Evaluation of Warfarin Therapy Management Protocols via PK/PD and Pharmacogenetic Simulation

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Introduction:
Warfarin:
- Effective and commonly prescribed anticoagulant. Estimated two million new prescriptions per year.
- Highly variable dosing requirements influenced by CYP2C9 and VKORC1 genes.
- FDA recently added pharmacogenetic (PGx) information to label.

Warfarin Dosing:
- Many published and non-published algorithms (“nomograms”) for initiation and maintenance dosing.
- Algorithms provide guidance, but leave much room for clinician judgment.
- Many clinicians follow such algorithms in general, but further individualize dose adjustments and INR monitoring schedule based on patient history and clinician judgment.

Approach:
- Computer simulation of this personalized medicine approach can be a powerful tool to explore dosing and treatment scenarios.
- We simulated the disposition (concentration time course) and clinical effect (INR time course) of oral warfarin administration by implementing a recently published population PK/PD model [4].
- We developed a flexible protocol simulation routine in R [5], which called upon the NDNME software [6] to perform the PK/PD simulation and used it to implement various adaptive dosing strategies, from warfarin initiation through a 60-day time horizon.

Objectives:
- Develop a PK/PD/PGx model-based simulation approach for prediction of variable clinical outcomes.
- Utilize this approach to compare simulated population study results of various dosing strategies.
- Investigate sensitivity of dosing algorithms to prescribed leeway in specification.
- Suggest potential improvements in dosing algorithms.
- Categorize clinical variability and sensitivity in terms of pharmacogenetics.

Simulation Details:
Demographics:
- Sample from distributions based on those reported in [4].

Simulation Complexities Include:
- Individual dosage and appointment scheduling based on INR
- Initiation and multiple maintenance routines in each simulation
- Switch between maintenance routines based on INR history (e.g. INR in range over previous 14 days appointments)
- Initiation routines based on genetic and other variation

Protocol Descriptions:
- Many published and non-published algorithms for dosage of warfarin exist.
- Most require clinician judgment to choose dosage and follow-up appointment schedule from within specified ranges.
- Advantage/disadvantage of simulation: cannot exercise “judgment”
- Simulation can expose sensitivities of methods to underlying assumptions

Maintenance dosing algorithms: e.g. “Wilson” [3]

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PK/PD Model:
- Warfarin INR and concentration for 50 year old subjects receiving 4 mg/day warfarin. Results are displayed by CYP2C9 polymorphism (left graphs) and for specified CYP2C9 and VKORC1 (BB = “wild type”) polymorphisms (right graphs).
- The “x” on each curve is the point at which INR or Concentration reach 90% of the day 60 level. Note, this is independent of dose level.
- For CYP2C9 variants, the delay in reaching stable state suggests a dosing strategy improvement:
  - A loading dose may improve early INR levels
  - Dose increase should be delayed to prevent oversaturation

References: