Phytonadione Injection 10 mg “TBC”

[INGREDIENT]

Each ml contains:

Phytonadione..……..10 mg

[DESCRIPTION]

Phytonadione injection, a prothrombogenic Vitamin, is an essentially clear, sterile, aqueous dispersion of Vitamin K_1.

[CLINICAL PHARMACOLOGY]

Phytonadione possesses the same type and degree of activity as does naturally occurring vitamin K, which is necessary for the synthesis in the liver of blood coagulation factors prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX) and Stuart factor (factor X).The prothrombin test is sensitive to the concentrations of factors II, VII and X . The mechanism by which vitamin K_1 promotes formation of these clotting factors in the liver is not known, but animal data suggest that it acts as an enzyme or catalyst upon a substrate within the liver or combines with an apoenzyme (AE) to form an active enzyme (AEK) which is then involved in prothrombin synthesis.

Following intramuscular injection, phytonadione is readily absorbed, almost entirely by way of the lymph. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. There is considerable evidence that the synthesis of prothrombin and the related vitamin K-dependent blood clotting factors are linked to a metabolic cycle in which vitamin K_1 is oxidized and reduced to its inactive 2,3 epoxide metabolite . This vitamin K epoxide cycle is mediated by at least two enzymes which have been partially characterized as phytonadione epoxidase and phytonadione epoxide reductase.
Phytonadione is known to cross the placenta.

Following intravenous administration of tritiated vitamin K_1, the half-life of elimination of phytonadione ranged from two to four hours. The lipid-soluble radioactivity in the plasma, which is assumed to represent the injected phytonadione, was rapidly cleared and resembles the clearance of orally administered phytonadione.

The action of the aqueous dispersion when administered parenterally is generally detectable within an hour or two, and hemorrhage is usually controlled within three to six hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

[INDICATIONS AND USAGE]

Phytonadione is indicated for:

*anticoagulant-induced prothrombin deficiency:

*prophylaxis and therapy of hemorrhagic disease of the newborn, and it may also be given to the mother before delivery;

*hypoprothrombinemia due to oral antibacterial therapy;

*hypoprpthrombinemia secondary to factors limiting absorption or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas and regional enteritis;

*other drug-induced hypoprothrombinemia (such as that due to salicylates) when it is definitely shown that the result is due to interference with vitamin K metabolism.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water-soluble vitamin K analogs.

[CONTRAINDICATIONS]

Phytonadione is contraindicated in patients with known hypersensitivity to the drug.

[WARNINGS]

Phytonadione does not directly counteract the effects of oral anticoagulants, but it promotes the synthesis of prothrombin by the liver, usually within two hours. Fresh plasma or blood transfusions may be required for severe blood loss or lack of response to vitamin K.
Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemla but anticoagulant therapy is still indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy.
Phytonadione is not a clotting agent, but overzealous therapy with vitamin K may restore conditions which originally permitted thromboembolic phenomena. Dosage, therefore, should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

[PRECAUTIONS]

General: Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant or one which has a different mode of action, such as heparin.

Since the liver is the site of metabolic synthesis of prothrombin, hypoprothrombinemia resulting from hepatocellular damage is not corrected by administration of vitamin K. Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory (Koller test.)

Failure to respond to vitamin K may indicate that a coagulation defect is present or that the condition being treated Is unresponsive to vitamin K.

Laboratory tests: The dose and frequency of administration and duration of treatment depend on the severity of the prothrombin deficiency and should be regulated by repeated determinations of prothrombin time.

Drug interactions: Because vitamin K_1 is a pharmacologic antagonist to coumarin and indanedione derivatives, patients being treated with these anticoagulants should not receive phytonadione except for the treatment of excessive hypoprothrombinemia.

Carcinogenesis, mutagenesis, impairment of fertility: Phytonadione has not undergone adequate animal testing to evaluate carcinogenic or mutagenic potential, or impairment of fertility.

Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with phytonadione. When menaquinone (vitamin K_2), which is structurally similar to phytonadione, was administered to mice and rats on gestation days 7 through 14 at maximum doses of 1000mg/kg/day(p.o.) and 100mg/kg/day(i.p.), no teratogenicity was observed . It is not known whether phytonadione can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Phytonadione should be given to pregnant women only if clearly needed.

