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Pharmacokinetic/Pharmacodynamic Modeling of Linezolid in Relation to Lactate as a Predictive Biomarker

Roberto Lozano[1*], Carina Bona[2]

[1]Department of Pharmacy, University clinical hospital"Lozano Blesa", Zaragoza, Spain.
*(Corresponding author)
jrlozanoo@gmail.com
[2]Unit for the Rational Use of Medicines, Aragon Health Service, Zaragoza, Spain.
cbonal@salud.aragon.es

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Abstract

Background: Linezolid, a synthetic oxazolidinone antibiotic, is effective against multidrug-resistant Gram-positive bacteria. However, prolonged use is associated with mitochondrial toxicity and lactic acidosis. Predictive modeling can enhance risk assessment and support therapeutic drug monitoring.
Objective: This study evaluates various PK/PD models to describe lactate elevation associated with linezolid therapy. Both simulated and clinical data were used to fit four mathematical models: Emax, piecewise linear, log-linear, and AUC-based. The goal is to assist clinicians in optimizing dosing strategies and anticipating potential toxicity.
Methods: Simulated linezolid concentration data (0–15 mg/L) were used to construct models in Python, employing NumPy for computations and Matplotlib for visualization. Each model was fitted to time-series lactate data extracted from a published clinical case report. Key parameters—such as EC_{50}, Hill coefficient, and exposure thresholds—were estimated to evaluate model performance.
Results: The Emax model captured threshold-like lactate dynamics, closely reflecting the onset of clinical lactic acidosis. The log-linear model showed a smooth, progressive increase in lactate and remained robust across all time points. The piecewise linear model offered interpretability but lacked physiological realism. The AUC-based model reflected cumulative exposure effects and was suitable for long-term monitoring, though less sensitive in early phases.
Conclusion: The Emax model provided the best fit for abrupt lactate elevation, while the log-linear model offered a balance between predictive accuracy and clinical utility. These models support individualized dosing strategies for at-risk patients undergoing prolonged linezolid therapy. Further validation in clinical cohorts is recommended.

1. Introduction

Linezolid is a widely used synthetic oxazolidinone antibiotic effective against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). While its antibacterial efficacy is well established, linezolid's safety profile, particularly concerning mitochondrial toxicity and lactic acidosis, raises concerns during prolonged use or in patients with impaired renal function. The onset of lactic acidosis has been attributed to linezolid's inhibition of mitochondrial protein synthesis, leading to reduced oxidative phosphorylation and increased reliance on anaerobic metabolism [1]. Therapeutic drug monitoring (TDM) of linezolid is recommended for at-risk populations [2,3,4], but predictive pharmacokinetic/pharmacodynamic (PK/PD) models offer additional clinical utility [5,6,7]. This study compares four PK/PD models—maximum effect (Emax), piecewise linear, log-linear, and Area Under the Curve (AUC)-based —to characterize the relationship between linezolid exposure and serum lactate elevation. The goal is to assist clinicians in forecasting adverse metabolic effects and optimizing linezolid dosing strategies.

2. Methods

We developed four mathematical models to describe the relationship between plasma concentrations of linezolid and the increase in serum lactate levels. The models were constructed using simulated data across a range of linezolid concentrations (0–15 mg/L). All data processing, statistical calculations, and graphical visualizations were performed using Python programming language. Specifically, numerical computations and data manipulation were conducted using the NumPy library (for efficient array operations and numerical functions), while Matplotlib was employed for generating high-quality plots and visual representations of the results, including time-course profiles, dose–response curves, and model fittings. This computational approach ensured reproducibility, flexibility, and precision in the analysis.

Additionally, to validate these models against real-world data, lactate vs.linezolid time values were extracted from a published clinical cases [8]. A graph was digitized using image processing and pixel coordinate transformation, yielding estimated lactate concentrations over time in a patient treated with linezolid. These data points were then used to fit Emax, log-linear, piecewise linear, and AUC-based models using nonlinear regression methods in Python.

