PRESCRIBING INFORMATION

VITAMIN K_1

(Phytonadione Injectable Emulsion USP)
10 mg / ml
1 mg / 0.5 ml

Sterile

Sandoz Canada Inc.
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CHEMISTRY

Phytonadione is a synthetic fat soluble naphthoquinone derivative which is identical to naturally occurring vitamin K_1. Vitamin K_1 differs from other naturally occurring types of vitamin K in the degree of saturation and length of its 20-carbon polyisoprenoid side chain. Phytonadione occurs as a mixture of cis and trans isomers, with the cis isomer not exceeding 20%. Phytonadione occurs as a clear, yellow to amber, very viscous, odourless or practically odourless liquid, having a specific gravity of about 0.967. It is stable in air, but decomposes on exposure to sunlight. Phytonadione is soluble in dehydrated alcohol, chloroform, ether, and vegetable oils. The drug is slightly soluble in alcohol and insoluble in water.

DETAILED PHARMACOLOGY

Phytonadione possesses the same type and degree of activity as naturally occurring vitamin K_1. The latter is necessary for the production by the liver of the following coagulation factors: prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). Studies indicate that vitamin K is involved in carboxylation of the preformed inactive precursors of these coagulation factors. The resulting gamma-carboxyglutamyl residues are required for the calcium-dependent phospholipid binding exhibited by active vitamin K-dependent clotting factors. In adequate doses, phytonadione reverses the inhibitory effect of coumarin and indanedione derivatives on the synthesis of these factors. A rare genetic mutation of the vitamin K receptor site which is associated with resistance to coumarin and indanedione derivatives anticoagulants and increased sensitivity to small amounts of exogenous vitamin K has occurred in some patients.

PHARMACOKINETICS

Following the parenteral administration of phytonadione, blood coagulation factors increase within 1 to 2 hours. Bleeding is usually controlled within 3 to 8 hours, and a normal prothrombin time may often be obtained 12 to 14 hours after administration. Only small amounts of phytonadione are stored in body tissues and the drug appears to cross the placenta to a limited extent. Phytonadione is distributed to milk

of breast feeding mothers. Little is known about the excretion of vitamin K. High fecal concentrations of vitamin K probably result from bacterial synthesis in the intestine.

INDICATIONS AND CLINICAL USE

Hypoprothrombinemia (Prophylaxis and Treatment):
Vitamin K is indicated for the treatment and prevention of various coagulation disorders involving impaired formation of factors II, VII, IX, and X resulting from vitamin K deficiency or impairment of vitamin K activity, including hypoprothrombinemia due to oral anticoagulants, salicylates, and some antibiotics. Vitamin K does not return abnormal platelet function to normal and does not counteract the anticoagulant activity of heparin. Vitamin K may not be effective in hepatic function impairment since prothrombin synthesis occurs in the liver.

Vitamin K Deficiency May Occur in the Following Persons or Conditions:
Patients receiving total parenteral nutrition (TPN); in malabsorption syndromes associated with pancreatic insufficiency (including cystic fibrosis), hepatic-biliary tract disease (obstructive jaundice internal biliary fistula), disease of the small intestine (celiac disease, tropical sprue, regional enteritis, ulcerative colitis, persistent diarrhea or dysentery, short bowel syndrome after extensive bowel resection); prolonged T-tube drainage; abetalipoproteinemia; infants receiving milk substitute formulas and those who are breast fed.

Deficiency may also occur when vitamin K is impaired by salicylates, sulfonamides, quinine, quinidine, moxalactam, dactinomycin, broad spectrum antibiotic therapy, or when absorption is decreased by concurrent administration of cholestyramine, colestipol, mineral oil, or sucralfate.

Hemorrhagic Disease of the Newborn (Prophylaxis):
The American Academy of Pediatrics recommends routine phytonadione administration at birth to prevent hemorrhagic disease of the newborn, since vitamin K from the mother may be inadequate because of poor passage through the placenta and because intestinal bacterium responsible for the natural synthesis of vitamin K are not present for 5 to 8 days following birth. In addition, the risk of hemorrhagic disease of the newborn is increased in infants of mothers who received anticonvulsants (e.g. phenobarbital, phenytoin) during pregnancy. In the newborn, phytonadione is preferred over other vitamin K preparations because of the lower risk of causing hyperbilirubinemia and hemolytic anemia, especially in premature infants.

