Warfarin Dosing Using Genetic Information
A Model for Hospital Policy Development

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Warfarin Pharmacogenomics

• **Part I** Background Information & Rationale

• **Part II** The Cedars-Sinai Experience
  Pathology and Pharmacy Task Force
First Principle of Medicine

• Primum non nocere
  “First, do not harm”

Hippocrates 460-377 BC
Pharmacogenetics

• Poison is in everything and nothing is without poison

• The dosage makes it either a poison or a remedy

Paracelcus (1493-1542)
Swiss Physician
Warfarin

• First developed as a rat poison by Wisconsin Alumni Research Foundation (WARF)

• Korean war inductee attempted failed suicide discovered anticoagulant properties

• President Eisenhower heart attack 1955

• Widely prescribed anticoagulant  
  – Americans spend $371 M on warfarin tablets per year
Genetics & Warfarin Dosing

- Single base pair changes in DNA sequence lead to reduced activities in two genes

- Two genes play a key role in the response to warfarin

- Variants significantly impact the rate of warfarin metabolism and amount of drug target available

- Pharmacokinetics – CYP2C9

- Pharmacodynamics – VKORC1
Warfarin Mode of Action & Metabolism

- **Pharmacodynamics**
  Mode of action of warfarin on VKORC1

- **Pharmacokinetics**
  Catabolism of warfarin by CYP2C9
Clinical Challenge
Warfarin Safety

• Widely prescribed *dangerous* drug
  – *2 million* on warfarin, *30 million* Rx a year
  – *87,000* major bleeding a year
  – *43,000* ER visits a year, 2nd to Insulin for ER adverse drug reaction (ADR)
  – *17,000* strokes a year
  – *10,000* deaths a year

• *2006 FDA Black Box Warning Bleeding Risk*

• *2007 FDA updates warfarin label with genotypic information*

• Heathcare cost ADR
  – Average cost of *bleeding episode*: $16,000 or 6 hosp days
  – Average cost of *clotting episode* $40,000
  – Including *genetic information* would save $1.5 billion/yr

FDA & AEI-Brookings Joint Center
Clinical Challenge Warfarin Dosing Inter-individual Variation

- Dosed by trial & error over past 50 years
- Narrow therapeutic index & non-linear response
- Marked inter-individual variation to achieve therapeutic INR
- Patients within target INR only 32% to 56% of time
- Dose influenced by age, ethnicity, drugs, environmental and genetic factors

Am J Cardiol 2005, 96(4):595-8
Sconce, Blood 2005, 106 (7): 2329
VKORC1 & CYP2C9
Inter-individual Genetic Variation

30% Wild-type
Standard dose

70% Genetic Variants
VKORC1 or 2C9
Lower Dose
# Warfarin Dose & CYP2C9

<table>
<thead>
<tr>
<th>Allele CYP2C9</th>
<th>Frequency</th>
<th>Metabolizer</th>
<th>Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>1</em>1 (wild-type)</td>
<td>56%</td>
<td>Extensive 100%</td>
<td>5 mg</td>
</tr>
<tr>
<td><em>1</em>2 (variant)</td>
<td>22%</td>
<td>Intermediate 50-70%</td>
<td>2.50-2.70 mg</td>
</tr>
<tr>
<td><em>1</em>3 (variant)</td>
<td>14%</td>
<td>Poor 10-15%</td>
<td>1.50-1.70 mg</td>
</tr>
<tr>
<td><em>2</em>2 (variant)</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>2</em>3 (variant)</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>3</em>3 (variant)</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_Herman et al, Pharmacogenomics J 2005; 4:1-10_
_Lesko LJ. CPSC Advisory Committee Meeting, November 14, 2005_
## Warfarin Dosage & VKORC1