2.1 *Emax Model*

The Emax model follows a sigmoidal relationship commonly used in PK/PD studies [6]. The formula used was:

$$L(t) = L_0 + [E_{max} * t^n] / [EC_{50}{}^n + t^n]$$

Where:

L(t): plasma lactate concentration (mmol/L) at time t (in days)
L_0=estimated baseline lactate concentration (mmol/L)
Emax=maximum possible increase in lactate attributable to linezolid
EC50=time (in days) at which half of Emax is achieved

n=Hill coefficient, describing the steepness of the response curve
Parameters used:
L_0: lactato basal (~1.0 mmol/L); E_{max}: producción máxima inducida (p. ej. +6.0 mmol/L); EC_{50}: concentración de linezolid que produce el 50% del efecto máximo (≈ 8 mg/L); n: coeficiente de Hill (describir pendiente de la curva, típicamente 2–3).

2.2 *Piecewise Linear Model*

$$L(t) = \begin{cases} L_0 & \text{si } C\_linez(t) \leq C\_safe \\ L_0 + k \cdot (C\_linez(t) - C\_safe) & \text{si } C\_safe < C\_linez(t) \leq C\_tox \\ L\_crit & \text{si } C\_linez(t) > C\_tox \end{cases}$$

The piecewise linear model assumes a threshold effect, where lactate remains constant up to a certain linezolid concentration, then increases linearly, and finally plateaus at a critical level [6]. The model is described as follows:

L(t): plasma lactate concentration at time t (in days)
L_0: initial (constant) lactate level during early treatment
t=6: critical time threshold (in days) for model transition
Parameters used:
L_0 = 1.0 mmol/L, C_safe = 6.0 mg/L, C_tox = 12.0 mg/L, k = 1.0.

2.3 *Log-Linear Model*

The log-linear model assumes a gradual, logarithmic increase in lactate with rising linezolid concentrations [6]. The equation used is:

$$L(t) = L_0 + \alpha * \log(t + 1)$$

Where:
L(t): plasma lactate concentration at time t (in days)
L_0=estimated baseline lactate level (mmol/L)
α: Sensitivity coefficient
log(t+1): time-transformed response to allow for smooth early-phase dynamics
Parameters used:
L_0**:** Baseline lactate (1.0 mmol/L); α**:** Sensitivity coefficient (e.g., 2.5); A value of 1 is added inside the logarithm to avoid log(0).

2.4 *AUC-Based Model*

An AUC-based model [6] was designed to reflect cumulative linezolid exposure over time. It assumes that total lactate production is proportional to the AUC:

$$L\_total(t) = \beta \times AUC(t)$$

Where:
L_{total}: cumulative plasma lactate concentration at time t (in days)
β=0.0212: proportionality constant linking cumulative exposure to lactate elevation (mmol/L·h per mg·h/L).
AUC: area under the linezolid exposure-time curve up to time t (in this simplified model, approximated as cumulative time due to the time-aligned data)

3. Results

3.1 *Emax Model Output*

The Emax model shows a slow increase in lactate up to 6–7 mg/L of linezolid, followed by a sharp rise as the concentration surpasses 8 mg/L. At concentrations ≥10 mg/L, lactate approaches 7 mmol/L, indicating a high risk of lactic acidosis.
In **Figure 1**, the Emax model shows an initial flat phase followed by a steep rise, closely matching the upper phase of the observed lactate data. The curve captures the threshold dynamics better than linear models, making it valuable for identifying exposure limits in dosing strategies.

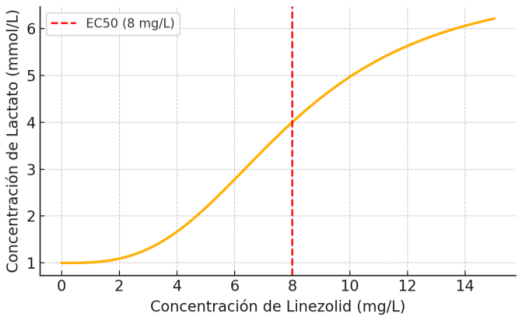

Figure 1. Emax model: Plasma linezolid concentration vs. lactate levels.

Model Interpretation:
The Emax model represents a sigmoid-shaped dose–response curve, allowing for a threshold effect and a maximum ceiling response. In this case, the steep Hill coefficient (n=3) produces a rapid rise in lactate levels once the critical exposure time is reached.
This behavior suggests that linezolid-induced lactic acidosis may be minimal at early stages, but escalate sharply after a certain duration of exposure.
Advantages:
Accurately models threshold-dependent toxicity, which aligns with clinical observations of abrupt lactate elevation in some patients.
Suitable for identifying critical treatment durations beyond which toxicity may sharply increase.

