Clinical Considerations in the Use of MEPHYTON

PLEASE SEE ENCLOSED FULL PRESCRIBING INFORMATION, INCLUDING IMPORTANT SAFETY INFORMATION.
Clinical Considerations in the Use of MEPHYTON

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Clinical Considerations in the Use of MEPHYTON

Overview

- Coagulation Disorders
  - Can be caused by vitamin K deficiency or interference with vitamin K activity
  - OTCs and supplements are not approved to treat these coagulation disorders, and changes in diet are not enough
- MEPHYTON is the only oral prescription vitamin K approved for treatment of these coagulation disorders
- MEPHYTON is approved for doses of 2.5 mg to 25 mg or more, and rarely up to 50 mg

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MEPHYTON® (Phytonadione) 5 mg:
Indications

- Indicated in coagulation disorders which are due to faulty formation of factors II, VII, IX, and X when caused by vitamin K deficiency or interference with vitamin K activity

- Anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives

- Hypoprothrombinemia secondary to antibacterial therapy

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Mephyton

SLIDE 3.

MEPHYTON® (Phytonadione) 5 mg:
Indications (cont.)

- Hypoprothrombinemia secondary to administration of salicylates

- Hypoprothrombinemia secondary to obstructive jaundice or biliary fistulas, but only if bile salts administered concurrently, since otherwise oral vitamin K will not be absorbed

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established with MEPHYTON

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Mephyton

SLIDE 4.
MEPHYTON Dosage Guidelines — Adults

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant-induced prothrombin deficiency (caused by coumarin or</td>
<td>2.5 mg – 10 mg or up to 25 mg (rarely</td>
</tr>
<tr>
<td>indanedione derivatives)</td>
<td>50 mg)</td>
</tr>
<tr>
<td>Hypoprothrombinemia due to other causes (antibiotics, salicylates or</td>
<td>2.5 mg – 25 mg or more (rarely up to</td>
</tr>
<tr>
<td>other drugs; factors limiting absorption or synthesis)</td>
<td>50 mg)</td>
</tr>
</tbody>
</table>

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Anticoagulant-induced prothrombin deficiency (caused by coumarin or indanedione derivatives)

Hypoprothrombinemia due to other causes (antibiotics, salicylates or other drugs; factors limiting absorption or synthesis)

SLIDE 5.

Pathogenesis of Vitamin K Deficiency


SLIDE 6.
Vitamin K Mechanism of Action

- Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the posttranslational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X.

- The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

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Vitamin K Mechanism of Action (cont.)

- In animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function; that is, to promote the hepatic biosynthesis of vitamin K-dependent clotting factors.

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Vitamin K Deficiency: Inflammatory Bowel Disease

- Despite sufficient intake, many individuals with inflammatory bowel disease (IBD) have inadequate vitamin K levels
  - 92% of patients with Crohn's disease
  - 36% of patients with ulcerative colitis
  - 31% of patients with Crohn's disease, ulcerative colitis, celiac sprue, or post-traumatic short bowel syndrome
  - Patients with Crohn's disease have significantly lower serum vitamin K levels than patients with ulcerative colitis


Vitamin K Deficiency: Liver Disease

- Prevalence estimate: 50%-68%
- In a study of cholestatic liver disease, 15/21 (71%) patients with an elevated PIVKA-II level were receiving supplemental vitamin K (7.8-700 mcg/kg/day)
- Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory

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PIVKA-II = prothrombin induced in vitamin K absence

Vitamin K Deficiency: Cystic Fibrosis

- In clinical studies, vitamin K deficiency was observed in:
  - 71%-81% of all patients with cystic fibrosis (CF)\(^1\)
  - 100% of patients with CF and liver disease\(^1\)
- Deficiencies occur, despite exogenous pancreatic enzymes\(^2\)
- Role of antibiotics in the risk of developing deficiency is unclear\(^2,3\)


Vitamin K Deficiency: Other Conditions

- Common post-bone marrow transplant\(^1\)
  - Secondary to the effects of chemotherapy, including drug interactions, hepatic dysfunction, decreased fat absorption, and inadequate intake
- In adults in the ICU, approximately half developed coagulopathy
  - Of those not developing a coagulopathy, more than 25% had evidence of vitamin K deficiency\(^2\)

ICU = intensive care unit

MEPHYTON® (Phytonadione) 5 mg: Dosing

Hypoprothrombinemia Due to Other Causes in Adults

A dosage of 2.5 mg to 25 mg or more (rarely up to 50 mg) is recommended; the amount and route of administration depending upon the severity of the condition and response obtained.

Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

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Correction of Excess Warfarin Anticoagulation: Meta-Analysis

- 21 studies analyzed
- Oral and IV routes were similar in effectiveness at 24 hours

Percentage of patients with a baseline INR <10 who achieved the target INR (1.8-4.0) 24 hours after administration of phytonadione or placebo. Each box represents 1 study arm. The diamond shapes represent the 95% confidence interval for the route of administration.
**Vitamin K₁ Formulations**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Multivitamins</th>
<th>Fat-soluble vitamin combination</th>
<th>OTC phytonadione supplements</th>
<th>Phytonadione injectable emulsion¹</th>
<th>MEPHYTON (phytonadione) tablets²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>IV, IM, SC</td>
<td>Oral</td>
</tr>
<tr>
<td>Amount of vitamin K₁</td>
<td>Varies (eg. 25 mcg)³,⁴</td>
<td>Varies (eg. 100 mcg)⁵</td>
<td>Varies (eg. 100 mcg and 10 mg)⁵,⁶</td>
<td>1 mg/mL or 10 mg/mL¹</td>
<td>5 mg (scored tablets)²</td>
</tr>
<tr>
<td>FDA-approved therapeutic indications</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

IM = intramuscular; IV = intravenous; OTC = over-the-counter; SC = subcutaneous

**MEPHYTON® (Phytonadione) 5 mg: Pharmacology**

- **Activity¹**
  - Same type and degree of activity as naturally-occuring vitamin K₁
- **Oral absorption**
  - Adequately absorbed from the gastrointestinal tract only if bile salts are present¹
  - After ingestion, vitamin K₁ is quickly taken up by the liver, skin, and muscle²
- **Storage**
  - Concentrated in the liver³
  - After 1 week of decreased dietary intake, partial depletion of stores are observed¹
  - Stores can also be depleted if bacterial production of vitamin K₂ is reduced¹

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MEPHYTON® (Phytonadione) 5 mg:
Important Safety Information

MEPHYTON® (Phytonadione) is contraindicated in patients with hypersensitivity to any component of this medication. An immediate coagulation effect should not be expected after administration. MEPHYTON will not counteract the anticoagulant action of heparin. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K₃ may restore conditions which originally permitted thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly. Failure to respond to vitamin K may indicate a congenital coagulation defect or that the condition being treated is unresponsive to vitamin K. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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SLIDE 17.

Drugs That May Impact Vitamin K Synthesis

- Warfarin
- Some antibiotics
- Some sulfa drugs
- Salicylates
- Anticonvulsants
- Mineral oil


SLIDE 18.
Vitamin K Content in Food and Supplements

- In equivalent terms, one MEPHYTON tablet is
  - 13.5 servings of spinach
  - 500 Standard Centrum Tablets
- MEPHYTON is the only approved oral prescription vitamin K therapy

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Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Measurement</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR (Prothrombin Time / International Normalized Ratio)</td>
<td>Prothrombin activity</td>
<td>Coagulation status</td>
</tr>
<tr>
<td>PIVKA-II (Proteins Induced by Vitamin K Absence)</td>
<td>Undercarboxylated vitamin K-dependent proteins</td>
<td>Vitamin K deficiency</td>
</tr>
</tbody>
</table>

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References


References


MEPHYTON® (Phytonadione)  

Repeatable doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate a congenital coagulation defect or that the condition being treated is unresponsive to vitamin K.

PRECAUTIONS

Hyperprothrombinemia Due to Other Causes in Adults
If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, anticoagulants) is suggested as an alternative to administering concurrent MEPHYTON. The severity of the coagulation disorder should determine whether the immediate administration of MEPHYTON is required in addition to discontinuation or reduction of interfering drugs.

A dosage of 2.5 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

The oral route should be avoided when the clinical disorder would prevent proper absorption. Bile salts must be given with the tablets when the endogenous supply of bile to the gastrointestinal tract is deficient.

HOW SUPPLIED

Tablets MEPHYTON, 5 mg vitamin K₃, are yellow, round, scored, compressed tablets, coded ATON 405 on one side and MEPHYTON on the other. They are supplied as follows:

NDC 25101-455-15 bottles of 100.

Stability:
Store in tight closed original container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature). Always protect MEPHYTON from light. Store in tightly closed original container and carton until contents have been used. (See PRECAUTIONS, General.)

Manufactured by:
Dean Specialty Pharmaceuticals, Inc. Toronto, Ontario M3J 3W8
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