<table>
<thead>
<tr>
<th>Allele VKORC1</th>
<th>Frequency</th>
<th>Metabolizer</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG (wild-type)</td>
<td>25 %</td>
<td>Extensive 100%</td>
<td>6.7 mg</td>
</tr>
<tr>
<td>GA (variant)</td>
<td>56 %</td>
<td>Intermediate 50-70%</td>
<td>4.2 mg</td>
</tr>
<tr>
<td>AA (variant)</td>
<td>19 %</td>
<td>Poor 10-15%</td>
<td>2.7 mg</td>
</tr>
</tbody>
</table>

Wadelius M et al Pharmacogenomics 2005
GG is wild-type for VKORC1
*1*1 is wild-type for CYP2C9
Genotyope & Time to Stable Dose
# CYP2C9 Ethnic Variation

<table>
<thead>
<tr>
<th>Allele</th>
<th>Metabolic Efficiency</th>
<th>Frequency Caucasian</th>
<th>Frequency Asian</th>
<th>Frequency African American</th>
<th>Frequency Hispanic American</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9*2</td>
<td>70%</td>
<td>12%</td>
<td>0%</td>
<td>3.2%</td>
<td>12%</td>
</tr>
<tr>
<td>CYP2C9*3</td>
<td>10%</td>
<td>8%</td>
<td>3.3%</td>
<td>1.3%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>
In Milestone, FDA Pushes Genetic Tests Tied to Drug
August 16, 2007

Warfarin Label Update Includes Genetic Information
Regulatory Guidance

The Legal Base of Prescribing is the Medical Product Label

• FDA Critical Path Initiative

• If evidence is available to support the safety and effectiveness of the drug only in selected subgroups, the label shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug

• Help select optimal dose and avoid harm to patients

» 21 CFR 201.57
Warfarin Label Update 2007
Pharmacology Pharmacogenomics

- **Meta-analysis of 9 studies involving 2775 patients** (99% caucasian)
  - Increased bleeding risk 2C9*2 or *3 alleles
  - Decreased dose requirements
    - *2, 17% reduction* dose compared to wild type *1/*1
    - *3, 37% reduction* dose compared to wild type *1*1

- **219 Swedish patients** grouped retrospectively
  - Number patients INR>3 first 2 weeks doubled if *2 or *3 allele

- **201 Caucasians** treated with stable warfarin doses
  - 30% variability dosing VKORC1 alone
  - 40% variability dosing VKORC1 and 2C9
  - 55% variability dosing genes, age, height, wt, drug interactions, indications

- **Precautions**
  - Numerous factors alone or in combination may influence the response of the patient
    - Diet, medications, botanicals
    - 2C9 and VKORC1 variants
Wafarin Dosing Factors

- VKORC1: 23%
- CYP2C9: 17%
- Weight: 9%
- Age: 7%
- Other: 44%
Other Factors in Warfarin Dosing
The Cedars-Sinai Warfarin Story
Once upon a time…
How we decided on Warfarin PGx a year ago

- Growing molecular laboratory
- What test to chose from
- Coagulation consultation
- Many physicians frustrated with last 50 years trial and error dosage warfarin
- Age of personalized medicine
Case

• 65 year old grandmother with DVT
• Put initially on 5 mg warfarin
• Discharged 3 days later with INR 2
• Admitted ER 10 days later with INR of 5 and GI bleed
• Genetic VKORC1 homozygous
• Resulted in therapeutic dose 2mg warfarin
Phase 1
Pharmacy Listens

- Presented warfarin genetic literature to Pharmacy
- Decided to compare warfarin initial and final dose
- Examined 19 random sample patients treated by conventional Pharmacy Protocol
- Compared initial dose to final therapeutic dose
- Retrospectively compare the dose distribution to known frequency of genetic variants
Cedars-Sinai Medical Center
Pharmacy Conventional Protocol

- Mostly based on age and weight
- Empirically adjust dose daily by trial and error based on INR
Pharmacy & Therapeutic Committee
Warfarin Dose CSMC Patients Study

