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MATHEMATICAL MODELING OF THE EFFECT OF WARFARIN ON BLOOD CLOTTING IN PATIENTS WITH PROSTHETIC HEART VALVES

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Warfarin is an important anticoagulant in use to prevent thromboembolic complications in patients with prosthetic heart valves. The effectiveness of warfarin therapy is monitored using the International Normalized Ratio (INR), with a target range of 2.0–3.5, to minimize the risks of thrombosis and bleeding. However, maintaining INR within this therapeutic range is challenging due to warfarin's narrow therapeutic window, significant inter-individual variability, and complex pharmacokinetics (PK) and pharmacodynamics (PD), which depend on individual patient characteristics. This study develops a mechanistic PK/PD model to describe warfarin dynamics including absorption, distribution, metabolism, elimination, and its effects on clotting factors and INR dynamics, particularly, in patients with prosthetic heart valves. The PK component models the drug's disposition in the body, while the PD component accounts for its inhibition of vitamin K-dependent clotting factors. The formulated model is solved using Python programming and some model parameters were estimated using clinical data, while the other parameters were obtained from existing literature. The model was validated using data from an additional 12 consecutive days. Further, a sensitivity analysis was performed to identify key parameters influencing INR stability and therapeutic outcomes. Furthermore, the model demonstrates how different warfarin dosing scenarios affect INR stabilization. Regular dosing achieves therapeutic INR (2-3.5) in approximately 4.31 days. Missed doses delay stabilization to 5.04 days, increasing thrombosis risk, while extra doses stabilize INR faster in about 2.45 days with quick spikes. However, extra doses increase the risk of excessive anticoagulation and bleeding. This model serves as a valuable tool for predicting individual responses to therapy and for optimizing personalized dosing strategies, ultimately improving patient care and enhancing the safety and efficacy of anticoagulation therapy.

Key Words: Anticoagulant, Prosthetic heart valves, Thromboembolic complications