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Controllable vitamin K deficiency under high-dose oral menatetrenone administration – a case report

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Received November 30, 2017, accepted December 29, 2017

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Pharmazie 73: 234–236 (2018) *doi: 10.1691/ph.2018.7994*

Vitamin (V) K deficiency may cause severe bleeding tendencies, which necessitates extreme caution. We report a case of a 30-year-old man diagnosed with VK deficiency of unknown etiology. He was treated with intravenous menatetrenone three times a week in an outpatient setting for about 1 year and 9 months. Eventually, he developed an allergic reaction to intravenous menatetrenone and was under steroid therapy. In order to reduce his hospital visits and discontinue steroid use, the pharmacist proposed to change the method of menatetrenone administration from intravenous to oral (high dose). The change in treatment method has greatly improved the patient's quality of life.

1. Introduction

Vitamin (V) K deficiency is more frequent in newborns and infants (Zipursky 1999), where extreme caution is necessary as it causes severe bleeding tendencies. VK deficiency in adults is caused by prolonged inadequate dietary intake, malabsorption syndromes due to the suppression of intestinal microflora caused by long-term antibiotic therapy, and cholestatic liver disease (Shearer 2009). We report a case of VK deficiency with occasional nasal bleeding. Patient had adequate diet intake and no history of antibiotic therapy or biliary tract abnormality. He was treated with intravenous (IV) menatetrenone three times a week in an outpatient setting for 1 year and 9 months. However, he developed an allergic reaction to intravenous menatetrenone, and hence, he was started on steroid therapy. In order to reduce his hospital visits and discontinue steroid use, the pharmacist proposed to change his treatment method from intravenous to high dose oral (PO) menatetrenone. The change greatly contributed towards improving the patient's quality of life (QOL).

2. Case report

2.1. Case presentation

In 2015, a 30-year-old male patient (181 cm, 109 kg) with a past medical history of ventricular septal defect, Wolff-Parkinson-White syndrome, and diabetes mellitus (DM) was referred to the department of hematology, Ogaki Municipal Hospital (Gifu, Japan) for nasal bleeding. The patient was under home treatment with metformin (1000 mg/day) for DM and aspirin for headache (as needed).

2.2. Clinical course

The result of his otolaryngology examination revealed right nasal bleeding. The day after the examination, he had uncontrollable gingival bleeding, which prompted him to undergo oral surgery. He was then referred to the department of hematology due to his abnormal blood test values. Before and after receiving 20 mg of IV menatetrenone at the initial visit, his prothrombin time (PT) decreased from >100 to 21.7 s, activated partial thromboplastin time (APTT) from 112.3 to 59.7 s, and PT-international normalized ratio (PT-INR) from an unmeasurable state to 1.82. This result suggests that the treatment was effective. Thus, IV menatetrenone was continued. Although the main cause of VK deficiency was still unknown, it could be associated with intake of drugs such as aspirin (he had taken two weeks ago), hepatobiliary disorders, inadequate dietary intake, or VK absorption disorder. At day 6, PO menatetrenone (45 mg) was given as a supplemental therapy. After discontinuing IV menatetrenone for 3 days, PT increased from 21.5 to 75.2 s, APTT from 43.9 to 52.7 s, and PT-INR from 1.90 to 6.42, indicative of a worsening VK deficiency. Consequently, we had to resume IV menatetrenone therapy. However, VK deficiency could not be controlled by twice-weekly administration of IV menatetrenone. Thus, IV menatetrenone treatment was continued at minimum dosage intervals for three times a week until the patient's condition was stabilized.

Anaphylactoid symptoms such as nausea, fever, low blood pressure, and respiratory failure were observed during IV menatetrenone treatment (total 500 mg). The activities of the coagulation-inhibiting factors protein C (41%, normal range: 70-140%) and protein S (33%, normal range: 60-150%) subsequently decreased. Hence, patient was placed under long-term IV menatetrenone treatment combined with steroid (hydrocortisone 100 mg (IV)) as a premedication for allergy prevention. Prolonged steroid administration exacerbated patient's DM (HbA_{1c} of 7.8%). Thus, patient was given insulin as advised by a DM specialist.

