CASE REPORT

Warfarin Re-initiation Gone Awry: A Case of Inadvertent Overdose Mandating Critical INR Management

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NTRODUCTION

Warfarin is a commonly used anticoagulant for the primary or secondary prevention of thrombotic events.[1] Tremendous inter-individual variability in warfarin dosing is apparent, necessitating frequent monitoring via the international normalized ratio (INR). The most feared complication of warfarin therapy is major bleeding, and the risk of this problem increases when the INR exceeds 4.0.[2] Critical INR values (defined in the Edmonton region of Alberta Health Services as an INR > 5.0; the definition may vary by jurisdiction) are reported urgently to clinicians to enable prompt patient management. For ambulatory patients who are not bleeding, strategies to manage critical INRs include withholding warfarin therapy, with the option of administering oral vitamin K_1, but guidelines vary and have changed over time (Table 1).[1,3,4]

It is common for patients who are taking warfarin to have their therapy interrupted, for example, when they undergo invasive procedures. For patients at higher risk of thrombosis, low-molecular-weight heparin (LMWH) is commonly prescribed during both the washout period for warfarin (before the procedure) and the build-up period for warfarin (after the procedure).[5] The duration of postprocedure LMWH depends on the time it takes for the patient's INR to reach a therapeutic level. Clinicians typically restart warfarin at the patient's prior maintenance dose,[6,7] although in a previous study, we found that it took a median of 20.5 days at the prior maintenance dose to reach a therapeutic INR[8]; prolonged LMWH therapy is needed during this time.

Reported here is a case of warfarin re-initiation, in which the clinic's usual strategy, based on prior maintenance dosing, resulted in inadvertent warfarin overdose requiring management of a critical INR. For both of these aspects of warfarin management (re-initiation of warfarin and management of critical INR),

the literature is reviewed and applied to this case, with emphasis on practical management issues.

CASE REPORT

A 25-year-old woman who was referred to the Anticoagulation Management Service at the University of Alberta Hospital in November 2008 had been taking warfarin (INR range 2.0–3.0) since having a saddle pulmonary embolism in July 2007.* Her previous medical history included antithrombin III deficiency, protein C deficiency, factor V Leiden mutation, and a family history of thrombophilia. She was not taking any other medications.

Under the care of the Anticoagulation Management Service, her INR was maintained within the therapeutic range with a total weekly dose of warfarin 86 to 91 mg. She was adherent with warfarin therapy and reported missing 1 or 2 doses per year. She indicated a desire to become pregnant, with plans to try to conceive in early 2012. In collaboration with the Obstetric Medicine Clinic, the clinic instructed her to continue taking warfarin while attempting to become pregnant and to perform pregnancy tests every 1 to 2 weeks. In May 2012, she reported a positive result on a pregnancy test, and it was determined that she was at 4 weeks' gestation. She was instructed to discontinue the warfarin, and enoxaparin 80 mg subcutaneously every 12 h was prescribed (serum creatinine 61 μmol/L in October 2011, weight 78 kg in May 2012). Throughout her pregnancy, the LMWH therapy was managed by the Obstetric Medicine Clinic. The patient gave birth on January 17, 2013, and the Anticoagulation Management Service became involved in her care again, for re-initiation of warfarin on February 1 (Figure 1). At that time, she was continuing to self-administer enoxaparin 80 mg subcutaneously every 12 h (weight 77 kg in February 2013).

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*The patient provided consent for publication of this case report.

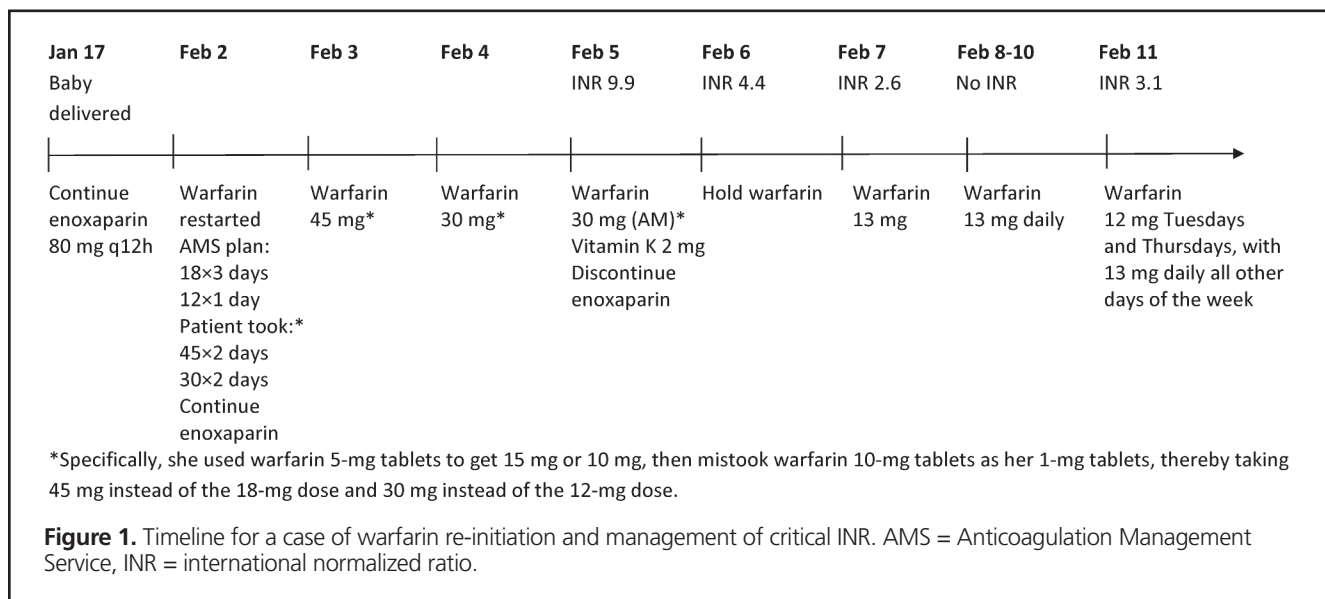**Table 1. Recommendations for Managing Critical International Normalized Ratio (INR)***

Source	Lower Critical Result	Higher Critical Result
ACCP (2008)[1]	"For patients with an INR ≥ 5.0 but < 9.0 and no significant bleeding, we recommend omitting the next 1 or 2 doses, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level (Grade 1C). Alternatively, we suggest omitting a dose and administering vitamin K_1 (1–2.5 mg) orally, particularly if the patient is at increased risk of bleeding (Grade 2A)."	"For patients with an INR ≥ 9.0 and no significant bleeding, we recommend holding warfarin and administering a higher dose of vitamin K_1 (2.5–5 mg) orally, with the expectation that the INR will be reduced substantially in 24–48 h (Grade 1B)."
ACCP (2012)[3]	"For patients taking VKAs with INRs between 4.5 and 10.0 and with no evidence of bleeding, suggest against routine use of vitamin K_1 (Grade 2B)."	"For patients taking VKAs with INRs > 10.0 and no evidence of bleeding suggest that oral vitamin K_1 be administered (Grade 2C)."
ESC/EACTS (2012)[4]	"… to stop oral anticoagulation and to allow the INR to fall gradually or to give oral vitamin K_1 in increments of 1 or 2 mg."	"If the INR is > 10, higher doses of oral vitamin K_1 (5 mg) should be considered."

ACCP = American College of Chest Physicians, ESC/ EACTS = European Society of Cardiology/ European Association for Cardio-Thoracic Surgery, VKA = vitamin K antagonist.
*Definitions of grades appearing in this table: Grade 1B = strong recommendation, moderate quality evidence; Grade 1C = strong recommendation, low or very low quality evidence; Grade 2A = weak recommendation, high quality evidence; Grade 2B = weak recommendation, moderate quality evidence; Grade 2C = weak recommendation, low quality evidence.

The patient had some warfarin left over from before her pregnancy and was also given new prescriptions for warfarin 1-mg, 5-mg, and 10-mg tablets, which she planned to fill as needed. Given that her prior warfarin requirement had been 12–13 mg daily, she was instructed to take 18 mg daily for 3 days and then 12 mg on the fourth day and to have standard laboratory venipuncture for an INR and complete blood count on the fifth day (i.e., February 5). The enoxaparin therapy was to be continued.

On the afternoon of February 5, her INR was reported to be 9.9, and her complete blood count was unchanged from previous results. The clinical assessment indicated no bleeding or bruising and did not reveal any reason (changes in health, medications, or lifestyle) for this critical INR value. Upon review of warfarin dosing, it was determined that she was taking the drug in the morning and that she had taken warfarin 18 mg on February 2 and 3 and warfarin 12 mg on February 4 and 5. The patient was instructed to discontinue enoxaparin and withhold

Figure 1. Timeline for a case of warfarin re-initiation and management of critical INR. AMS = Anticoagulation Management Service, INR = international normalized ratio.

warfarin. Oral vitamin K_1 2 mg was prescribed, and the patient was counselled about the increased risk of bleeding and general precautions to be taken with a critical INR. She was instructed to have blood drawn for INR on February 6 (i.e., the next day) and to not take any warfarin that morning.

Early on February 6, the patient called back to report that on February 2 through 5, she had mistaken her warfarin 10-mg tablets for warfarin 1-mg tablets; as a result, she had inadvertently taken warfarin 45 mg on February 2 and 3 and warfarin 30 mg on February 4 and 5. Later that day (February 6), her INR was 4.4, and she continued to deny any notable findings. Withholding of warfarin was continued, and on February 7, her INR was 2.6. Warfarin 13 mg daily was then prescribed (to start on February 7), and INR measured on February 11 was 3.1. Ultimately, her warfarin requirements to maintain her target INR (84–90 mg weekly) were similar to prepregnancy dosing.

DISCUSSION

This case featured 2 distinct aspects of warfarin management: re-initiation of warfarin in the setting of known maintenance dosing and management of critical INRs in an ambulatory, nonbleeding patient. Warfarin re-initiation with known prior maintenance dosing differs from de novo initiation of warfarin therapy, as the prior warfarin requirements can be used to guide future dosing decisions, the most conservative strategy being re-initiation at the prior maintenance doses. Guidelines for management of critical INRs have been published by North American[1,3] and European[4] organizations, but they differ from one another and have changed over time (Table 1). This variability highlights the need to individualize management strategies, particularly in unique clinical cases.

Re-initiation of Warfarin in the Setting of Known Maintenance Doses

Restarting warfarin in the setting of known prior maintenance doses most commonly occurs when periprocedural management is required. Supporting data take the form of expert opinion based on observational studies, with randomized trials currently underway.[5] Most authorities suggest restarting warfarin at the usual maintenance dose the evening of the day on which the procedure or surgery has taken place.[1,6,9,10] In our experience, however, resuming warfarin at the patient's usual maintenance dose following an elective procedure that did not require hospital admission resulted in a long delay (median 20.5 days) to achieve an INR of 2.0 or above.[8] During this prolonged interval, many patients must continue taking LMWH. These findings were supported by another anticoagulation management service, which reported that the duration of LMWH administration was significantly longer (mean ± standard deviation 12.0 ± 8.2 days) than that reported in clinical trials.[11] Patients' frustration with

this prolonged delay to reach an INR of 2.0 is attributable to the ongoing cost of the LMWH and the need to continue self-administration by injection.

The study institution's Anticoagulation Management Service typically restarts warfarin at 1.5 times the known maintenance dose for the first 2 to 3 days, followed by step-down to the usual maintenance dose for 1 to 2 days, with subsequent dosing guided by INR assessment.[8] As such, it takes a median of 5 days to achieve a therapeutic INR in the clinic's ambulatory population. This dosing strategy takes into consideration the delayed effect of warfarin and provides for 1 or 2 maintenance doses before the INR is measured to allow more time to see the effects of the initial reloading doses. Using a slightly different approach, others have resumed warfarin at twice the usual warfarin dose the evening of the procedure and reported the mean time to achieve INR above 2.0 as 4.6 days (range 2–10).[12]

As in the case reported here, the Anticoagulation Management Service at the study institution administers warfarin loading doses in conjunction with therapeutic LMWH administration, given the theoretical potential to induce a hypercoagulable state with depletion of proteins C and S. In the current case, the intent was to have the patient self-administer about 1.5 times the maintenance dose for 3 days, followed by her regular dose on day 4 and INR measurement on day 5. The patient typically took her warfarin in the morning, so she started her warfarin the morning after the consultation (i.e., February 2) and intended to take warfarin 18 mg for the first 2 days, followed by warfarin 12 mg daily. Given her morning warfarin intake, she had already taken her warfarin dose on February 5, the day when the critical INR result was obtained. She later realized that confusion with her tablets had resulted in an overt overdose. Specifically, on the first and second days (February 2 and 3), she used warfarin 5-mg tablets to get 15 mg and intended to take three 1-mg tablets for the total dose of 18 mg; similarly, on the third and fourth days (February 4 and 5), she used warfarin 5-mg tablets to get 10 mg and intended to take two 1-mg tablets for the total dose of 12 mg. However, for all of these doses, she mistook warfarin 10-mg tablets for 1-mg tablets, so her total doses were 45 mg on February 2 and 3 and 30 mg on February 4 and 5.

Warfarin Overdose

Cases of warfarin overdose (involving about 250 mg) were reported as early as 1978, and those early cases were treated with multiple days of very high doses of vitamin K_1 (repeated daily dosing of 10–40 mg),[13] on the hypothesis that the turnover rate of vitamin K_1 was much faster than that of warfarin.[14] In 2003, Isbister and others[15] published 3 cases of intentional warfarin overdose (120–150 mg). For patients at increased thromboembolic risk, where subtherapeutic warfarin therapy would necessitate heparin (as in the current case), these authors suggested to assess the INR every 6 h, with titration of IV vitamin K_1 0.5–2 mg as

long as the INR remains above 5.0.[15] The current case differed from these cases, however, in that the overdose involved much less warfarin, likely because the overdose was unintentional. The patient notified the Anticoagulation Management Service of the tablet mix-up the day after the critical INR was obtained, which meant that pharmacy staff had to initially manage this result as a critical INR without a clearly defined cause.

Management of Critical INR

Management of critical INRs in an ambulatory care setting encompasses making a determination that outpatient management can continue (by ruling out bleeding, bruising, or any other concerning issue that requires further assessment or referral to an emergency department), assessing the individual patient's risk of bleeding versus clotting (to determine the aggressiveness of INR management in the particular case), and assessing factors that might be causing or contributing to the critical INR result. In this case, the patient reported no bleeding or bruising, and no reason could be identified as contributing to this critical INR on the day it was reported. Her past history indicated that she was at high thromboembolic risk, given her extensive pulmonary embolus and documented hypercoagulable states. Her bleeding risk was low, with no identified risk factors for bleeding, which lent support to the attempt to prevent overcorrection of her warfarin therapy. The 2 strategies considered were withholding of warfarin (although she had already taken her warfarin on the day the critical INR result was obtained) and oral administration of vitamin K_1.

Withholding Warfarin

In the setting of critical INR management, all available data support holding warfarin therapy for 1 or 2 days, followed by INR reassessment.[3,4] A study assessing the rate of INR decay among patients with a mean entry INR of 8.1 (range 6.1–29.8) showed that after warfarin was held, 33% of the patients had an INR below 4 within 24 h, 55% within 48 h, 73% within 72 h, and nearly 90% within 96 h.[16] The patients with entry INRs above 10 (n = 13) took longer to reach an INR below 4 (mean 3.6 days) than those with entry INRs between 6.1 and 10.0 (n = 92; mean 2.9 days). This pattern was confirmed by another study, in which warfarin was withheld for patients with an entry INR above 10.0; for nearly half of the patients (n = 7 [47%]), the INR remained above 5.0 on day 3.[17]

In the case reported here, on the day that the patient's critical INR was reported, no reason could be identified for the critical INR, which left pharmacy staff to contemplate either laboratory error or an alteration in previous warfarin requirements as the cause of the INR value. Although laboratory error does occur, it is rare, and it was decided to not repeat INR testing the same day and to manage the critical INR accordingly. Even if the patient had taken the warfarin as prescribed (i.e., 18- and 12-mg doses instead of the later-discovered 45- and 30-mg doses), evidence[16,17] indicates that simply holding her warfarin dose the next day would have left the INR at a critical level (INR > 5.0) for at least another 48 to 72 h, exposing the patient to unnecessary risk of bleeding. As such, the option of oral vitamin K_1 therapy was pursued.

Administration of Oral Vitamin K_1

Numerous case series[17-24] and a few small randomized trials[25-28] support the use of small doses of oral vitamin K_1 (ranging from 1 to 5 mg) to reverse asymptomatic over-anticoagulation (INR > 4.5) in a reliable and predictable manner (Table 2). The amount given is guided by the specific level of the INR. Data support oral vitamin K_1 1–2.5 mg for those with INRs between 4.5 and 10,[20,21,24,25-28] whereas doses of 2–5 mg are supported for INRs exceeding 8.[18,19,22-24,27]

Although data support oral administration of vitamin K_1 to rapidly reverse supratherapeutic INRs to therapeutic INRs, it is still unknown whether this strategy reduces the likelihood of bleeding.[22,25] In a randomized, blinded trial evaluating 716 nonbleeding patients with INRs between 4.5 and 10 who received either oral vitamin K_1 1.25 mg or placebo, there was no significant difference in any aspect of bleeding at 90 days, despite a significantly greater decline in INRs in the vitamin K_1 group (from 5.95 to 3.17 in the vitamin K_1 group and from 5.75 to 4.40 in the placebo group; p < 0.001).[25] In a parallel cohort study of patients with INRs above 10, designed to assess whether low-dose (2.5 mg) oral vitamin K_1 reduced bleeding events, the overall bleeding rate was 22%, with 3.7% of patients having major bleeding within 90 days of the index INR.[22] This study lacked a control group,[22] and the placebo-controlled, randomized trial of patients with INRs between 4.5 and 10 described above[25] was underpowered to detect differences in major bleeding. Despite attempts to assess patient outcomes (i.e., bleeding) as opposed to surrogate measures (INR results), this question remains unanswered. In general, there is less merit to administering oral vitamin K_1 if the INR is between 5.4 and 7[25,28]; however, the more prolonged interval to decay for those with INR exceeding 8 suggests that there may be some benefit in doing so for these patients.[17-19,23,24]

In the case reported here, it was decided to administer oral vitamin K_1 2 mg and to reassess the INR the next day. This approach was based on the patient's young age (and anticipated quicker rate of warfarin decay) and the goal of sustaining an INR of at least 2, given her thromboembolic risk. The rationale for administering vitamin K_1 was 2-fold: first, the patient had already taken her warfarin dose that morning and it was anticipated that she would not experience any reduction in INR until she had missed her next dose the following morning; second, no reason for the critical INR could be discerned. Use of a 2-mg

Table 2. Effect of Oral Vitamin K_1 on Critical INR

Source and INR Eligibility	No.*	INR at Entry	Vitamin K_1 Dose (mg)	Outcome
Crowther et al. (2000)[26] INR 4.5–10	45	Mean ± SD 5.4 ± 1.0 (range 4.5–9.8)	1	INR next day: mean ± SD: 2.6 ± 0.9 < 1.8 for 16% 1.8–3.2 for 56% > 3.2 for 28%
Crowther et al. (1998)[21] INR 4.5–10	62	Mean 5.7 (95% CI 5.48–6.09), range 4.5–9.5	1	INR at 16 h: 2.86 (95% CI 2.50–3.23)
Crowther et al. (2002)[20] INR 4.5–10	26	Mean ± SD 5.8 ± 1.2	1	INR next day: mean ± SD: 2.9 ± 0.8 < 1.8 for 12% 1.8–3.2 for 57% > 3.2 for 31%
Crowther et al. (2009)[25] INR 4.5–10	347	Mean 5.95 (95% CI 5.83–6.07)	1.25	INR next day: mean 3.17 (95% CI 3.06–3.28)
Patel et al. (2000)[28] INR 6.0–10	15	Mean 7.2 (range 6.0–9.2)	2.5	Mean time ± SD to INR < 4: 1.4 ± 0.5 days Mean INR decrease ± SD: 4.85 ± 1.4 units
Weibert et al. (1997)[24] INR > 5	81	> 5.0 (n = 10 with INR > 10)	2.5	INR at 24 h: < 2.0 for 17% 2–5 for 72% > 5 for 10% (4 patients had entry INR > 10)

Lubetsky et al. (2003)[27]
 	
INR > 6
	47	INR category 6–10:
		  mean ± SD 7.7 ± 1.1
		  (range 6.1–9.6)
			2.5	INR next day:
				mean ± SD: 2.9 ± 0.8

	9	INR category > 10:
		  mean ± SD 13.0 ± 1.7
		  (range 10.4–15.1)
			5	INR at 48 h:
				mean ± SD: 2.8 ± 1.2

Denas et al. (2009)[23] INR > 10	104	Median 11.3 (IQR 10.6–13.1)	3	INR next day: median 2.9 (IQR 2.2–3.7)
Crowther et al. (2010)[22] INR > 10	107	Mean 12.6 (range 10–26.6)†	2.5	INR in 24 h: mean 4.7 (range 1.3–20.2)
Baker et al. (2006)[18] INR > 8	166	INR category 8.0–11.9	2.5	INR next day: median 3.5 < 2 for 8% 2–4.9 for 79% > 4.9 for 13%
	36	INR category 12.0–20.0	5	INR next day: median 3.0 < 2 for 17% 2–4.9 for 52% > 4.9 for 31%
	21	INR category > 20	5	INR next day: median 2.9 < 2 for 29% 2–4.9 for 42% > 4.9 for 29%
Chirputkar et al. (2006)[19] INR > 8	59	INR category 8–8.9	2	INR next day: < 2 for 21% 2–4 for 63% > 4 for 16%
	41	INR category 9–10.9	2	INR next day: < 2 for 20% 2–4 for 46% > 4 for 34%
	26	INR category > 11	2	INR next day: < 2 for 7% 2–4 for 70% > 4 for 22%

CI = confidence interval, INR = international normalized ratio, IQR = interquartile range, SD = standard deviation.
*Number of patients receiving vitamin K_1 with follow-up.
†Does not include 10 cases in which INR was above the limit of measurement.

dose was supported by the findings of a literature review[18,19,22,23] and the belief that this was a conservative amount of vitamin K_1, given the patient's high thromboembolic risk. The patient's INR was assessed the next day (result: 4.4), following which staff learned of the inadvertent overdose. Warfarin was again withheld, INR the next day was 2.6, and a maintenance dose of warfarin 13 mg daily was then instituted. When feasible, practice in the Anticoagulation Management Service is to routinely assess the INR the day after oral administration of vitamin K_1 to assess the patient's status and to ensure that warfarin is restarted in a timely manner to prevent subsequent subtherapeutic anticoagulation.

Previous studies assessing the use of oral vitamin K_1 have recommended restarting warfarin once the INR returns to the desired therapeutic range (often using an expanded range of ±0.2 INR units)[21,25] or once the INR falls below a critical level, either less than 5[18,24] or less than 4.[28] Delaying the re-initiation of warfarin places the patient at risk of subtherapeutic anticoagulation. The front-line clinician must appreciate that after 16–24 h, the effect of oral vitamin K_1 will be evident (when administered in small doses); however, the full impact of withholding warfarin will continue. As such, clinical practice at the study institution is to restart warfarin when the INR approaches or drops below 4 for most patients.

The root cause of the critical INR in this case was a warfarin tablet mix-up, which occurred despite the patient being reliable, well educated, and adept at taking different doses of warfarin on different days of the week. Given the variability in daily dosing, it is the clinic's practice, for most patients, not to prescribe a single warfarin tablet strength, but use of a single strength might have prevented the problem that occurred in this case.

CONCLUSION

This case featured several unique aspects of daily warfarin management, including re-initiation of therapy in the setting of known prior maintenance dosing and management of critical INRs, specifically by withholding warfarin, administering oral vitamin K_1, and re-initiating warfarin in a timely fashion afterward. Upon restarting warfarin in the setting of known prior maintenance dosing, use of higher warfarin doses (about 1.5 times the usual maintenance dose) for 2 or 3 days, followed by step-down to the maintenance dose, expedites the achievement of a therapeutic INR.[8] While it can be concluded that data support the use of oral vitamin K_1 to more quickly achieve a therapeutic INR in the setting of critical INR management in nonbleeding ambulatory patients,[25-28] no outcome data are available to support the contention that oral vitamin K_1 reduces bleeding.[22,25] Data do suggest that it is more compelling to administer oral vitamin K_1 to those with higher critical INRs (e.g., INR > 8), given the longer interval for the INR to decay back to the therapeutic range.[18,19,22-24,27] Ultimately, the use and dose of oral vitamin K_1 should be guided by the specific level of

the INR, the underlying reason for the critical INR, whether warfarin doses have already been administered on the day of the critical INR, and the individual patient's overall risk of thrombosis and bleeding. Prompt attention should be given to warfarin re-initiation once the INR is no longer critical, in an attempt to avoid subtherapeutic anticoagulation. Finally, patient education and clarity about warfarin dosing are paramount. Although the patient in this case was knowledgeable and familiar with warfarin therapy, an important dosing error still occurred, reinforcing the need to avoid making assumptions.

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