Antibiotic Associated Hypoprothrombinemia

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Abstract:

Vitamin K is an important substance in synthesis of several clotting factors, most important of which is prothrombin. Many antibiotics have effects on intestinal micro organisms which are necessary for synthesis of Vitamin K and thus formation of essential clotting factors is interfered with. This antibiotic associated hypoprothrombinemia can lead to hemorrhage. Clinical set up for such a happening is generally easily recognized. Management includes parenteral administration of Vitamin K, plasma transfusion, or "Prothrombin Complex" in serious hemorrhagic conditions. Antibiotic associated hypoprothrombinemia can be prevented by prophylactic use of Vitamin K in situations likely to result in bleeding, e.g. post-operative conditions.

Blood coagulation process is a complex cascade involving several factors. Vitamin K is very important in synthesis of several of these including factors II (Prothrombin), VII, IX, and X. Prothrombin is synthesized in the liver with Vitamin K as a co-factor which is required for gamma-carboxylation of glutamic acid residues in the final step of its biosynthesis.[1, 11] Prothrombin is acted upon in the final common pathway by prothrombinase, which consists of other coagulation factors, to form thrombin which, in turn, acts on fibrinogen to result in formation of fibrin. A deficiency of Vitamin K results in synthesis of abnormal and hypofunctional prothrombin (and other Vitamin K dependent factors), which impair normal coagulation process with consequent bleeding problems.[1]

Etiology and Pathogenesis

Hypoprothrombinemia results either from deficiency of Vitamin K or by decreased utilization by the liver. In addition, there are other causes which can lead to hypoprothrombinemia (Table I). Synthesis of the vitamin by the gut flora is an important endogenous source. Elimination of these bacteria by the use of potent antibiotics deprives the body of this important source. When such a situation is accompanied by a decreased oral intake, this could give rise to an ideal setting for the deficiency of Vitamin K.[2, 3] About 80% of patients in one series were on antibiotics when they developed Vitamin K deficiency.[3] Surgical patients who may have received antibiotics to sterilize their bowels and had been kept without food and on intravenous fluids in the post-operative period constitute a common clinical setting for such a deficiency. This happens more frequently in the elderly. Neither nutritional deficiency nor gut sterilization alone usually result in Vitamin K deficiency, probably due to low daily requirement, as total starvation for four weeks did not produce such deficiency.[4] This setting, however, is not limited to surgical patients as medical patients on antibiotics and particularly those with renal disease and cancer also developed Vitamin K deficiency associated hypoprothrombinemia.[2, 3]

Many antibiotics (Table II) have been reported to have caused hypoprothrombinemia by eliminating the gut flora if used for long enough times. This happens more in the elderly patient with poor oral intake who is on more than one antibiotic at a time. Deficiency becomes apparent generally about the seventh day of

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TABLE I
CAUSES OF HYPOPROTHROMBINEMIA

1. Decreased synthesis due to Vitamin K deficiency
   - i. Dietary deficiency
     - Newborn
     - NPO in post-operative patient
   - ii. Poor absorption
     - a. Gastrointestinal disorders
       - Malabsorption
       - Celiac disease
       - Inflammatory Bowel disease
       - Fistula
     - b. Unavailable bile salts
       - Absent: Obstructive jaundice
       - Bound: Cholestyramin
   - iii. Decreased gut synthesis
     - a. Not enough colonization
       - Newborn
     - b. Interference with bacterial action
       - Antibiotics (Table II)
       - Excessive Vitamin A[9]
   - iv. Vitamin K Antagonists
     - Excessive Vitamin A[9]
2. Decreased utilization due to liver disease
   - Infectious and toxic hepatitis, cirrhosis
3. Interference with action of prothrombin
   - Coumarin drugs
   - Salicylates[10]
   - Lupus inhibitors[7]
4. Destruction of prothrombin
   - Tropical American pit viper[10]
5. Vitamin K sensitive hypoprothrombinemia in pregnancy[11]

TABLE II
ANTIBIOTICS REPORTED TO HAVE INDUCED HYPOPROTHROMBINEMIA SECONDARY TO VITAMIN K DEFICIENCY

Penicillin[3, 5]	Sulfa ("Septra")[3, 5]
Ampicillin[3]	Streptomycin[3, 5]
Cloxacillin[3]	Gentamycin[3]
Cephalosporin	Kanamycin[3]
Cephaloridine[3]	Neomycin[5]
Cefamandole[12, 13]	Erythromycin[3]
Moxalactum[This case, 13]	Tetracycline[3, 5, 6]
Cefoperazone[13]	Chloramphenical[3, 6]

antimicrobial therapy.[3] These drugs presumably impair Vitamin K production by the intestinal bacteria flora by inhibiting synthesis of menadiones.[1, 6] Certain cephalosporin may cause bleeding due to their chemical structure.[13]

Manifestations

Hemorrhage is the major feature of hypoprothrombinemia associated with antibiotic use. Bleeding can occur in the gastro-intestinal or genito-urinary tracts or intracranially. Ecchymosis, epistaxis, bleeding gums, or subconjunctival bleeding may occur and the patient may have some predisposing underlying factors like hypertension, peptic ulcer disease, and cystitis, etc.[11] Hemoptypsis in general is uncommon.[10] A serious post-operative hemorrhage may occur and may be confused with disseminated intravascular coagulation (DIC). Gastro-intestinal hemorrhage, however, is commonest[6] as is seen in the following case.

