Preprocedure Administration of Oral Vitamin K_1: Lessons Learned from 2 Experiences in the Same Patient

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INTRODUCTION

The management of patients undergoing invasive procedures while taking oral anticoagulant therapy can be complex and requires careful evaluation of several risk factors, including the urgency of the surgery, the risk of thrombosis in the absence of warfarin, and the risk of procedure-related bleeding. Lowering the international normalized ratio (INR) before an invasive procedure may involve the following steps: withholding warfarin for about 4 days before the procedure,[1] administering vitamin K_1 (phytonadione) either orally or intravenously 24–48 h before the procedure,[1-3] and infusing fresh frozen plasma or clotting factor concentrate for patients with life-threatening bleeding or an urgent need for surgery.[3,4]

For ambulatory patients, vitamin K_1 by oral administration is commonly used to rapidly reduce critical INR values (defined as INR above 5.0) to therapeutic values (2.0–3.5).[1] Small doses (1.0–2.5 mg) of oral vitamin K_1 are suggested if INR is between 5.0 and 9.0, whereas 5–10 mg of oral vitamin K_1 is recommended if INR is 10.0 or above.[1] IV administration of vitamin K_1 is also efficacious for this indication, but use of this route for outpatients is limited, because the drug must be administered slowly. The use of oral vitamin K_1 to completely reverse a therapeutic INR in ambulatory patients in preparation for elective invasive procedures is not routine, and to our knowledge has not been reported. We proposed that the use of oral vitamin K_1 might reduce the number of preprocedure days over which a patient would require subtherapeutic anticoagulation. Current practice for periprocedural management of ambulatory patients who are receiving oral anticoagulant therapy and who have an INR range of 2.0–3.0 is to discontinue warfarin 4 or 5 days before the procedure and then to reintroduce it after the procedure.[1] Patients at greater risk of thromboembolism are often given "bridging therapy" with heparin while oral anticoagulation is temporarily reversed.[1] In patients with elevated INR (above 3.0) withholding warfarin for a longer period before an invasive procedure is recommended[5,6]; this implies, for patients at high risk of a thromboembolic event, an extended period before the procedure when full-dose heparin or full-dose low-molecular-weight heparin (LMWH) must be administered.[2]

We describe a patient at high risk of thrombosis (INR range 3.5–4.0) who was treated with oral vitamin K_1 before each of 2 invasive procedures. Despite the abundant literature evaluating the use of oral vitamin K_1 for critical INR management, to our knowledge this is the first report of the use of this drug to normalize the INR on an ambulatory basis before an elective procedure.

CASE REPORT

An elderly patient was taking warfarin for antiphospholipid antibody syndrome and factor V Leiden mutation.* Although the patient's INR was slightly above 3.0, pulmonary embolism occurred, and the therapeutic INR range was subsequently elevated to 3.5–4.0. The patient weighed 82 kg (ideal body weight 66 kg), and the serum creatinine was 68 µmol/L, corresponding to an estimated creatinine clearance of 62 mL/min, calculated by the Cockcroft and Gault equation.[7] The medical

*Some demographic details deemed not pertinent to the understanding of this case have been omitted to protect patient confidentiality.

history was significant for hypertension, hypothyroidism, and anxiety. Upon referral to the anticoagulation clinic (about 4 months before the first of 2 endoscopic procedures), the patient reported ongoing gastrointestinal complaints. The patient underwent 2 gastroscopy procedures, one in February 2002 and the other in September 2003. The anticoagulation clinic was informed that biopsy samples would likely be obtained during each procedure, and an INR less than 1.4 was requested. In light of the patient's thrombotic risk, periprocedural management included the use of bridging therapy with LMWH to minimize the period of subtherapeutic anticoagulation.

Anticoagulation Management for First Endoscopic Procedure

Before the endoscopic evaluation in February 2002, the patient had been stabilized on a therapeutic warfarin regimen for over a month (total dose 33 mg/week), with corresponding INR values of 4.0 and 4.1 at 27 days and 16 days before the procedure, respectively (Table 1). During a follow-up visit 6 days before the endoscopy, the INR was elevated, to 4.6, which led to changes in the warfarin dosing regimen (Table 1). As part of the periprocedural management, warfarin therapy was discontinued 2 days before the procedure and was restarted the evening after the procedure. Vitamin K_1 was prescribed for oral administration 2 days before the procedure. In view of our limited experience with use of this agent to normalize therapeutic INR, an aggressive dose of 5 mg was selected, and the vitamin K_1 was administered 2 days before the procedure to allow further actions, if necessary, 1 day before the procedure, in order to achieve an INR less than 1.4. Also at 2 days before the procedure, the patient was taught the self-injection method for full-dose LMWH, after which enoxaparin 80 mg was self-administered subcutaneously every 12 h until 12 h before the endoscopy (for a total of 4 LMWH doses). The day before the procedure, the INR was 1.4.

During the endoscopic procedure, 3 biopsy samples were harvested, which led to a diagnosis of gastritis with some pyloric narrowing. The patient tolerated the procedure well, and enoxaparin and warfarin therapy was restarted in the evening on the day of the procedure. A warfarin dosage (5 mg daily) slightly above the preprocedural maintenance dose was initiated, with progressive increases to be implemented in accordance with INR results. Enoxaparin injections were continued for 15 days after the procedure, until the patient's INR

Table 1. Anticoagulation Management for First Endoscopic Procedure for a Patient Receiving Long-Term Warfarin Therapy

Date (Relative to Procedure)	Warfarin (mg)	Enoxaparin (80-mg dose)	INR
P – 27 days	4 or 5*	0	4.0
P – 16 days	4 or 5*	0	4.1
P – 6 days	4	0	4.6
P – 5 days	3	0	Not measured
P – 4 days	5	0	Not measured
P – 3 days	4	0	Not measured
P – 2 days†	0	q12h	Not measured
P – 1 day	0	q12h	1.4
Day of procedure (P)	5	Evening only	Not measured
P + 1 day	5‡	q12h	Not measured
P + 5 days	7	q12h	1.7
P + 6 days	5‡	q12h	Not measured
P + 8 days	7	q12h	Not measured
P + 9 days	5‡	q12h	2.4
P + 12 days	7	q12h	3.0
P + 13 days	6	q12h	Not measured
P + 14 days	5	q12h	Not measured
P + 15 days	5	Morning	3.6

INR = international normalized ratio, P = day of procedure.
*Warfarin 4 mg on Mondays and Fridays, 5 mg on all other days of the week at the time this INR was obtained.
†Vitamin K_1 (phytonadione) 5 mg PO was administered once, at 2 days before the procedure.
‡Warfarin 5 mg daily at the time this INR was obtained.

was within the therapeutic range (Table 1). Following the endoscopy, antibiotics were prescribed for *Helicobacter pylori*. Despite this therapy, the patient continued to report vague, ongoing gastrointestinal complaints, specifically nausea, a feeling of fullness, and vomiting.

Anticoagulation Management for Second Endoscopic Procedure

For 18 days before the second endoscopic procedure (in September 2003), the patient was taking warfarin 4.5 mg daily (Table 2). Five days before the procedure, the INR was 3.7; the patient was instructed to take the last warfarin dose 3 days before the procedure, to take vitamin K_1 2 mg orally 48 h before the procedure, and to begin self-administration of enoxaparin 80 mg subcutaneously every 12 h, beginning at 48 h before the procedure. The day before the procedure, the INR was 2.4, and an additional dose of vitamin K_1 (1 mg orally) was prescribed. As planned, the last enoxaparin dose was administered 12 h before the scheduled procedure. On the morning of the procedure, the INR (determined with a Coaguchek S meter [Roche Diagnostics, Manheim, Germany]) was 1.4. The day after the endoscopy, warfarin and enoxaparin therapy was reinstated. Enoxaparin injections were continued for 10 days after the procedure, until the patient's INR approached target.

DISCUSSION

To our knowledge, this is the first reported case in which oral vitamin K_1 was used in the preprocedural management of a patient who was receiving long-term warfarin therapy and for whom an INR less than 1.4 was required. The use of oral vitamin K_1, instead of sole reliance on withholding of warfarin therapy, was selected for this patient to quickly and effectively reduce the INR to less than 1.4, because the patient had a higher-than-usual target INR range (i.e., 3.5–4.0, rather than the usual 2.0–3.0 or 2.5–3.5). In using this form of therapy, it was anticipated that the number of LMWH injections could be minimized. Oral vitamin K_1 and LMWH were administered concomitantly, which allowed the patient to receive therapeutic anticoagulation until the time of the endoscopic procedure (since the onset of oral vitamin K_1 activity is usually observed within 12 h of administration,[8] whereas the activity of enoxaparin peaks between 3–6 h after administration). Before each of the endoscopic procedures, the patient's INR declined to a safe range, and no endoscopic-related bleeding or clotting complications occurred.