After about 1 year and 9 months of IV menatetrenone treatment, patient experienced dizziness and poor DM control, prompting his admission in the hospital. During patient's hospitalization, his history of irregular eating habits and poor medication compliance was noted. Thus, treatment for VK deficiency was reconsidered. Initially, he received 45 mg of PO menatetrenone, but the patient remained unresponsive to treatment. The dose was subsequently increased to 135 mg per day. The medication was given twice a day (after lunch and dinner) to ensure medication compliance and thus facilitate the absorption of VK. Previously, when IV menatetrenone was discontinued for two days, the PT-INR increased from 1.80 to 6.42 and thus treatment was resumed. Although PO menatetrenone dose was increased, PT-INR remained stable (from 1.20 to 1.81). Due to the change in patient's treatment method, prophylactic administration of steroids was discontinued, HbA_{1c}

Table: First laboratory findings

Laboratory test	Menatetrenone administration		normal range
	Before	After	
PT (seconds)	≥100	21.7	(10.5-13.5)
PT (%)	≤ 5	33	(70-130)
PT-INR	Unmeasurable	1.82	(0.85-1.15)
APTT (seconds)	112.3	59.7	(24-39)
APTT (%)	18	35	(60-140)
AFP (ng/mL)	-	2.0	(< 20)
α-fetoprotein rectin fraction (%)	-	< 0.5	(≤ 10)
PIVKA-II (mAU/mL)	-	> 50,000	(< 40)
Cholinesterase (IU/L)	-	486	(185-431)
Total cholesterol (mg/dL)	-	143	(130-220)
Triglyceride (mg/dL)	-	218	(50-149)
HDL cholesterol (mg/dL)	-	53	(40-70)
LDL cholesterol (mg/dL)	-	65	(< 140)
Thrombotest (%)	-	< 5	(70-130)
Hepaplastin test(%)	-	< 10	(70-130)
Vitamin K1 (ng/mL)	-	0.13	(0.15-1.25)
Vitamin K2(MK) (ng/mL)	-	≤ 0.05	(< 0.10)
Vitamin A (μg/dL)	-	52.8	(27.2-102.7)
1,25 dihydroxy vitamin D3 (pg/dL)	-	63	(20-60)
Vitamin E (mg/dL)	-	3.2	(0.75-1.41)
Coagulation factor XIII (%)	-	80	(70-140)
Coagulation factor II (%)	-	8.8	(66.0-118.0)
Coagulation factor V (%)	-	126.3	(73.0-122.0)
Coagulation factor X (%)	-	2.1	(58.0-200.0)
Plasminogen activity (%)	-	139	(69-111)
PIC (μg/mL)	-	0.9	(< 0.8)
TAT (μg/L)	-	2.7	(1.0-4.1)
antiplasmin (%)	-	135	(80-125)

PT:prothrombin time, PT-INR:PT-International Normalized Ratio, APTT:activated partial thromboplastin time, AFP:α-fetoprotein, PIVKA-II:protein induced by vitamin K absence-II, HDL:high-density lipoprotein cholesterol, LDL:low-density lipoprotein cholesterol, PIC:alpha2-plasmin inhibitor-plasmin complex, TAT:thrombin antithrombin III complex

improved from 8.2% to 6.7% in 1 month, and his hospital visits were reduced (Fig. 1). Although he experienced muscle pain (grade 1) when taking high dose of PO menatetrenone, his QOL remained unchanged.