Limitations:
Assumes all patients reach a maximum effect (plateau), which may not be realistic in diverse clinical populations.
May overpredict toxicity if Hill coefficient is overfitted to a small dataset.

3.2 *Piecewise Linear Model Output*

In contrast, the piecewise linear model presents a three-phase pattern: stable lactate levels up to 6 mg/L, linear increase between 6 and 12 mg/L, and a plateau at 7 mmol/L for concentrations above 12 mg/L.

In **Figure 2**, the piecewise model displays a sharp inflection at day 5, aligning with several mid-phase data points. Although it does not account for continuous progression, the model offers a conservative clinical rule: toxicity is unlikely before day 5, and likely above it.

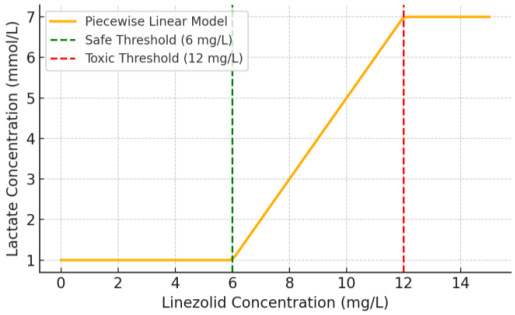

Figure 2. Piecewise linear model: Plasma linezolid concentration vs. lactate levels.

Model Interpretation:
This model reflects a two-phase behavior in lactate dynamics: a stable early phase with no change in concentration, followed by a stepwise increase to a new plateau. The threshold at day 6 indicates a clinically meaningful tipping point, after which systemic accumulation or metabolic shift may occur.
The flat slope before t=6 represents minimal toxic accumulation during initial therapy, while the abrupt change suggests a latent onset of adverse metabolic response.
Advantages:
Easy to interpret and implement in clinical protocols with clear exposure thresholds.
Useful for settings where toxicity emerges after a specific treatment duration, such as in prolonged antibiotic regimens.
Limitations:
May oversimplify the physiological transition by ignoring gradual trends.

Assumes instantaneous shift in lactate levels, which may not reflect actual metabolism.

3.3 *Log-Linear Model Output*

In **Figure 3**, the log-linear model follows the observed clinical data with good overall agreement, especially in the mid- and late-phase data points. The curve remains smooth and bounded, avoiding overfitting while maintaining clinical plausibility.

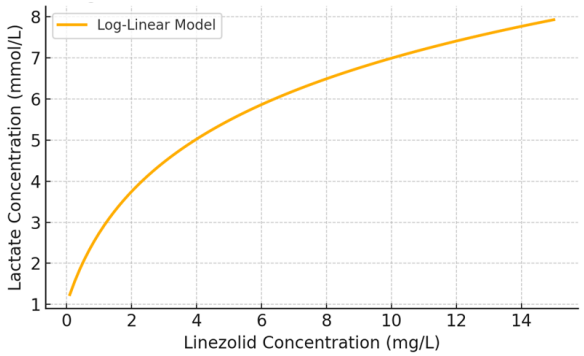

Figure 3. Log-linear model: Linezolid concentration vs. lactate response.

Model Interpretation:

The model was fitted to time-series lactate data, where lactate concentrations rose progressively over 16 days of linezolid therapy. Unlike the Emax model, the log-linear model does not impose a defined toxicity threshold. Instead, it describes a gradual and continuous increase in lactate with time, capturing subtler accumulation patterns.

It effectively reflects moderate or slow accumulation over time, especially in clinical settings where acute toxicity may not develop, but risk builds cumulatively.

Advantages:

Captures gradual physiological trends, suitable for outpatient or long-term treatment scenarios.

Represents metabolic burden without abrupt inflection points.

Limitations:

May not accurately model acute or nonlinear toxicities.

Doesn’t provide a clear threshold to guide clinical intervention.

3.4 *AUC-Based Model Output*

The AUC-based model illustrates a direct, linear relationship between the total exposure to linezolid and cumulative lactate production. Such an approach is particularly valuable in assessing delayed onset toxicity and may be integrated into pharmacokinetic simulations.

In **Figure 4**, the AUC-based model displays a linear increase in lactate over time, capturing the upward trend seen in real-world patient data. While less precise in early-phase prediction, it reflects the cumulative metabolic stress seen in prolonged linezolid therapy and may serve as a conservative model for toxicity forecasting.