CONTRAINDICATIONS

Hypersensitivity to the drug or to any of the ingredients in the formulation.

WARNINGS AND PRECAUTIONS

Phytonadione is relatively nontoxic. However, severe reactions, including fatalities, have been reported rarely and only during or immediately after the administration of the drug by the IV route. These severe reactions, which may occur in patients receiving phytonadione for the first time, resemble hypersensitivity or anaphylaxis (see ADVERSE REACTIONS). Therefore, it is recommended that the IV route be restricted to those situations where other routes are not feasible and the serious risk involved is considered justified. Although it has not been reported, the possibility of an allergic reaction, including anaphylaxis, should be kept in mind when phytonadione is administered by the IM or the SC routes.

An immediate coagulant effect should not be expected after administration of vitamin K_1. Since a delay of 3 hours or more may be required to stop active bleeding, administration of fresh, whole blood or plasma may be necessary when bleeding is severe.

Vitamin K_1 will not counteract the anticoagulant action of heparin and will not return abnormal platelet function to normal.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia in patients where anticoagulant therapy is still indicated, administration of excessive doses may restore the condition that originally required administration of anticoagulant drugs and large doses of coumarin or indanedione anticoagulants may be required to reinstate anticoagulant therapy. In such patients, dosage of vitamin K_1 should be kept as low as possible, and a regular monitoring of the prothrombin time should be performed. If anticoagulation is needed following overdosage of phytonadione, heparin may be used.

Repeated large doses of vitamin K are not warranted in liver disease if the response to the initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate a congenital defect or that the condition being treated is not vitamin K-dependent and repeated large doses of the drug are contraindicated.

Pregnancy and Lactation: Animal reproduction studies have not been performed. Also, inadequate information exists as to whether this drug may affect fertility in human males or females and about its teratogenic potential or other adverse effects on the fetus. Vitamin K may appear in breast milk of nursing mothers.

Temporary resistance to prothrombin depressing anticoagulants may result, especially when larger doses of vitamin K_1 are used. If relatively large doses have been employed, it may be necessary, when reinstating anticoagulant therapy, to use somewhat larger doses of the prothrombin depressing anticoagulant, or to use one which acts by a different mechanism, such as heparin sodium.

ADVERSE REACTIONS

Phytonadione is relatively nontoxic. However, severe reactions have occurred rarely and only during or immediately after the administration of the drug by the IV route. These reactions, which may occur in patients receiving phytonadione for the first time, resemble hypersensitivity or anaphylaxis. Symptoms include cramp-like pains, convulsive movements, cardiac irregularities, chest pains, cyanosis, dulled consciousness, flushing of the face, a sense of chest constriction, circulatory collapse, bronchospasm, hyperhydrosis, dyspnea, alteration of taste, dizziness, rapid and weak pulse, brief hypotension, shock, cardiac and/or respiratory arrest, and death. It is not known whether these adverse reactions are caused by the drug or the injection vehicle. Dilution and slow infusion may not prevent severe reactions; therefore, the IV route should be restricted to emergency use only. The possibility of allergic reactions, including anaphylaxis, should also be considered when phytonadione injection is given by the IM or SC routes.

Pain, swelling and tenderness at the injection site occur rarely after parenteral administration of phytonadione. Reactions resembling erythema perstans have been reported rarely after repeated injections.

Hyperbilirubinemia and severe hemolytic anemia have been reported rarely in neonates, particularly in premature neonates, following the administration of large doses of phytonadione (10 to 20 mg). However, the incidence of these adverse effects is much less with phytonadione than with other vitamin K preparations.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

DRUG INTERACTIONS

Because vitamin K_1 is a pharmacologic antagonist to prothrombin inhibiting anticoagulants, patients being treated with these drugs should not receive phytonadione except for the treatment of excessive hypoprothrombinemia.