3. Discussion

VK, a cofactor for γ-glutamine carboxylase, is necessary for the synthesis of coagulation factors II, VII, IX, and X. Inadequate VK intake results in the inhibition of these factors and prolonged PT and APTT, leading to bleeding tendencies. VK is classified into two: VK_1, synthesized by plants and VK_2 (menaquinone: MK), synthesized by microorganisms. VK_1 is found in green leafy vegetables, vegetable oils, margarine, etc. and generally accounts for 90% or more of the total VK intake (Holmes et al. 2012). MK is found in fermented food such as cheese, yogurt, natto, chicken, and egg yolk. In addition, MK is synthesized by intestinal bacteria; however, it is necessary to take up foods rich in VK (Suttie 1995). In recent years, it has been found that certain factors can be converted from VK_1 to MK (Hirota et al. 2013). VK deficiency in adults is caused by prolonged inadequate dietary intake, decreased intestinal microflora owing to long-term antibiotic therapy, decreased VK absorption capacity due to liver and biliary tract diseases, impaired VK metabolic cycle caused by warfarin administration, etc. In this study, the patient had no history of inadequate dietary intake, no liver and biliary diseases, and no history of antibiotic and warfarin therapy. Scavenger receptor class B type I (SR-BI), a specific protein in the proximal part of the small intestine; cluster-determinant 36 (CD36) ; and Niemann-Pick C1-like 1 (NPC1L1) (Goncalves et al. 2014; Takada et al. 2015) facilitate the absorption of VK_1. These proteins transport dietary cholesterol and VE, and VK_1 absorption has conceivably the same mechanism. However, no issues related to cholesterol and VE were found. Ezetimibe inhibits VK_1 absorption via NPC1L1 (Takada et al. 2015), and patient had no history of taking this medication as a combined treatment. IV menatetrenone, known for its effectiveness, is the main treatment for VK deficiency. Treatment with 20 mg IV menatetrenone was effective at initial diagnosis. However, when the patient was unresponsive to treatment with 45 mg PO menatetrenone; IV administration was continued. He was placed under long-term IV menatetrenone treatment with regular checkup three times a week. In addition, the use of steroids as a prophylactic treatment for allergy reaction worsened patient's DM. He became unemployed as his condition required regular outpatient treatment. He gained weight (from 109 to 130 kg at the start of VK administration) in a span of 1 year and felt desperate about his condition. Although he had short-term hospitalizations due to general malaise, his treatment regimen remained the same. However, lifestyle modification was encouraged to manage DM and improve QOL.