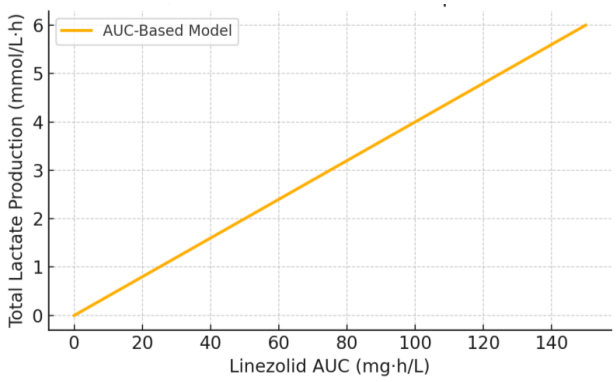

Figure 4. AUC-based model: Linezolid AUC vs. total lactate production.

Model Interpretation:

The AUC-based model posits that lactate elevation is directly proportional to cumulative drug exposure, rather than peak concentration or instantaneous levels.

This is especially relevant in chronic therapy, where toxicity may emerge gradually from persistent low-to-moderate drug levels.

In this case, time itself serves as a surrogate for cumulative AUC, under the assumption of roughly consistent linezolid concentrations over the interval.

Advantages:

Ideal for evaluating long-term treatment effects, particularly in patients with altered drug clearance (e.g., renal impairment).

Supports pharmacokinetic-informed decision-making by focusing on total exposure burden.

Limitations:

Requires actual AUC data for accuracy; here, we use time as a proxy due to data availability.

May oversimplify exposure dynamics by not accounting for concentration peaks or troughs.

3.5 *Comparative Model Fitting to Clinical Data*

Figure 1 shows the comparative fit of all four models to data extracted from Park et al. [8], which report lactate evolution over 16 days of linezolid therapy.

Mathematical Representation of PK/PD Models and Fitted equations:

Emax Model:

$L(t) = 3.98 + [5.47 * t^{10}] / [9.44^{10} + t^{10}]$

Piecewise Linear Model:

$L(t) = 4.02$ if $t \leq 5$; $L(t) = 6.48$ otherwise

Log-Linear Model:

$L(t) = 0.19 + 2.73 * \log(t + 1)$

AUC-Based Model:

$L\_total(t) = 0.0212 \times AUC(t)$, where AUC is cumulative time ($\int_0^t$ time dt)

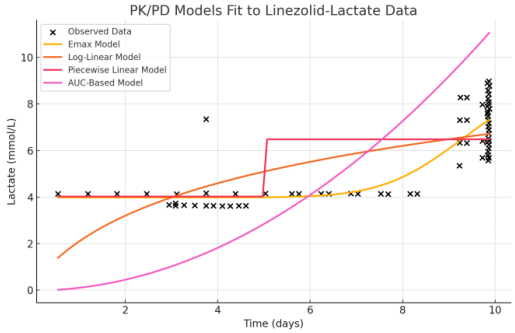

Figure 5. Comparison of PK/PD model fits to observed lactate data during linezolid therapy.

Based on the fitting results shown in **Figure 5**, the log-linear model provides the most consistent and reliable representation of the observed clinical data [8]:

The log-linear model demonstrates a gradual and smooth rise in lactate levels over time, closely matching the trajectory of the experimental data throughout the 16-day observation period.

It avoids overfitting and maintains biological plausibility, particularly in settings where lactate accumulation is progressive rather than abrupt.

While the Emax model fits well in the later phase and captures potential threshold effects, it introduces parameter sensitivity that may be problematic when applied to sparse or noisy clinical data.

The piecewise model, although visually aligned with a sudden shift, is less physiologically realistic due to its discontinuity and simplification of dynamics.

The AUC-based model provides a broad cumulative perspective, but it tends to underestimate early increases and overestimate late-phase accumulation due to its assumption of linearity.

Upon visual and quantitative inspection of the fitted curves (Figure 5), the Emax model provides the best overall fit to the clinical data:

Its sigmoidal shape, driven by a high Hill coefficient (n=10), effectively captures the initially flat lactate levels followed by a steep rise observed around day 10–14.

This behavior reflects the threshold-like progression of lactic acidosis often seen with prolonged linezolid exposure.

