A deep-learning-based two-compartment predictive model (PKRNN-2CM) for vancomycin therapeutic drug monitoring

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I. Introduction

Vancomycin (VAN) is a widely used antibiotic that requires therapeutic drug monitoring (TDM) for optimized individual dosage. The pharmacokinetic (PK) parameters for VAN TDM can be estimated using deep learning (DL) techniques that have the advantage of handling irregularly sampled time series electronic health record (EHR) data [1]. When developing population PK models, it is necessary to determine how many compartments will be included in the model to describe the PK of drugs. One-, two-, and three-compartment models have been applied to describe VAN PK, with a two-compartment model most commonly considered to describe VAN PK in adults [2]. However, previous DL attempt PKRNN [1], a recurrent neural network (RNN) model to predict VAN concentration, was only focused on a one-compartment (1CM) model. Here, we aimed to develop a two-compartment (2CM) VAN TDM model (PKRNN-2CM) and compare its performance with PKRNN.

II. Methods

Similar to the PKRNN model [1], the PKRNN-2CM model is an autoregressive RNN model with a PK prediction head. The input data first go through an EHR code embedding layer. Then an RNN layer is used to predict PK parameters per time step. Finally, the PK layer calculates VAN concentrations with a 2CM PK model. This study utilized the same dataset as the PKRNN paper [1], which included 5,483 patients with 9,504 encounters who received VAN from Memorial Hermann Hospital System (MHHS). Due to this dataset's sparseness and irregular sampling, simulation is necessary to enhance data regularity and guide the PKRNN-2CM model development and deployment. Thus, it is essential to use the simulation for model evaluation under different sampling strategies. Simulated datasets are designed to follow as much actual patient clinical information as possible to resemble real-world data. A PKRNN-2CM model was first trained on MMHS data to serve as the underlying model for simulation, with sampling points aligned to the infusion cycle. The simulated measurements were taken either 2-3 hours (peak dataset) or 10 hours (trough dataset) after each dosing. We then run the inference models PKRNN and PKRNN-2CM with either the measurements at peaks or at the troughs. Evaluation of the simulation output was based on hours and followed the same peak and trough definitions for the sampling strategy. To evaluate how our inference models can capture the entire VAN concentration curve, we evaluated the RMSE at both peak and trough time points. The dataset was split 70:15:15 for training, validation, and test sets.

III. Results and discussion

For real data, PKRNN-2CM exhibited a better RMSE of 5.62 compared to PKRNN with an RMSE of 5.84 (p-value= 0.01, unpaired two sample t-test). The simulation results (Table 1) indicate that the PKRNN-2CM model outperforms the PKRNN model, even at time points where the curve was not sampled. The results that the best RMSE was obtained by sampling peak inputs suggest that in a noise-free scenario, accurate peak measurements may enhance model performance. Overall, the results highlight the potential of the PKRNN-2CM model to improve personalized VAN TDM.

TABLE I. Results: PKRNN-2CM outperforms PKRNN.

Model		**Avg. test RMSE (Standard Deviation)**	
PKRNN		5.84 (0.10)	
PKRNN-2CM		5.62 (0.02)	
Sampling time points		**Avg. RMSE (Standard Deviation) from the inference model**	
Input	***Output***	***PKRNN***	***PKRNN-2CM***
Peak	Peak	6.09 (0.11)	1.71 (0.09)
	Trough	3.29 (0.2)	**1.25 (0.16)**
Trough	Peak	10.48 (0.52)	4.34 (0.30)
	Trough	7.90 (0.53)	3.49 (0.24)

References

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