Nonteratogenic effects: Retardation of skeletal ossification has been reported in mice with vitamin K_2 (menaquinone).

Nursing mothers: A study has shown that vitamin K is excreted in human milk. This should be considered if it is necessary to administer phytonadione to a nursing mother.

Pediatric-use: Hemolysis and jaundice in newborns, particularly in premature infants, may be related to the dose of phytonadione. Therefore, the recommended dose should not be exceeded (See Adverse Reactions and Dosage and Administration sections).

[ADVERSE REACTIONS]

Allergic reactions: The possibility of allergic reactions, including an anaphylactoid reaction, should be kept in mind.

Miscellaneous: Pain, swelling and tenderness at the injection site have occurred rarely.

Although phytonadione has a greater margin of safety than the water-soluble vitamin K analogs, hyperbillirubinemia has been reported in the newborn, particularly in prematures when used at 5 to 10 times the recommended dosage. This effect, with the possibility of attendant kernicterus, should be considered if such dosages are deemed necessary.

In patients with severe hepatic disease, large doses of phytonadione may further depress liver function. Paradoxically, the administration of excessive doses of vitamin K or its analogs in an attempt to correct the hypoprothrombinemia associated with severe hepatitis or cirrhosis may actually result in a further depression of the concentration of prothrombin (also see Precautions: General Section).

[OVERDOSAGE]

There are no data available on overdosage of phytonadione in man, Phytonadione is nontoxic to animals, even when given in huge amounts. The acute toxicity of vitamin K_1 is as follows:

Species	Route	LD_{50}
Mouse	p.o.	> 25 Gm/kg
Mouse	i.p.	> 25 Gm/kg
Mouse*	i.v.	57(48-112)mg/kg

*Phytonadione formulation used

If anticoagulation is needed following overdosage of phytonadione, heparin may be used.

[DOSAGE AND ADMINISTRATION]

The U .S. Recommended Daily Allowances for vitamin K in humans have not been established officially. The adequate daily dietary intake of vitamin K for adults has been estimated to be 70 to 140 mcg; for infants 10 to 20 mcg; for children and adolescents 15 to 100 mcg . The dietary abundance of vitamin K normally satisfies the requirements except for the neonatal period of 5 to 8 days.

INFANTS

Neonatal hemorrhage due to hypoprothrombinemia:

0.5 to 1 mg I.M. immediately after birth, which maybe repeated if the mother has received anticonvulsant drug theraphy, or if the infant developes bleeding tendencies .

1 to 5 mg I.M. may be given to the mother 12 to 24 hours before delivery.

ADULTS

hypoprothrombinemia due to.

*Anticoagulant theraphy (except of heparin type) -5 to 10 mg I.M.

Initially; up to 20 mg, if necessary.

*Antibacterial theraphy -5 to 20mg I.M.

*Other drugs (e.g ., saticylates) 2 to 20 mg I.M.

I.M. Injection is the usual route of administration. It could be administered Intravenously and Subcutaneously when necessary. When administered Subcutaneously, it should not exceed 20 mg. By I.V. route, it should be given very slowly, not exceeding 10 mg per minute, it may be diluted by normal saline or glucose injection.

In older children and adults, injection of phytonadione should be in the upper outer quadrant of the buttocks. In infants and young children, the anterolateral aspect of the thighs or the deltoid region is preferred so that danger of sciatic nerve injury is avoided.
It is recommended that phytonadione be injected by itself, since phytonadione injection has been reported to be incompatible with many drugs in admixtures.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight opalescence may occur with phytonadione ampules, but this does not affect the safety or potency of the product.

Phytonadione is stable in air, but it is photosensitive, decomposing with loss of potency on exposure to light. Therefore, it should be stored in a dark place and protected from light at all times, phytonadione need not be refrigerated.

[PACKAGE]

100 Ampoules × 1 ml

[STORAGE CONDITION]

Store below 25°C. Do not freeze. Protect from light at all times.

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