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Incidence and risk factors of linezolid-induced lactic acidosis

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SUMMARY

Background: The use of linezolid has increased with the emergence of multidrug-resistant bacteria. Serum lactic acidosis has been reported as a serious side effect of linezolid use, therefore we evaluated the incidence and characteristics of linezolid-related lactic acidosis.
Methods: Patients admitted to an 860-bed university hospital were enrolled. The patients were divided into two groups, those who used linezolid and those who used teicoplanin (control group). The study was conducted by review of the medical charts.
Results: Seventy-two patients were included in the linezolid group. The control group comprised 72 patients matched to those in the linezolid group for age and indication for antibiotic use. Lactic acidosis occurred in five cases (6.8%) in the linezolid group. None of the patients who used teicoplanin developed lactic acidosis, which was a comparable result. The median change in anion gap in the linezolid group was −0.8 mmol/l (interquartile range (IQR) −3.55 to 1.28 mmol/l), which was significantly higher than in the teicoplanin group, 0.05 mmol/l (IQR −1.75 to 2.3 mmol/l) ($p = 0.026$). The number of increased anion gap events in patients who used linezolid for more than 6 weeks was higher than in the group who used linezolid for less than 6 weeks ($p = 0.0014$). However, no statistically significant difference was observed according to age, estimated glomerular filtration rate, or diabetes.
Conclusions: Linezolid showed an association with treatment-related lactic acidosis. A longer duration of linezolid use (>6 weeks) was one of the risk factors for metabolic acidosis. We suggest checking serum lactate concentrations regularly, especially in those on long-term use.

1. Introduction

Linezolid (LZD), an antibiotic of the oxazolidinone class, has activity against most Gram-positive bacteria. LZD is used in the treatment of multidrug-resistant (MDR) Gram-positive bacteria, such as vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant Enterococcus (VRE), as an alternative therapy for patients suffering from the side effects of glycopeptides, and for the treatment of MDR tuberculosis. In addition, the use of LZD is increasing due to the emergence of prosthetic infections in the elderly and an elevation of the vancomycin minimum inhibitory concentration (MIC).

LZD-induced lactic acidosis was first reported by Apodaca and Rakita in 2003.[1] LZD-induced lactic acidosis can occur as a serious problem, resulting in death and multi-organ failure. However, most people are not considered as having LZD-induced lactic acidosis, and there are no data on the incidence and risk factors of LZD-induced lactic acidosis. Therefore, we evaluated the incidence and characteristics of LZD-related lactic acidosis.

2. Materials and methods

2.1. Case identification and study population

Patients admitted to an 860-bed university hospital from April 2003 to July 2012 were enrolled. They received either oral or intravenous antibiotic administration. Patients were divided into two groups: those who used LZD and those who used teicoplanin (control group). The two groups were matched for age (within 5 years) and the indications for antibiotic use. The study was conducted by retrospective review of the medical charts. Demographic data, underlying diseases, duration of antibiotic use, and the results of laboratory examinations were analyzed.

Patients who developed hypoxia ($n = 11$), sepsis ($n = 3$), acute blood loss ($n = 2$), diabetic ketoacidosis ($n = 1$), and progression of

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Table 1
Clinical characteristics of patients at the time that the prescriptions for the study antibiotics were filled

Characteristics	Teicoplanin	Linezolid
Prescriptions, *n*	72	72
Age, years, mean ± SD	59.19 ± 19.3	61.4 ± 17.0
Female, *n* (%)	38 (52.8%)	39 (54.1%)
Reason for antibiotic use, *n* (%)		
Skin and soft tissue infection[a]	40 (55.6%)	40 (55.6%)
Pneumonia	7 (9.7%)	7 (9.7%)
Bacteremia and CRBSI	11 (15.3%)	11 (15.3%)
Intra-abdominal infection	3 (4.2%)	3 (4.2%)
Other infection[b]	11 (15.3%)	11 (15.3%)
Coexisting conditions, *n* (%)		
Diabetes mellitus	13 (18.0%)	20 (27.8%)
Chronic liver disease[c]	2 (2.8%)	3 (4.2%)
Duration of antibiotic use, days, median (IQR)	13.00 (7.0–21.7)	14.95 (13.6–17.0)
Duration of hospitalization, days, median (IQR)	15.65 (14.1–17.4)	14 (8.0–24.0)
Initial chemistry		
White blood cell count, × 10^9/l	8.1± 6.2	8.0 ± 7.6
Hemoglobin, g/dl	10.3 ± 1.4	10.1 ± 1.4
Platelet count, × 10^9/l	244.2 ± 139.7	213.4 ± 138.3
Blood urea nitrogen, mg/dl	20.7 ± 17.6	25.2 ± 23.9
Creatinine, mg/dl	1.3 ± 1.1	1.3 ± 1.0
eGFR, ml/min/1.73 m^2 [d]	82.0 ± 53.1	86.0 ± 56.2
Sodium, mEq/l	134.5 ± 4.8	137.5 ± 4.8
Potassium, mEq/l	3.9 ± 0.7	3.8 ± 0.6
HCO_3, mmol/l	24.0 ± 4.3	23.6 ± 3.9
Anion gap, mmol/l	15.35 (14.05–17.40)	14.95 (13.62–17.00)