- Zero (0) line is final stable dose
- Most patients (70%) are initially above therapeutic dose (red bars)
- Most patients are initially on target dose (green bars) using Gage PGx
Phase 2
Pharmacy approves test of change

• Run 100 samples
• Pharmacy protocol unchanged
• Parallel genotyping of samples
• Compare initial dose to final dose using
  – Actual Conventional protocol dosing
  – Predicted Pharmacogenomics dosing
## Cedars-Sinai Medical Center
### Pathology & Pharmacy Test of Change Protocol

<table>
<thead>
<tr>
<th>Factors in Conventional Protocol</th>
<th>Factors in Gage Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Weight</td>
<td>Age, Sex, Ethnicity, Weight</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Drug Interactions</td>
</tr>
<tr>
<td>Baseline &amp; Target INR</td>
<td>Baseline &amp; Target INR</td>
</tr>
<tr>
<td></td>
<td>Indication (DVT, PE, AF…)</td>
</tr>
<tr>
<td></td>
<td>Liver Function</td>
</tr>
<tr>
<td></td>
<td>Smoking status</td>
</tr>
<tr>
<td></td>
<td><strong>Genotype</strong></td>
</tr>
<tr>
<td><strong>Provides dose based on daily INR</strong></td>
<td><strong>Provides initial and maintenance dose</strong></td>
</tr>
</tbody>
</table>

- Run in parallel genotype of all patients put on warfarin for the first time
- Retrospectively analyze INR variation based on genotype
- Retrospectively compare final therapeutic dose to initial dose Convl vs. Gage
INR as Surrogate End-Point of Clinical Outcome

<table>
<thead>
<tr>
<th>INR range</th>
<th>Risk of Stroke</th>
<th>Risk Intracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>1.75-4.94</td>
<td>----</td>
</tr>
<tr>
<td>2 to 3</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>---</td>
<td>2.4</td>
</tr>
<tr>
<td>4 to 6</td>
<td>---</td>
<td>16</td>
</tr>
<tr>
<td>&gt;6</td>
<td>---</td>
<td>27</td>
</tr>
</tbody>
</table>

Analysis of data from the Anticoagulation and Risk Factors in Atrial Fibrillation Study by Dr. Elaine Hylek; comparison of INRs from 169 patients with stroke and 55 patients with hemorrhage. http://www.neurologyreviews
Genotype & INR

‘Normal’ Wild type

Conventional Warfarin Dosing

Note smooth trend in INR with increasing dose.
Note increasing unpredictability in INR trend and erratic dosing as a result.
Note erratic INR trend and erratic dosing as a result.
**Initial Dose vs Final Dose:** Gage Dosing vs Conventional Dosing

\[ N = 25 \text{ cases} \]

### Comparison of Initial and Final Dose

- **Conventional Dosing:**
  - > 2 mg Outside of Final Dose: 28%
  - % Within 2 mg of Final Dose: 72%
  - % > Final Dose: 52%

- **Gage Predicted Dosing:**
  - > 2 mg Outside of Final Dose: 76%
  - % Within 2 mg of Final Dose: 24%
  - % > Final Dose: 16%

### % of Doses >, < or Within 2mg of Final Dose

- **Conventional Dosing:**
  - > Final Dose: 20%
  - % Within 2mg of Final Dose: 52%
  - < Final Dose: 28%

- **Gage Predicted Dosing:**
  - > Final Dose: 8%
  - % Within 2mg of Final Dose: 76%
  - < Final Dose: 20%

Legend:
- Yellow: > 2 mg Outside of Final Dose
- Purple: % Within 2 mg of Final Dose
- Cyan: % Within 2mg of Final Dose
- Orange: % < Final Dose
- Grey: % > Final Dose
Validation of Genetic Model

• Patient distribution 72% off the final stable dose by ≥ 2 mg indicative of high frequency of genetic variants

• 52% patients initially > 2mg off final dose (Gage 8%)

• 20% patients initially <2mg final dose (Gage 16%)

• 28% patients initially within 2 mg final dose (Gage 76%)

References


• Gage et al, Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose, NEJM June 2005, vol 352, N22, p 2285

• Gage et al, Pharmacogenetics-Based Coumarin Therapy, ASH 2006
Proficiency Improvement Committee

- Cardiology PIC
- Medicine PIC
- Resistance to adoption until perform a prospective study using genotyping upfront for dosage
Phase 3 IRB study
Prospective PGx Dosing

• 100 patients dosed prospectively by Gage PGx
• DVT/PE 5th floor CSMC
• Close monitoring of INR
• Use INR as surrogate endpoint to bleeding
  – Time to reach therapeutic INR (2 to 3)
  – Time stays within therapeutic INR (2 to 3)
• If INR > Predicted Goal at any time
  – Change to pharmacy protocol for dose adjustment
Phase 3 Expected Outcome

• Initial dose should be closer to final therapeutic dose based on INR
• Time to final stable dose should be shorter.
Cedars-Sinai Warfarin Test Offered

• How do I order this test @ CSMC?
  – Write Order @ Nurse Station: Warfarin PGX

• What is the turn around time?
  – 24 hours @ CSMC Molecular Pathology Laboratory

• How often is this test run?
  – Currently 3x/week excluding weekends
  – Will be increased based on demand
RESULT

Single Nucleotide Polymorphism(s) is/are detected for

- CYP2C9*2  --- Wild (CC)  --- Heterozygous (CT)  --- Homozygous (TT)
- CYP2C9*3  --- Wild (AA)  --- Heterozygous (AC)  --- Homozygous (CC)
- VKORC1    --- Wild (GG)  --- Heterozygous (AG)  --- Homozygous (AA)

Clinical Utility

Increased Warfarin sensitivity leading to increased INRs is observed in approximately 70% of Caucasians and less commonly in other groups. It accounts for major bleeding or stroke in about 10% of patients. Polymorphisms in CYP2C9*2, CYP2C9*3 and VKORC1 account for the majority of warfarin sensitivity variation (about 55%).

A suggested estimated Warfarin starting dose using a Gage* or modified partial Gage algorithm is ___. It is based on a multivariate regression model including indication, height, weight, age, medications, and genetic polymorphism.

This algorithm may be used as an adjunct with other relevant clinicopathological data in suggesting an initial Warfarin dosage but is not a substitute for periodic INR monitoring and may need individual modification.

Method ___

References  *Brian F Gage, ASH 2006, p 467, and WarfarinDosing.org
Estimate of Warfarin Dose

Estimated therapeutic dose: 5.1 mg/day.
Today's prescribed dose: __________ mg.
Patient Code (e.g. BG or 007)*: __________

Recommendations

To get a better estimate of the therapeutic dose, first save this record by entering a patient code and your email address. Then, return to this site after 1, 2, and/or 3 warfarin doses and enter that day's INR.

Additional Information

Email the results to: __________
Address email to: Dr. __________ First Name: __________ Last Name: __________
Email copy to: __________
Text to accompany email: __________
When would you like an email to remind you to check the INR: In __________ hours.

* All information entered into this site is kept confidential. Your e-mail address will not be shared, sold, or rented. It is required to save and to access this record.
Estimate of Warfarin Dose

Estimated loading dose: 2.7 mg for initial warfarin dose.
Estimated therapeutic dose: 1.2 mg/day.

Today's prescribed dose: __________ mg.
Patient Code (e.g. BG or 007)*: __________

Recommendations

To get a better estimate of the therapeutic dose, first save this record by entering a patient code and your email address. Then, return to this site after 1, 2, and/or 3 warfarin doses and enter that day's INR.

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Email the results to: __________
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* All information entered into this site is kept confidential. Your email address will not be shared, sold, or rented. It is required to save and to access this record.
Personalized Medicine
Each patient on warfarin receives the right dose upfront
Thank you for the opportunity to present and for your attention

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