



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

David H. Salinger¹, Paolo Vicini¹, Danny D. Shen², David L. Veenstra²
Departments of ¹Bioengineering and ²Pharmacy, University of Washington, Seattle, WA, USA



Introduction:

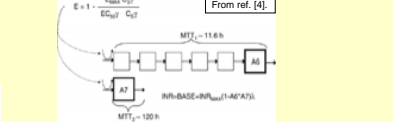
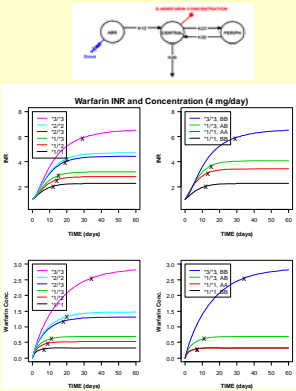
- Warfarin:**
- Effective and commonly prescribed anticoagulant. Estimated two million new prescriptions per year.
 - Highly variable dosing requirements influenced by **CYP2C9** and **VKORC1** genes.
 - FDA recently added pharmacogenetic (PGx) information to label.
- Warfarin Dosing:**
- Many published and non-published algorithms ("nograms") 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 data/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 [6], which called upon the NONMEM software [5] 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

PK/PD Model:

PD response (INR) described by transit compartment model [4].



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 over medicating

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]

INR	Suggested dose adjustment	From ref. [8]	Recheck INR
Warfarin dosing algorithm for maintenance of INR: 2.0-3.0			
6.3	Increase dose by 50%	5-7 days	
5.3	Increase dose by 35%	5-7 days	
4.8	Increase dose by 25%	5-7 days	
3.9	Increase dose by 10%	7-14 days	
2.8-3.8	No change	14-28 days	
2.9-3.1	Reduce dose by 10%	7-14 days	
2.2-2.5	Reduce dose by 25%	7-10 days	
1.6-2.7	Reduce dose by 35%	5-7 days	
2.0-3.0	Hold for 1 day, reduce dose by 35%	3-5 days	
4.0-4.4	Hold for 1 day, reduce dose by 35%	3-5 days	
4.5-5.0	Hold for 2 days, reduce dose by 35%	3-5 days	
5.1-6.0	Hold for 3 days, reduce dose by 35%	3-5 days	
6.1	To be determined by attending clinician	-	

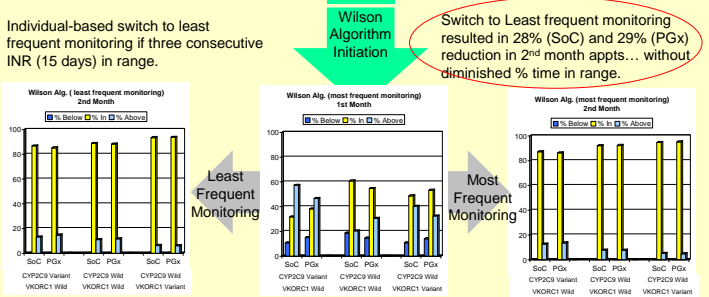
- Dosing initiation routines** (for first 4-7 days):
- "Standard of Care" (SoC): 5 mg/day (2.5 mg/day if >72 y.o.).
 - "Pharmacogenetic" (PGx [8] and PG2 [1]): Linear regression to choose dose based on CYP2C9 and VKORC1 variant and age and body weight.
 - "Loading dose" - either of above but with double dose on days 1-2.

References:

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 [2] Kovacs MJ, Rodger M, Anderson DR, et al (2003). Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. *Ann. Intern. Med.* 138 (9): 714-9.
 [3] Wilson SE, Costantini K, Crowther MA. (2007) Paper-based dosing algorithms for maintenance of warfarin anticoagulation. *Journal of Thrombosis and Thrombolysis* 23:3, 195-198.
 [4] Hamburg A-K, Dahl ML, Barbon M, Scordo M G, Wadelius M, Pengo V, Padrini R and Jonsson EN (2007) A PK-PD Model for Predicting the Impact of Age, CYP2C9, and VKORC1 Genotype on Individualization of Warfarin Therapy *Clinical Pharmacology & Therapeutics* (2007) 81, 529-538.
 [5] NONMEM Users Guides, (1989-98). Beal, S.L. and Sheiner L.B. (Eds.), Icon Development Solutions, Ellicott City, Maryland, USA.
 [6] R Development Core Team (2006). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. URL http://www.R-project.org/
 [7] Mckelvey LA, Gudgion JM, Anderson JL, Williams MS, Veenstra DL. (2008) Should genetic testing be used to guide warfarin therapy? 10th Anniversary of Public Health Genomics at CDC, Atlanta, GA, USA
 [8] Mckelvey LA and Veenstra DL (2007, unpublished)

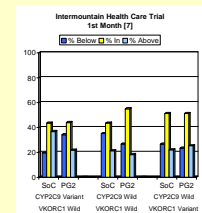
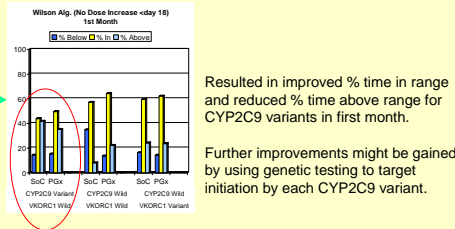
Preliminary Results and Discussion:

All plots: - Percent of time below, in and above therapeutic range (INR 2-3)
 - Grouped by genotype for Standard of Care (SoC) or Pharmacogenetic (PGx) initiation



Modified Wilson Algorithm:
 • Loading dose (2x dose on days 1-2)
 • No dose increase until day 18

Loading Dose Initiation



Compare: IHC Trial Vs. Simulation

- Used same SoC and PG2 initiation
- Day 5-7 dose based on Kovacs 10mg [2]
- Day 8+ dose based on IHC protocol [1]
- Trial: followed algorithm "in general"