SD, standard deviation; CRBSI, catheter-related blood stream infection; IQR, interquartile range; eGFR, estimated glomerular filtration rate.
[a] Skin and soft tissue infection: cellulitis, necrotizing fasciitis, myositis, osteomyelitis, prosthetics joint infection, postoperative infection.
[b] Other infection: urinary tract infection, vascular infection, neutropenic fever, endocarditis.
[c] Chronic liver disease: liver cirrhosis, hepatocellular carcinoma.
[d] Modification of Diet in Renal Disease (MDRD) equation.

cancer ($n = 1$) were excluded. Patients for whom the anion gap could not be obtained ($n = 20$) were excluded.

2.2. Definition of lactic acidosis

'Definite' lactic acidosis was defined as a serum pH of <7.25 and serum lactate >4 mmol/l. 'Probable' lactic acidosis was defined in the case where metabolic acidosis was confirmed but serum lactate was unidentified, or where elevated serum lactate was confirmed but serum pH was unidentified. Lactic acidosis by drug was in accordance with the probable grade of the Naranjo criteria for adverse drug reactions.[2]

2.3. Data analysis

If lactic acid and arterial pH data were available, lactic acidosis was evaluated directly; if there were no data, it was evaluated indirectly by anion gap. The anion gap was calculated using the formula $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$. The baseline result was that obtained prior to starting LZD, and the end-point result was that obtained when LZD was stopped. The change in anion gap was defined as the difference between the initial anion gap and the end-point anion gap. If there was no laboratory data on the day of initiation or termination of LZD and teicoplanin, the first result after starting the drug or the last result before stopping the drug was used. In such cases, the duration of antibiotic use was defined as ceasing at the day of the last result. For the subgroup analysis, we used the change in the anion gap or the number of increased anion gap events. An increased anion gap event was defined as a change in anion gap >4 mmol/l. When expressing the anion gap and duration of antibiotic use, medians and interquartile ranges (IQR) were reported because the Shapiro–Wilk test showed that the outcome measures did not have a normal distribution. The Chi-square test was used for the comparison of lactic acidosis incidence between groups. Fisher's exact test or the Mann–Whitney *U*-test was used for comparisons of subgroups. The duration of antibiotic use was analyzed by minimal *p*-value approach for cut-off optimization. Two tailed *p*-values of <0.05 were considered statistically significant. The data analysis was performed using SPSS statistical software version 18 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. General characteristics

Seventy-two patients were included in the LZD group and 72 patients who used teicoplanin, matched to the LZD group for age and indication for antibiotic use, were included in the control group. Underlying diseases were skin and soft tissue infection (55.6%), bacteremia and catheter-related blood stream infection (15.3%), pneumonia (9.7%), intra-abdominal infection (4.2%), and other infections (15.3%).

The mean patient age was 61.4 ± 17 years in the LZD group and 59.2 ± 19.3 years in the teicoplanin group. The median duration of antibiotic use was 19.7 ± 18 days in the LZD group and 19.4 ± 21.5 days in the teicoplanin group.

No significant differences in demographic characteristics were noted between the LZD and control groups (sex, initial white blood cell (WBC) count, anion gap, estimated glomerular filtration rate (eGFR)) (Table 1).

The median duration of hospitalization for the LZD group was 14 days (IQR 8.00–24.00 days), which was shorter than that of the teicoplanin group, 15.65 days (IQR 14.05–17.40 days). However, considering that neither drug is generally used as a first-line drug and that there was no significant difference in initial WBC count, hemoglobin, creatinine, sodium, potassium, or HCO_3 between the two groups, there was no considerable difference in disease severity.

Table 2
Anion gap and incidence of lactic acidosis after antibiotic use

	Teicoplanin	Linezolid	*p*-Value
Post-antibiotic anion gap, mmol/l, median (IQR)	15.25 (14.10 to 16.98)	16.4 (13.80 to 18.05)	
Change in the anion gap, mmol/l[a], median (IQR)	−0.05 (−2.30 to 1.75)	0.8 (−1.28 to 3.55)	0.026[d]
'Definite' lactic acidosis[b], *n*	0	2	0.154
'Probable' lactic acidosis[c], *n*	0	3	0.080
'Definite' + 'probable' lactic acidosis, *n*	0	5	0.023[d]

[a] Change in anion gap = (the end-point anion gap) – (the initial anion gap).
[b] 'Definite' lactic acidosis: lactic acid above 4 mEq and acidosis of below pH 7.25.
[c] 'Probable' lactic acidosis: lactic acid above 4 mEq or acidosis of below pH 7.25.
[d] Significant difference.