Vitamin K Supplementation with Oral Anticoagulation

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Vitamin K

- Vitamin K belongs to a group of fat-soluble 2-methyl-1,4-naphthoquinone derivatives.

- Carried through the body by lipids and stored in fat tissue.

- Vitamin K is essential for the functioning of several proteins involved in blood clotting, bone mineralization, vascular health and cell growth.

- As with other lipid-soluble vitamins, a normal flow of bile and pancreatic enzymes is necessary with the presence of dietary fat to enhance absorption.
Primary forms of vitamin K

Vitamin K\textsubscript{1} (phylloquinone)

- The most important dietary source for humans.
  Synthesized by plants, and found in greater quantities in leafy greens and other green vegetables.

Broccoli, and other leafy greens, are a key source of vitamin K.
Vitamin \( K_2 \) (menaquinones; MK-3 – MK-14)

- Differentiated by side chains lengths of a variable number of unsaturated isoprenoid units; designated as MK-n, where n specifies the number of isoprenoids (side chain) attached to the napthoquinone ring.

- Two primary menaquinones commercially available for human nutrition: \( MK-4 \) and \( MK-7 \).
Functions of vitamin K in blood clotting

- Vitamin K is a necessary cofactor for normal clotting of blood in humans. Specifically, vitamin K is required for activation of the coagulation proteins II, VII, IX and X.

- Other anticoagulation clotting factors that depend on vitamin K are proteins C, S and Z.

- Deficiency of vitamin K or disturbances of liver function (for example, severe liver failure) may lead to deficiencies of these clotting factors, causing excess bleeding.
Warfarin is a coumarin derivative.

Vitamin K (natural vitamin)

Warfarin (vitamin K antagonist)
Mechanism of action of warfarin

Warfarin inhibit Vitamin K reductase, which leads to accumulation of Vitamin K epoxide.

Vitamin K epoxide is converted to Vitamin KH₂ by Vit K reductase, which is then activated by Carboxylase to Vitamin K (quinone).

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Response to warfarin is variable

- >10-fold difference in dosage requirement
  
  \[\text{Genetics : CYP2C9 & VKORC1}\]
  \[\text{Age}\]
  \[\text{Body size}\]
  \[\text{Concurrent medication}\]
  \[\text{Co-morbidity}\]

- ~50% fail to stabilize within target INR range
  - Constant review of anticoagulation
    
    \[\text{Inconvenience to patient}\]
    \[\text{Expense to the NHS}\]
Safety of warfarin

- 10-24 episodes of haemorrhage per 100 patients. Account for 3.6% of all drug-induced AEs
- Among the top 10 drugs with greatest frequency of SAEs
- Responsible for 1 in 10 hospital admissions

Pirmohamed, British Med J 329:15-19, 2004
Dietary modification leading to under/over anticoagulation

- **Warfarin sensitivity**
  Severe coagulopathy with Vitamin K deficiency

  Life threatening bleeding after cessation of liver consumption

- **Warfarin resistance**
  Vitamin K supplementation

  Ingestion of green leafy vegetables or liver

- **Vitamin K and INR**
  In stable patients, for every 100µg increase of vitamin K intake over the previous 4 days, the INR fell by 0.2
Impact of vitamin K intake on stability of anticoagulation

- Dietary vitamin K evaluated in unstable patients
- Patients completed dietary diaries for 14 days
- Dietary vitamin K quantified using Microdiet® Programme
Patients with unstable control have a poorer dietary intake of vitamin K than stable patients

- Mean daily intake for unstable patients (29±17µg) was considerably lower than for stable patients (76±40µg)

Can vitamin K supplementation improve stability of anticoagulation control?

- Menus of constant dietary intake of vitamin K have been advocated
  - *Difficult for patients and carers to implement*

- Daily supplementation with oral vitamin K may lessen impact of variable dietary intake
  - *Leading to a more stable and safer treatment*
Supplementation with vitamin K

Hypothesis:
‘Stabilising the body stores of vitamin K and reducing the relative variability in the daily dietary intake, could increase stability of anticoagulation control.’
Vitamin K supplementation - study 1

- Randomised double-blind trial

- 70 patients with unstable anticoagulant control received a daily amount of 150µg oral vitamin K or placebo for six months.

- Measures of stability of anticoagulation control in the 6 month study period were compared to those in the 6 months immediately prior to it.
Comparison of anticoagulation control between vitamin K and placebo treated patients

<table>
<thead>
<tr>
<th></th>
<th>Vitamin K group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-study</td>
<td>Intervention period</td>
</tr>
<tr>
<td>SD of INR</td>
<td>0.72±0.11</td>
<td>0.47±0.17</td>
</tr>
<tr>
<td>% Time in range</td>
<td>59±20</td>
<td>87±14</td>
</tr>
<tr>
<td>No of dose changes Mean</td>
<td>5 (3,7)</td>
<td>2 (0,5)</td>
</tr>
<tr>
<td></td>
<td>Mean (range)</td>
<td></td>
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</tbody>
</table>

† p<0.001
‡ p<0.01
Vitamin K supplementation (Cont’d)

- Anticoagulation control improved in 33/35 patients on vitamin K
  - 19 fulfilled the criteria for stable control

- Only 24/33 patients receiving placebo with some degree of improvement
  - 7 fulfilled the criteria for stable control

Improvement in stability of control with vitamin K supplementation (Study 2 ongoing)

- A double-blind RCT - investigating the impact of daily supplementation on stability of anticoagulation in unselected patients on warfarin therapy.

