Conceptual framework for the design of individualized anti-infective impregnated bone cement : a voriconazole example

Andras Farkas, Pharm.D[1,2]; Douglas Unis, MD[3]; Angela Koo, Pharm.D[2]; George Mckinley, MD[2]; Christine Stavropoulos, MD[2]

Optimum Dosing Strategies, Bloomingdale, NJ[1] ; Mount Sinai West Hospital, NY, NY[2]

ABSTRACT

Background: Intravenous voriconazole is a powder antifungal that is suitable for addition to bone cement for the localized treatment of fungal orthopedic infection. The aim of our experiment was to establish a framework for the rational design of individualized bone cement that takes into consideration the mechanical and pharmacokinetic properties of antimicrobial-loaded bone cement (ALBC) using the example of voriconazole.

Methods: Published voriconazole impregnated polymethylmethacrylate (PMMA) cement compressive strength data and a voriconazole pharmacokinetic model were used in this experiment. Linear regression analysis was used to establish the relationship between the concentration of voriconazole in the cement and the resultant compression strength of the ALBC from data in published literature. These results were then used to calculate the compression strength with voriconazole doses of 100, 200 and 300 mg per 40 g of PMMA. The goal was to maintain average strength that is within at least 90% of the 70 MPa ISO 5833 requirement. Voriconazole systemic absorption and pharmacokinetic properties were then estimated with Monte Carlo simulation for these three dosing regimens to establish the probability of maintaining systemic concentrations below the toxic level of 5 mg/L at 1, 2 and 5 days post-implantation.

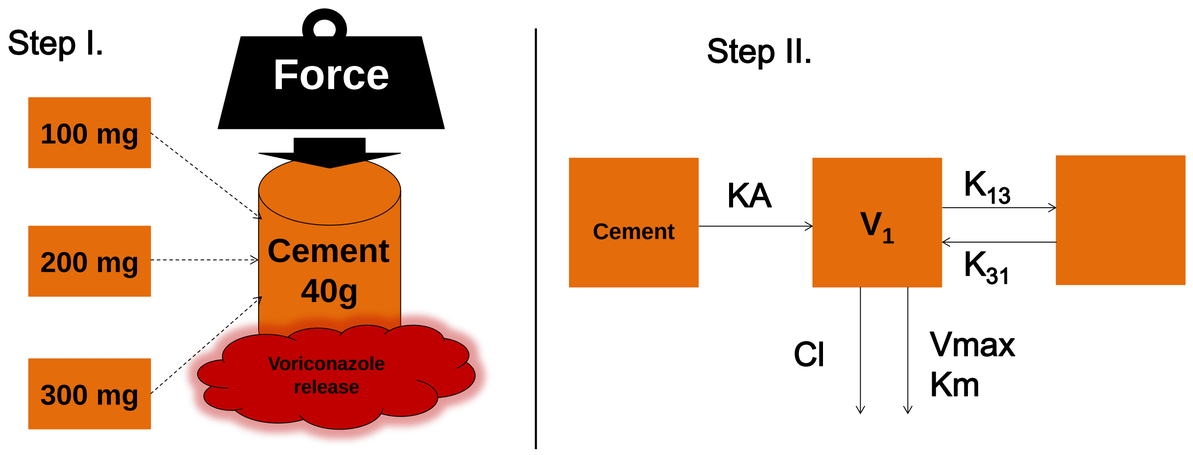
Results: Mean compression strengths and 95% prediction intervals of 74.05 (55.2,92.8) MPa, 64.03 (45.66, 82.42) MPa, and 54.01 (35.88, 72.16) MPa were estimated for the 100, 200, and 300 mg voriconazole regimens per 40 g of PMMA, placing the 100 and 200 mg approaches within 10 % of the ISO 5833 requirement. No simulated patients using the three regimens were expected to have systemic concentrations above 5 mg/L, with models showing a mean (IQR) blood concentrations at day 5 of 0.033 (0.013, 0.042) mg/L, 0.068 (0.027, 0.088) mg/L and 0.105 (0.042, 0.136) mg/L for the 100 mg, 200 mg and 300 mg, respectively.

