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

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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.

Material/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.

Conclusions: 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/optimal based on ISO 5833 standards. The risk of concentration-dependent systemic toxicity appears to be minimal using any of the three dosing regimens.