- 180 patients randomised to vitamin K (150 μg daily) or matching placebo for 6 months.

- Primary outcome:
  - Percent time within target INR in 6 months

- Secondary outcomes:
  - The number of warfarin dose changes
  - Incidence of INR <1.5 and >4.0.
  - Markers of lack of efficacy including recurrent thrombosis
  - Days attending anticoagulation clinic to monitor and achieve target INR.
  - Clinical events of major (defined as bleeding that led to loss of 2 units of blood over a 7 day period or was otherwise life-threatening) and minor (all other bleeds, including bruising) complications
  - Perceived health status, quality of life and cost-effectiveness

- Study results will be available in summer 2013!
Limitations of warfarin

- Onset/Offset: delayed
- Unpredictable response: require monitoring
- Narrow therapeutic index: require monitoring
- Factors influence response: require monitoring
- Side-effects: bleeding
- Reversibility: slow
- Frequent dose changes: require management
The opportunities for new and better anticoagulants

- No need for parenteral treatment (UFH, LMWH, Penta)
- No need for monitoring (long-term)
- Lessen the burden of initial management (in hospital or home therapy)
- Lessen the long-term management
- Potentially provide safer therapy
- Increase the use of AC in AF and lessen SAEs
- Direct thrombin and Factor Xa inhibitors marketed / under development.
Vitamin K (quinone) → Vitamin KH$_2$ → Carboxylase → VII → VIIa → X → Xa → II → IIa → Fxa inhibitors

Vitamin K reductase

Vitamin K (epoxide)
Does diet (vitamin K) affect anticoagulation response to novel oral anticoagulants?
The influence of vitamin K deficiency on the pharmacological activity of ximelagatran in vivo in rats
Study flow chart

Study duration

Rats with normal diet

- Control (Group A; n=15)
- Ximelagatran (Group B; n=15)
- Warfarin (Group C; n=15)

Rats with vitamin K deficient diet

- Control (Group D; n=15)
- Ximelagatran (Group E; n=15)
- Warfarin (Group F; n=15)

Blood sampling schedule

7 days                      7 days
Prothrombin Time (PT)

*P<0.01; **P<0.001

Normal diet

Vitamin K deficient
Activated Partial Thromboplastin Test (APTT)

**P<0.001**

Group A: Normal diet

Group B: Ximelagatran

Group C: Warfarin

Group D: Control

Group E: Ximelagatran

Group F: Warfarin

Vitamin K deficient
Ecarin Clotting Time (ECT)

**P<0.001

**P<0.001

Normal diet

Vitamin K deficient
Plasma vitamin K concentration

Controls
Ximelagatran
Warfarin

*P<0.005; †P<0.001
Limitations of new anticoagulants

- Lack of suitable test for anticoagulation monitoring
- No antidote available
- Patient compliance an issue regarding drug efficacy/toxicity
- Kidney function and drug toxicity
- Drug interactions still a problem
- Potential for interaction with diet
Conclusions

- Pharmacogenomic approach could improve safety of warfarin particularly during the initiation of therapy (EU-PACT; COAG)

- Vitamin K supplementation may improve stability of anticoagulation control during maintenance therapy

- Our findings counter the view of ‘no food interactions’ with novel oral anticoagulants. Currently investigating the impact of diet on anticoagulant activity of Dabigatran (Pradaxa®) and Rivaroxaban (Xarelto®) in humans.
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Peter Wood

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## Coagulation assays after 7 days treatment with drugs

<table>
<thead>
<tr>
<th></th>
<th>Control (no drugs)</th>
<th>Warfarin</th>
<th>Ximelagatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT normal diet</td>
<td>9.37±1.04</td>
<td>12.08**±1.30</td>
<td>12.76*±1.68</td>
</tr>
<tr>
<td>PT vitamin K</td>
<td>15.24±4.13</td>
<td>148.49**±65.29</td>
<td>77.36**±36.34</td>
</tr>
<tr>
<td>APTT normal diet</td>
<td>21.16±5.86</td>
<td>28.05**±6.16</td>
<td>32.99**±7.70</td>
</tr>
<tr>
<td>APTT vitamin K</td>
<td>30.73±7.26</td>
<td>145.40**±36.41</td>
<td>85.38**±17.53</td>
</tr>
<tr>
<td>ECT normal diet</td>
<td>25.61±0.94</td>
<td>31.15**±3.09</td>
<td>124.71**±33.67</td>
</tr>
<tr>
<td>ECT vitamin K</td>
<td>35.68±4.04</td>
<td>50.25**±3.80</td>
<td>364.66**±167.61</td>
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</tbody>
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All values marked with asterisks are significantly different from the controls.  
*P<0.01; **P<0.001.
### Vitamin K recommended Daily Allowance (RDA)

<table>
<thead>
<tr>
<th>Population</th>
<th>Age</th>
<th>µg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 mo</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>7-12 mo</td>
<td>2.5</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 y</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>4-8 y</td>
<td>55</td>
</tr>
<tr>
<td>Male adults</td>
<td>9-3 y</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>14-18 y</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>19 - &gt;70 y</td>
<td>120</td>
</tr>
<tr>
<td>Females</td>
<td>9-13 y</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>14-18 y</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>19- &gt;70 y</td>
<td>90</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>≤ 18 y</td>
<td>75</td>
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<tr>
<td></td>
<td>19-30 y</td>
<td>90</td>
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<tr>
<td>Lactation</td>
<td>≤ 18 y</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>31-50 y</td>
<td>90</td>
</tr>
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*Source: The National Academy of Sciences guidelines for daily Adequate Intake*