study population
From January 2004 to July 2019, we monitored patients admitted to an 860-bed university hospital who were receiving either oral or intravenous linezolid (Zyvox; Pfizer, New York, NY, USA). Linezolid should be used at our hospital only after consultation by an infectious disease specialist; however, children under the age of 15 were excluded from the study because they were supervised by the division of pediatric infectious diseases and not by the division of infectious diseases.
All the recommendation methods for serum lactate monitoring, that is, education, documented recommendation, and verbal recommendation, were used; however, it is difficult to confirm it retrospectively. For this reason, patients were divided into two groups based on the time since we recommended routine testing of serum lactate levels: a non-recommendation period group (January 2004–September 2011) and a recommendation period group (October 2011–July 2019). Patients admitted to departments other than the Department of Infectious Diseases were divided into two groups (January 2004–April 2012 vs May 2012–July 2019) because the timing of the recommendation was different. The scheme of this study is shown in Figure 1.

2.2. Event definition

The weekly frequency of serum lactate monitoring was calculated as follows: \[
\frac{\text{number of serum lactate measurements during linezolid treatment}}{\text{total days of linezolid treatment}} \times 7\text{days}.
\]
Adherence to monitoring was defined as a patient undergoing more than one test every two weeks (weekly frequency > 0.5). Patients with linezolid treatment duration of less than one week were considered as having had no time to receive serum lactate monitoring and were excluded from the adherence analysis.

To assess the outcomes of serum lactate monitoring, linezolid-induced lactatemia, lactic acidosis, critical illness, and death were compared between the two periods. Lactatemia was defined as serum lactate $\geq 4$ mg/dL, and lactic acidosis was defined as serum pH $< 7.25$ plus lactatemia. If there was an apparent increase in anion gap due to linezolid (without ketoacidosis, other toxin-related, and renal failure), it was included in the case, even if serum lactate was not measured. Critical illness was defined as death, shock, or hemodialysis in patients with linezolid-induced lactic acidosis.

Linezolid-induced events were based on probable cases according to the Naranjo criteria for adverse drug reactions.\(^6\) The exclusion criteria for linezolid-induced events were shock, lactic acidosis, hypoxemia, bleeding, cancer progression, or exposure to other medications.

2.3. Data analysis

Because the Shapiro–Wilk test did not provide a normal distribution, the duration of antibiotic administration and number of patients for whom serum lactate levels were monitored were presented using median and interquartile range. Student’s t test and chi-squared test were used to compare general characteristics between the non-recommendation and recommendation period groups. Fisher’s exact test and Mann–Whitney test were used to compare outcomes between the two periods. Two-tailed P values $< .05$ were considered statistically significant. Data analysis was performed using SPSS statistical software (v.20; SPSS Inc., Chicago, IL).

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**Figure 1.** Scheme of the present study. Figure 1 shows the non-recommendation and recommendation periods in this study. Monitoring adherence was analyzed only for patients who used more than 7 days.
Ethical approval from the Inha University Hospital Institutional Review Board (Incheon, Republic of Korea) was obtained prior to the study. All patient records were anonymized.

3. Results

3.1. General characteristics of patients treated with linezolid

A total of 316 patients treated with linezolid were monitored between January 2004 and July 2019. Of these, 112 were in the non-recommendation period group and 204 in the recommendation period group (Table 1). Median linezolid treatment duration was reduced from 13 days to 11 days after the recommendation for serum lactate monitoring ($P < 0.031$) because linezolid administration was often interrupted due to the monitoring results. Lactic acid levels were measured during linezolid treatment in 111 patients at least once, and linezolid-induced serum lactate elevation was identified in 11 patients. Of these patients, four were identified in $\leq 2$ weeks, three in 2 to 4 weeks, and four in $\geq 4$ weeks (Table 2).

3.2. Comparison between the non-recommendation and recommendation period groups

Mean weekly frequency (number of serum lactate monitoring events per week) increased from 0.07 in the non-recommendation period group to 1.08 in the recommendation period group ($P < .001$). Only 6.1% of patients were adequately monitored before the recommendation, with the ratio increasing to 60.1% after the recommendation ($P < .001$).

Although the incidence of linezolid-induced lactatemia was higher in the recommendation period group than in the non-recommendation period group, the difference was not statistically significant. However, the incidence of critical illness related to linezolid-induced lactic acidosis decreased from 3/112 patients to 0/204 patients ($P = .044$). There was no rescue from linezolid-induced events during the non-recommendation period - two patients died and one patient experienced shock and hemodialysis. During the recommendation period, all eight patients with lactatemia were rescued after early discontinuation of linezolid (Table 3).

4. Discussion

Because lactic acidosis is fatal and has no effective treatment, early detection of linezolid-induced lactic acidosis is impor-

### Table 1

Comparisons of general Characteristics Pre-recommendation and recommendation period.

| Variables               | Pre-recommendation | Recommendation | $P$ value |
|-------------------------|--------------------|----------------|-----------|
| Total Number            | 112                | 204            |           |
| Gender: male            | 53                 | 115            | .128      |
| Age, years              | 60.2 (SD 16.8)     | 62.3 (SD 16.0) | .277      |
| Comorbidities           |                    |                |           |
| Cardiovascular diseases | 11                 | 22             | .850      |
| Diabetics               | 32                 | 57             | .897      |
| Liver cirrhosis         | 5                  | 8              | .776      |
| Chronic kidney disease  | 9                  | 23             | .438      |
| Antibiotics duration, days | 13.0 (IQR 6.0–25.8) | 11.0 (IQR 5.0–16.0) | .031 |

*IQR* = interquartile ranges, *SD* = standard deviation.