Conclusion: Our experimental design suggests that 200 mg of voriconazole may be added to each 40 g of the PMMA cement without significantly affecting the compression strength, while providing safe systemic exposure. The compressive strength of ALBC with 300 mg voriconazole is less than desirable and suboptimal based on ISO 5833 standards. The risk of concentration-dependent systemic toxicity appears to be minimal using any of the three dosing regimens.

INTRODUCTION AND METHODS

- Local delivery of antifungals is valuable in treating orthopedic infections to maximize local efficacy and minimize systemic toxicity.
- Objective of this study was to utilize previously published data of voriconazole used in local orthopedic bone cement to establish a voriconazole dose to PMMA weight ratio that provides safe systemic exposure and minimally affects compression strength.
- The R® software application with the deSolve and Rjags packages were used to build the structural model for the analysis of pharmacokinetic and mechanical properties of ALBC.[1]
- Step I. Previously published voriconazole impregnated polymethylmethacrylate (PMMA) cement compressive strength and drug elution data were used in this experiment. Linear regression analysis was used to establish the relationship between the concentration of voriconazole in the cement and the resultant compression strength of the ALBC, while Bayesian modelling was used to establish the rate constant for drug release from the cement. [2]
- Step II. Voriconazole serum concentration time profiles were simulated and anticipated compression strength was calculated for 100 mg, 200 mg, and 300 mg of drug regimens per 40 g of cement. [3]
- Then, the three mixtures of drug and cement combinations were evaluated against the ISO 5833 requirement for compression strength and for the probabilities of contributing to systemic voriconazole toxicity. [4]

METHODS



Ka represents the release and absorption of voriconazole from the cement, *Cl* is the clearance, *V1* is the volume of the central compartment , V_{max} is the maximum rate of clearance by the Michaelis-Menten clearance mechanism (in milligrams per hour), K_m is the concentration of VOR where the clearance by the Michaelis-Mentenn mechanism is half maximal (in milligrams per liter), *K13/31* are the inter-compartmental transfer rate constants