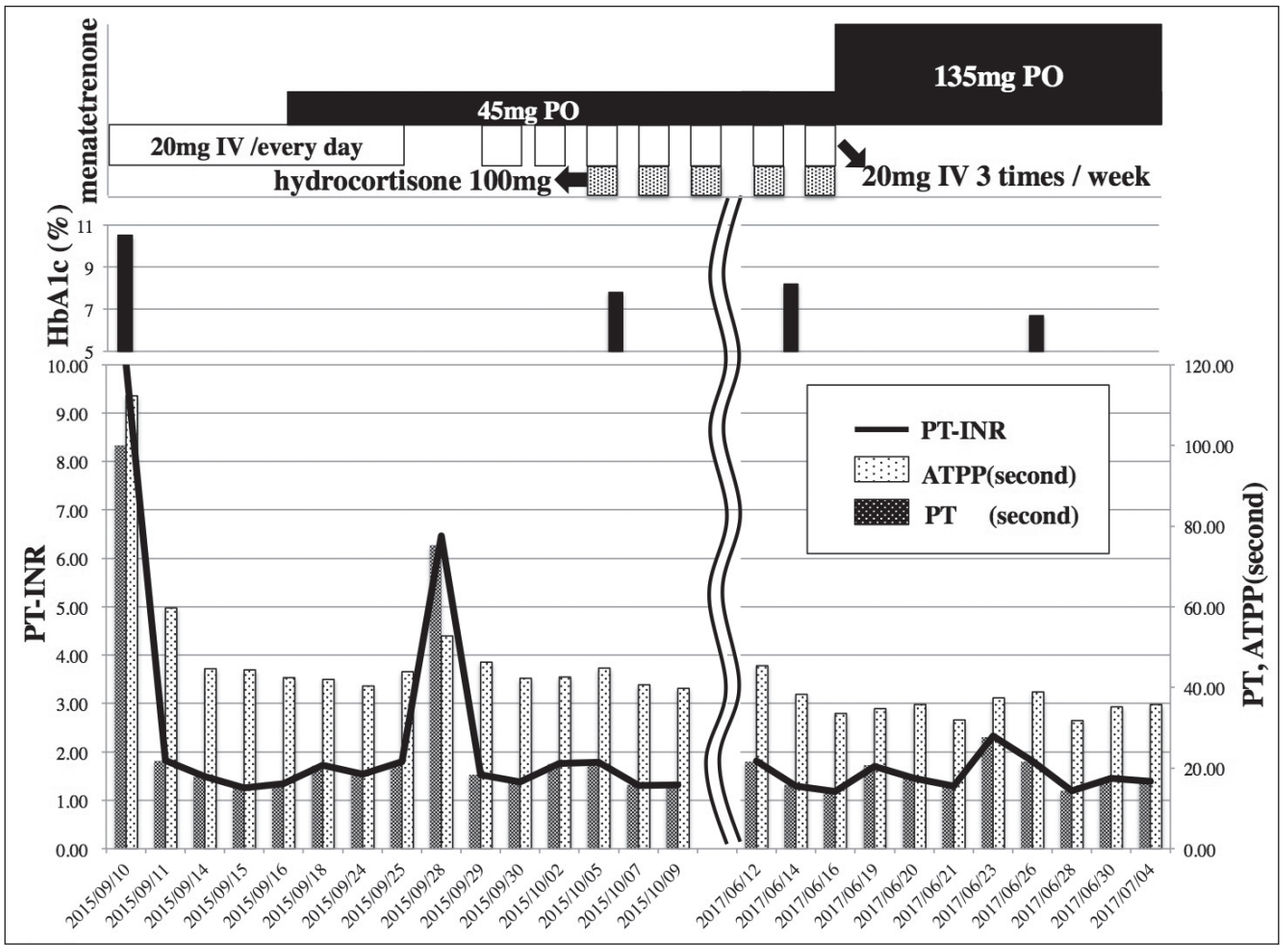

Fig: Clinical course from initiation menatetrenone administration
PO: oral administration, IV: intravenous administration, PT-INR:prothrombin time International Normalized Ratio, APTT:activated partial, PT:prothrombin time, HbA1c:Hemoglobin A1c

Food intake influences the pharmacokinetics of 15 mg PO menatetrenone. The fasting area under the concentration-time curve (AUC) is 165.0 ng/h/mL, whereas after breakfast, AUC is 1114.5 ng/h/mL. This result suggests that the AUC between fasting and after breakfast is significantly different. Additionally, absorption greatly depends on the fat content370.6±194.2 ng/h/mL for regular breakfast (fat content 8.8 g) and 1,024.4±341.4 ng/h/mL for high fat diet (fat content 34.9 g). Food content and fat ingestion greatly influences the absorption of medicines. Due to lack of understanding regarding the effects of diabetes, patient continued living an unhealthy lifestyle. He skipped breakfast, ate vegetables for lunch or consumed light meals, and ate oily foods for dinner. With this, the absorption of 15 mg PO menatetrenone given three times a day was affected. As the patient had poor drug compliance, IV treatment for VK deficiency was recommended. The AUC of 10 mg IV menatetrenone is 3,900 ng/h/mL; however, AUC increases to about 6,800 ng/h/mL at a dose of 20 mg, which is equivalent to 7 to 18 capsules. Although the patient received a normal dose of 45 mg of PO menatetrenone per day, his VK deficiency remained uncontrolled. Thus, a maximum PO menatetrenone dose of nine capsules (135 mg) per day, based on the Phase II study in Japan, was given. Fortunately, the patient experienced no side effects. As a result, PT-INR was stabilized without IV menatetrenone and VK deficiency was managed without subsequent serious bleeding tendencies. Hospital visits and steroid treatment were no longer required, and patient's QOL improved.

In conclusion, we reported a case of VK deficiency with unknown etiology. Patient received long-term IV menatetrenone treatment. During his treatment period, he experienced frequent hospital visits (three times a week), had poor DM control, and received steroid therapy. A pharmacist also advised the patient regarding lifestyle modification. However, patient's VK deficiency was managed with high-dose PO menatetrenone, improving patient's QOL.

Conflicts of interest: None declared.

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