### Table 2

Cases of linezolid-related events.

| No. | Age | Sex | Period       | Duration of linezolid, days | Frequency of serum lactate | Serum lactate, mg/dL | Lactic acidosis | Critical illness | Death | Comorbidity |
|-----|-----|-----|--------------|-----------------------------|---------------------------|----------------------|-----------------|-----------------|-------|-------------|
| 1   | 77  | M   | Non rec-period | 30                          | 2                         | 20.0                 | Yes             | Yes             | Yes   | —           |
| 2   | 64  | M   | Non rec-period | 42                          | 2                         | 16.0                 | Yes             | Yes             | Yes   | Diabetics   |
| 3   | 52  | F   | Non rec-period | 5                           | —                         | —                    | Yes             | Yes             | —     | —           |
| 4   | 76  | F   | Rec-period    | 7                           | 1                         | 4.5                  | —               | —               | —     | —           |
| 5   | 69  | F   | Rec-period    | 39                          | 8                         | 4.8                  | —               | —               | —     | —           |
| 6   | 60  | M   | Rec-period    | 33                          | 3                         | 4.1                  | —               | —               | —     | —           |
| 7   | 89  | M   | Rec-period    | 27                          | 2                         | 10.4                 | Yes             | —               | —     | —           |
| 8   | 56  | M   | Rec-period    | 22                          | 3                         | 4.1                  | —               | —               | —     | Diabetics and chronic kidney disease |
| 9   | 69  | F   | Rec-period    | 20                          | 4                         | 4.7                  | —               | —               | —     | —           |
| 10  | 61  | F   | Rec-period    | 12                          | 1                         | 4.0                  | —               | —               | —     | —           |
| 11  | 76  | M   | Rec-period    | 11                          | 1                         | 7.1                  | —               | —               | —     | Diabetics   |

Non rec-period = Non-recommendation period, Rec-period = recommendation period.

*This case presented increased an-ion gap (23 mg/dL) and pH 7.19, without other cause except LZD.*

*Case 1–5 were described in a previous study.*
increase in lactate when linezolid was administered for 3 of 10 patients with increased serum lactate levels had an lactic acid,[10] but it is unknown whether such monitoring is induced lactic acidosis, and some articles recommend monitoring statistical signi
cancer. Nevertheless, many patients were rescued before experiencing critical complications. We suggest increasing adherence to serum lactate monitoring. Lack of education or the absentmindedness of attending physicians may be the main cause of low adherence. It may be possible to increase adherence to serum lactate monitoring by repeatedly educating physicians about its importance, and by introducing automatic lactate-test prescribing in computer systems for patients treated with linezolid.

Table 3
Comparisons of outcomes between Pre-recommendation and Recommendation period.

| Variables                      | Pre-recommendation | Recommendation | \( P \) value |
|-------------------------------|--------------------|----------------|--------------|
| Total number                  | 112                | 204            | \(< .001\)   |
| Adherence to serum lactate monitoring | 5/82 (6.1%)      | 86/143 (60.1%) | \( .752\)    |
| Linezolid-related event       |                    |                |              |
| Lactatemia                    | 3                  | 8              | \( .752\)    |
| Lactic acidosis               | 3                  | 1              | \( .129\)    |
| Lactic acidosis-related critical illness* | 3                  | 0              | \( .044^*\) |
| Death                         | 2                  | 0              | \( .125\)    |

* Critical illness includes shock, hemodialysis and death.

The rate of adherence to serum lactate monitoring was 60.1%, which was lower than expected. Nevertheless, many patients were rescued before experiencing critical complications. We suggest increasing adherence to serum lactate monitoring. Lack of education or the absentmindedness of attending physicians may be the main cause of low adherence. It may be possible to increase adherence to serum lactate monitoring by repeatedly educating physicians about its importance, and by introducing automatic lactate-test prescribing in computer systems for patients treated with linezolid.

This study has some limitations. First, it was conducted as a retrospective, single-center trial, such that the personal opinion of one physician may have been involved in several lactate-test prescriptions. Therefore, we divided the groups into different time periods to reduce these potential confounding factors. Second, the study results did not show a significant difference in mortality between the two periods. However, this was probably due to the small patient population, and further research is needed. Third, despite the recommendation period, the documented recommendation was only 59/138. The main reason for non-compliance with monitoring was an oral approval. In an emergency, the prescription was orally approved without any documentation. In this oral approval, we were unable to review if the serum lactate monitoring recommendations were followed.

Conclusively, the recommendation for serum lactate monitoring led to early detection of lactic acidosis in patients in this study. Thus, we recommend routine serum lactate monitoring for all patients treated with linezolid.

Author contributions

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