Figure 1. Structural mathematical model applied in this analysis

RESULTS

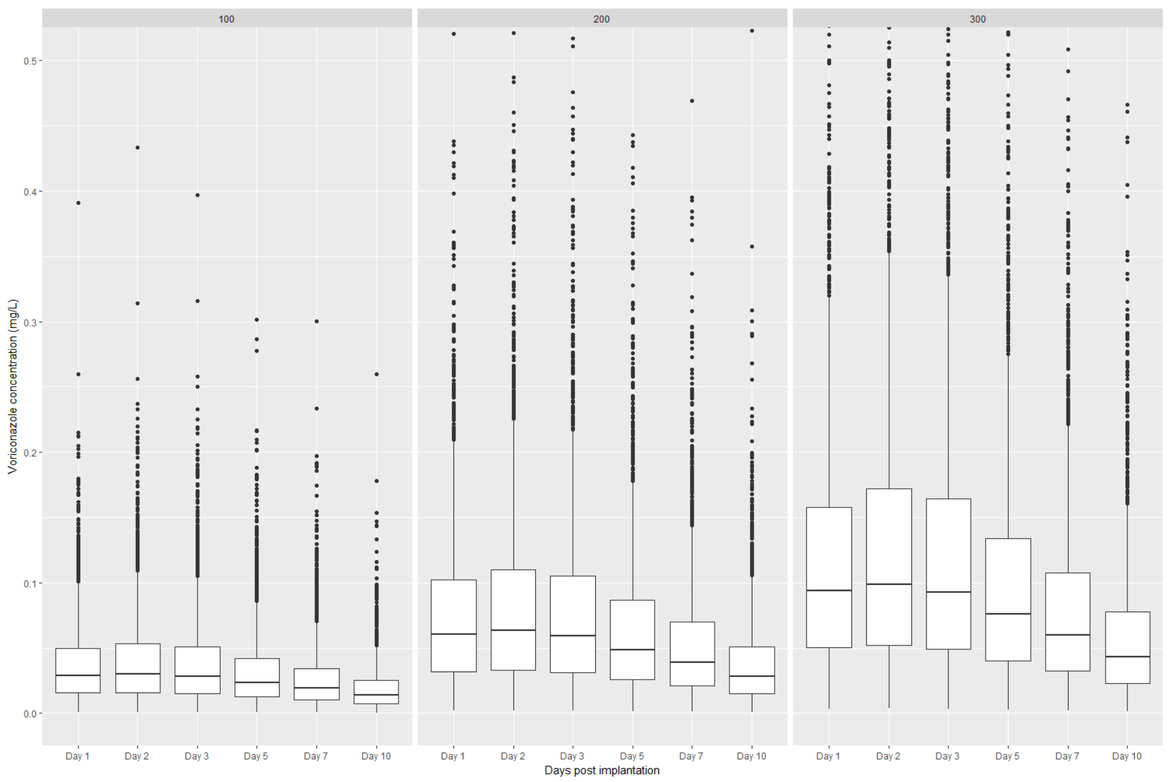


Figure 2 . Boxplots of simulated voriconazole plasma concentrations

RESULTS

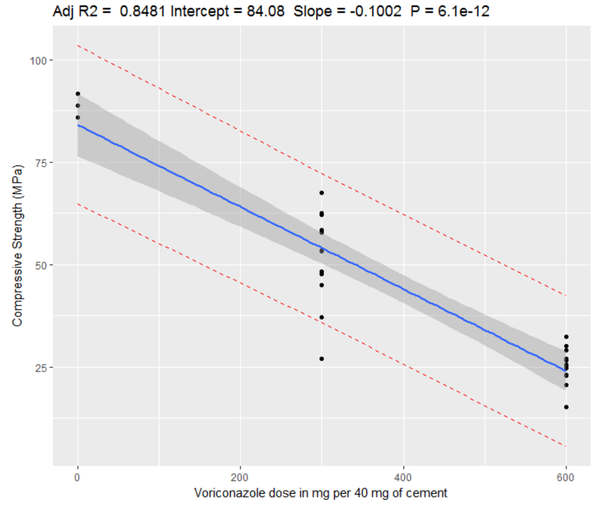


Figure 3. Confidence and prediction intervals of the regression model between dose and strength

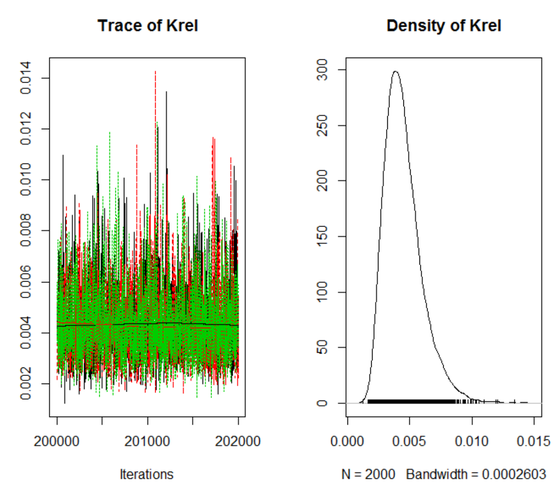


Figure 4. Posterior sample chain and density plot for the rate of voriconazole release from cement

CONCLUSION

Based on our experimental design, 200 mg of voriconazole may be added to each 40 g of the PMMA cement without significantly affecting the compression strength while providing safe serum concentrations. The compressive strength of ALBC with 300 mg voriconazole does not meet ISO 5833 ± 10% standards.

REFERENCES

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Mount Sinai West

Contact: Andras Farkas, Pharm.D, andras.farkas@mountsinai.org