The Emax model also incorporates a maximum effect (E_{max}) and an EC_{50} parameter, enabling it to simulate saturation kinetics consistent with mitochondrial toxicity mechanisms.

In contrast:

The log-linear model offers a smoother, monotonic increase and performs reasonably well across the full time range, but it lacks the ability to model the accelerated late-phase increase.

The piecewise linear model, while approximating a clinical inflection point, imposes an artificial and abrupt transition that may not fully reflect physiologic processes.

The AUC-based model captures the cumulative exposure concept but underrepresents early-phase variability and may overestimate late toxicity under linear assumptions.

In summary, the Emax model best captures the dynamic behavior of lactate accumulation in this case and is the preferred PK/PD model for describing linezolid-induced lactic acidosis in similar exposure scenarios.

Discussion

The Emax model provides a biologically plausible nonlinear response consistent with mitochondrial toxicity, especially suited to represent the complex pharmacodynamics of drugs like linezolid. However, the piecewise linear model offers clinical simplicity, capturing clear thresholds at which intervention might be required.

Both models can inform TDM and patient monitoring strategies. The Emax model may be more accurate for research and simulation purposes, while the piecewise linear model is useful in decision support systems due to its transparency. Notably, both predict a steep increase in lactate near concentrations of 8–10 mg/L, aligning with clinical data [2,9].

In practice, combining these models may provide the best predictive accuracy: using the piecewise model for early screening and the Emax model for patients with rising levels to estimate potential severity. Future studies should validate these predictions using clinical cohorts and adjust for renal clearance, duration of exposure, and patient comorbidities.

The log-linear model describes a continuous and progressive increase in lactate as plasma concentrations of linezolid increase. This response does not feature a sharp inflection, making it particularly suitable for modeling low to moderate lactate elevations in clinical situations where linezolid accumulation may be gradual or where patient-specific variability prevents distinct toxicity thresholds. Such an approach aligns with real-world pharmacokinetics, especially in outpatient therapy or intermittent monitoring contexts. Also, this model adds value by modeling continuous risk without relying on sharp thresholds. This is advantageous for cases where patients may not demonstrate clear toxicity limits but still accumulate lactate over time. In environments with variable renal clearance or delayed drug elimination, this model provides early warning indicators before more dramatic increases, bridging the gap between initial screening and advanced modeling. It complements both the piecewise and Emax approaches by filling the gap in low-exposure but prolonged-risk scenarios.

Finally, the AUC-based model provides a cumulative view of lactate production, assuming it is directly proportional to the total exposure to linezolid over time. It is particularly relevant in cases of chronic dosing or extended therapy where toxicity arises not from peak levels but from sustained presence. The linear nature of this model supports its use in long-term pharmacokinetic simulations and population studies. This model serves as a predictive tool for evaluating cumulative toxicity risk, especially useful when evaluating patients on prolonged regimens, or those with fluctuating pharmacokinetics due to renal impairment. Unlike threshold-based models, this approach considers time-integrated exposure, aligning well with the observed cases of delayed-onset lactic acidosis. In clinical pharmacology, this model supports dosing adjustments and monitoring strategies based on total drug burden rather than instantaneous levels.

Additionally, and based on Park's data, the Emax model demonstrates the best overall fit to the clinical data [6], particularly during the later phase, where lactate concentrations increase sharply. Its sigmoidal shape—defined by a high Hill coefficient (n = 10)—effectively captures the threshold-like response observed in linezolid-induced lactic acidosis.

Conversely, the log-linear model emerges as the best compromise between predictive accuracy, clinical interpretability, and mathematical robustness. It offers smooth, time-consistent predictions, making it particularly useful for describing progressive lactate elevation under prolonged linezolid exposure.

From a purely curve-fitting standpoint, the Emax model yields the closest alignment with the observed data, though at the expense of increased structural complexity and heightened sensitivity to parameter estimation.

Conclusion

These findings are consistent with previous pharmacodynamic modeling literature [10,11,12], and the selected Emax and log-linear models align well with observed clinical data from case reports [8,9]. This supports the applicability of PK/PD modeling in predicting linezolid-associated metabolic toxicity [13].

Incorporating these models into clinical tools can help tailor linezolid therapy, especially in patients with compromised renal function or prolonged treatments,

as supported by prior PK/PD research. Future studies should evaluate these models prospectively across diverse populations to validate their predictive value in real-world settings.

5. References

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