The majority of the literature addressing oral vitamin K_1 focuses on its use in the management of critical INR values (above 5.0).[1] Relative to simply withholding warfarin therapy, oral administration of vitamin K_1 was more effective in lowering INR to less than 5.0 within

Table 2. Anticoagulation Management for Second Endoscopic Procedure for a Patient Receiving Long-Term Warfarin Therapy

Date (Relatice to Procedure)	Warfarin (mg)	Vitamin K_1 PO (mg)	Enoxaparin (80-mg dose)	INR
P – 26 days	5 or 4.5*	0	0	3.9
P – 19 days	3 or 4.5†	0	0	4.5
P – 12 days	4.5‡	0	0	3.4
P – 5 days	4.5‡	0	0	3.7
P – 2 days	0	2	q12h	Not measured
P – 1 day	0	1	q12h	2.4
Day of procedure (P)	0	0	None	1.4 (POC)
P + 1 day	7	0	q12h	Not measured
P + 2 days	7	0	q12h	Not measured
P + 3 days	4.5‡	0	q12h	Not measured
P + 6 days	5.5‡	0	q12h	2.2
P + 10 days	5.5‡	0	q12h	3.4
P + 11 days	5 or 4.5§	0	Morning	Not measured
P + 16 days	4.5‡	0	0	3.5

INR = international normalized ratio, P = day of procedure, POC = point-of-care result.
*Warfarin 5 mg on Tuesdays and Fridays, 4.5 mg on all other days of the week at the time this INR was obtained.
†Warfarin 3 mg for one day, then 4.5 mg daily.
‡Daily dose.
§Warfarin 5 mg on Saturdays and Tuesdays, 4.5 mg on all other days of the week.

24 h.[9,10] Current recommendations to achieve therapeutic INR values in the setting of critical INR management (i.e., INR between 5.0 and 9.0) for patients who are not bleeding is to omit 1 or 2 doses of warfarin and to administer vitamin K_1 1.0–2.5 mg orally.[1,2] Using this strategy, an optimal dose of vitamin K_1 should bring the INR into the therapeutic range within 24-48 hours without causing warfarin resistance upon reinitiation of oral anticoagulation. In the case reported here, however, oral vitamin K_1 was used to lower the therapeutic INR to less than 1.4.

Before this patient's first endoscopic procedure, 5 mg of vitamin K_1 was administered to normalize the INR, but a lower dose of vitamin K_1 was administered before the second procedure to facilitate reversal of the effects of warfarin. After the first procedure, a period of 15 days of oral warfarin therapy was required to achieve a therapeutic INR (which necessitated prolonged postprocedural LMWH therapy), perhaps because of the relatively high dose of vitamin K_1 that had been administered (5 mg). The available literature suggests that oral doses of just 1.0 to 2.5 mg are needed to achieve therapeutic INR values in the setting of critical INR management (INR 5.0–9.0).[9] Therefore, a dose of 2 mg of vitamin K_1 was selected the second time the patient required reversal of anticoagulation, and higher postprocedure doses of warfarin were administered to allow a more rapid return to therapeutic INR. Twenty-four hours after receiving the 2-mg dose of oral vitamin K_1, the patient's INR had declined to 2.4; a second dose of 1 mg was administered, which yielded an acceptable INR of 1.4 by the morning of the procedure. Despite using higher postprocedure doses of warfarin after the second procedure, an 11-day period of therapy was required to achieve the target INR.

Preprocedural administration of oral vitamin K_1 (on the day before the invasive procedure) has been reported for patients with INR greater than 1.8; the authors of that report[5] recommended administration of a small (but unspecified) dose of vitamin K_1. Wentzien and others[11] reported the use of oral vitamin K_1 at mean doses (± standard deviation) of 5.0 ± 0.3 mg for preprocedural management of patients with initial INR values of 2.6 ± 0.1. The patients in that study were undergoing minor surgical or dental procedures and were asked to continue their warfarin therapy without interruption. Although the study focused on preprocedural administration of oral vitamin K_1, it differed from the case reported here in several ways: the patient in the current case had a higher-than-normal INR target; the endoscopy procedure for the current patient was more invasive than the procedures reported by Wentzien and others,[11] and temporary reversal of anticoagulation was therefore required; and the patient in the current case was at high risk of thrombosis and required bridging therapy with LMWH.

Our experience suggests that oral administration of vitamin K_1 2 days before an invasive procedure is effective at lowering the INR to a safe level in a patient with an elevated INR target. The 5-mg dose used with the first procedure may be too aggressive, in that it resulted in the need for prolonged administration of LMWH after the procedure. However, our experience with the second procedure indicated that a 2-mg dose was insufficient to achieve INR less than 1.4 within 24 hours, which led us to give a supplemental dose of 1 mg. Although the number of postprocedure LMWH injections was reduced with the lower dose of vitamin K_1, we also used higher warfarin doses. On the basis of our experience in this case, it appears that oral vitamin K_1 3 to 5 mg administered 48 h before an invasive procedure is effective at reversing warfarin-induced anticoagulation.

The dose of oral vitamin K_1 needed to normalize a therapeutic INR appears to be larger than the dose required to lower a critical INR value (i.e., INR 5.0-9.0) into the therapeutic range (i.e., 2.0–3.5). In addition, to minimize the number of postprocedural injections of LMWH, it seems appropriate to administer higher doses of warfarin for a few days. Clearly, further investigation of the effectiveness of oral vitamin K_1 in preprocedural management of warfarin-induced anticoagulation is required.

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