Case Report:

This 91 year old female was admitted with a diagnosis of ischemic heart disease and bronchitis. She was weak and refused to eat. A chest roentgenogram showed bilateral pneumonia. She was treated with intravenous Gentamycin and Moxalactum with improvement of respiratory symptoms and decrease in temperature. On the sixth day of treatment, the patient had massive upper and lower gastro-intestinal bleeding with drop in hemoglobin of 2 grams which required a transfusion of packed cells. Coagulation profile revealed Protime (PT) of 55 seconds (Control 11.5 sec.), partial thromboplastin time (PTT) of 63 seconds (Control 35 sec.), platelets of 496,000, and normal bleeding time. Several doses of Vitamin K were given intramuscularly (Table III) with rapid restoration of PT and cessation of bleeding. Prophylactic Vitamin K was given intramuscularly for further four days and a full course of antibiotics was completed without any further hemetemesis or malena. Meanwhile, her general condition improved, and she was able to eat regular food.

TABLE III
EFFECT OF VITAMIN K IN HYPOPROTHROMBINEMIA

	12/3/82	12/4	12/4	12/4	12/5	12/8
PT (seconds)	55	39	22	13	15	
PTT (seconds)	63	55	34			
Platelets	496,000					
Packed cell transfusion	2 units					
Vit. K IM (mg)	10		10		10	
Gentamycin	IV	IV	IV	IV	IV	Stopped
Moxalactum	IV	IV	IV	IV	IV	Stopped
Bleeding	yes	yes	yes	no	no	no

Comment:

This case has perfect clinical setting for antibiotic related hypoprothrombinemia. The patient is elderly, not eating well, and on combination broad spectrum antibiotics. An associated structural defect of gastro-intestinal tract is a possibility, but this, unfortunately, could not be determined due to patient's refusal of undergoing any further diagnostic tests.

Management

Diagnosis is usually easy, keeping in mind the clinical setting,[2] prolonged PT and its prompt correction after the administration of Vitamin K.[3] Bleeding time, platelet count, and factors not dependent on Vitamin K are not influenced.[11]

Parenteral administration of Vitamin K is considered to be the effective treatment. Vitamin K_1 (Phytonadione), is given intramuscularly in 10-20mg doses and generally abolishes coagulation abnormalities within 24 hours (Table IV). Higher doses may, sometimes, be needed. Inadequate response should indicate complicating processes like liver disease or

TABLE IV
TREATMENT OF HYPOPROTHROMBINEMIA

MODALITY	DOSAGE	COMMENTS
1. Vitamin K		
K_1 (Phytonadione)	10-20 mg IM or PO as needed	Rapid IV administration may cause flushing, dyspnea, death
K_3 (Menadione)	10-20 mg IM or PO as needed	May cause hemolytic anemia hyperbilirubinemia
2. Plasma	500 ml and as needed	
3. "Prothrombin Complexes"	1-2 infusions as needed	May cause hepatitis

DIC, etc. If underlying defect cannot be rectified soon, small doses can be given daily to prevent bleeding until the cause can be eliminated. Synthetic Vitamin K_3 (menadione), may give a transient response than natural Vitamin K_1. Rapid intravenous administration of phytonadione may result in flushing, dyspnea, chest pain, and rarely death.[10] Moderate doses of menadione have caused hemolytic anemia, hyperbilirubinemia, and kernicterus in newborn, especially premature and those with congenital glucose 6-phosphate dehydrogenase deficiency.[10, 11]

Plasma transfusion may provide prothrombin (and other coagulation factors) and may be needed in severe bleeding.[11] Replacement therapy with "Prothrombin complex" has been used in serious hemorrhage. Vitamin K deficiency acquired hypoprothrombinemia has been effectively corrected by commercially prepared parothrombin complex concentrate ("Konyne") when given in 1-3 intravenous infusions although there is some risk of post-transfusional hepatitis.[8]

Prevention of antibiotic associated hypoprothrombinemia essentially means awareness of the clinical setting in which it occurs. As Vitamin K deficiency induced coagulopathy is commonly an iatrogenic disorder with well known predisposing features, it has been recommended that Vitamin K supplements be added to intravenous fluids given to the patients undergoing major abdominal surgery who are on antibiotics;[3] but special care is necessary since these patients are inclined to develop thrombo-embolic complications.[11]

Summary

Antibiotics can induce hypoprothrombinemia due to Vitamin K deficiency by destroying intestinal bacterial flora in association with poor oral intake, which can lead to varying degrees of hemorrhagic manifestations. The problem is easily recognized and can be promptly corrected by Vitamin K administration.

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