ADMINISTRATION

Vitamin K_1 is administered by intramuscular or subcutaneous injection.

If the intravenous administration is unavoidable, it should be injected at a rate not exceeding 1 mg/minute (see **WARNINGS AND** PRECAUTIONS). The drug may be diluted for infusion with dextrose 5% or sodium chloride 0.9%. The drug should be administered immediately after dilution, and any unused portion of the dilution must be discarded.

DOSAGE

Anticoagulant-Induced Hypoprothrombinemia:
To correct oral anticoagulant-induced prothrombin deficiency, when bleeding is not present or immediately threatened, 2.5 to 10 mg of phytonadione may be administered initially by IM or SC injection. In rare instance, higher doses (25 to 50 mg) may be required. The dose may be repeated 6 to 8 hours later if the initial response is not satisfactory. When bleeding is present or immediately threatened, 10 to 50 mg of phytonadione (depending on the severity of the bleeding) may be administered by slow IV and repeated every 4 hours if needed. In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

The smaller doses are recommended for patients being treated with the shorter acting anticoagulants, and in those in need of continued anticoagulant therapy. The smallest effective dose should be sought to obviate the temporary refractoriness to further anticoagulant therapy, and to avoid lowering the prothrombin time to far below that consistent with an effective level of anticoagulant therapy.

Hemorrhagic Disease of the Newborn:
For prophylaxis of hemorrhagic disease of the newborn and treatment of neonates whose mothers received anticonvulsant drugs during pregnancy, phytonadione in doses of 0.5 to 1 mg IM or SC should be administered to the neonate immediately after delivery and repeated if necessary 6 to 8 hours later. Rarely, it may be necessary to repeat the dose 4 to 7 days later. If the mother has been receiving oral anticoagulant therapy during pregnancy, larger doses may be necessary. Large doses should not be used in an attempt to raise neonatal prothrombin levels to adult levels. Phytonadione administration to women before delivery to prevent hemorrhagic disease of the newborn is not recommended by most authorities.

Empiric administration of vitamin K_1 should not replace proper laboratory evaluation of the coagulation mechanism. A prompt response (shortening of the prothrombin time within 2 to 4 hours) following vitamin K_1 administration is usually diagnostic of hemorrhagic disease of the newborn and failure to respond indicates another diagnosis or coagulation disorder.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and phytonadione injection should be given concurrently.

Hypoprothrombinemia from Other Causes:
For the treatment of prothrombin deficiency resulting from malabsorption syndromes or from therapy with broad-spectrum antibiotics, salicylates, sulfonamides, quinine, quinidine, moxalactam, or dactinomycin, doses of 2 to 25 mg may be administered to adults initially and repeated if necessary, depending on the severity of the deficiency and the response to the drug. Up to 50 mg may be given but doses higher than 25 mg are rarely required. For the treatment of prothrombin deficiency in pediatric patients, infants may receive 2 mg and older children may be given 5 to 10 mg by the IM or SC routes.

For the prevention of hypoprothrombinemia associated with vitamin K deficiency in patients receiving total parenteral nutrition or prolonged hyperalimentation, it has been recommended that adults be given 5 to 10 mg of phytonadione IM once weekly and children receive 2 to 5 mg IM once weekly.

Infants who are breast fed or receiving milk substitute formulas should be given 1 mg of phytonadione per month by IM or SC injection whenever the vitamin K content in the diet is lower than 100 mcg/L. For the prevention of hypoprothrombinemia in breast fed infants with diarrhea for a duration longer than several days, a single 1 mg IM dose has been recommended.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Supplied:

Vitamin K_1 is a clear yellow preservative free solution, for IM, IV or SC injection.

Adult Formulation: Each mL contains phytonadione 10 mg, polyethylene glycol-15-hydroxystearate 10%, propylene glycol 2% in water for injection. Supplied in 1 mL ampoules, boxes of 10.

Pediatric Formulation: Each 0.5 mL contains phytonadione 1 mg, polyethylene glycol-15-hydroxystearate 7%, propylene glycol 2% in water for injection. Supplied in 0.5 mL ampoules, boxes of 10.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light.

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