CLINICAL RESEARCH STUDY

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Reversal of Overanticoagulation in Very Elderly Hospitalized Patients with an INR above 5.0: 24-Hour INR Response after Vitamin K Administration

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ABSTRACT

BACKGROUND: Reversal of overanticoagulation to minimize the bleeding risk is important in elderly inpatients receiving vitamin K antagonist therapy. However, no study has specifically focused on this population. The objective of this study is to evaluate whether guidelines based on American College of Chest Physicians recommendations for the management of overanticoagulation (international normalized ratio [INR] ≥5.0) can apply to elderly inpatients, and notably allow 24-hour INRs to return to the 1.8-3.2 range in this population. The influence of different factors on the vitamin K response also was evaluated.

METHODS: Inpatients aged ≥75 years with INR ≥5.0 were included in this observational study. INRs were assessed on the day of the overdosage (Day 0) and on the following day (Day 1).

RESULTS: Of 385 Day 0 INRs ≥5.0 (239 patients; 86 ± 6 years), 217 were managed according to recommendations, with a mean INR decreasing from 6.8 ± 2.4 (range: 5.0-20.0) on Day 0 to 2.7 ± 1.3 (range: 1.1-10.1) on Day 1 ($P < .0001$); 55% of INRs were within the 1.8-3.2 range, 20% <1.8, and 25% >3.2. In the subset of Day 0 INRs between 5.0 and 6.0, mean INR decreased from 5.5 ± 0.3 to 2.7 ± 1.0 ($P < .0001$) on Day 1 after oral administration of 1 mg vitamin K1 (n = 121) and from 5.3 ± 0.3 to 5.0 ± 1.6 ($P = .149$) without vitamin K1 administration (n = 48). Among covariates entered in the multivariate analysis, including co-medications, only the vitamin K1 dose influenced Day 1 INRs, with higher doses of vitamin K1 associated with Day 1 INRs <1.8 ($P < .0001$).

CONCLUSION: In elderly inpatients with INR ≥5.0, both vitamin K antagonist dose omission and vitamin K1 administration according to recommendations were effective in reversing overanticoagulation, allowing most INRs to return to the 1.8-3.2 range without excessive overcorrection. Therefore, American College of Chest Physicians recommendations may be applied to elderly inpatients.

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KEYWORDS: ACCP recommendations; Elderly; INR; Overanticoagulation; Vitamin K; Vitamin K antagonist

The number of elderly patients who require anticoagulation is rising steadily, as the aging of the population is translating into increased prevalence of both atrial fibrillation and venous thromboembolism. Vitamin K antagonists (VKAs) are highly effective in preventing thromboembolism, yet remain underused in elderly patients.[1] VKAs have a narrow therapeutic index; so achieving effective, yet safe, anticoagulation is challenging in older patients. There is evidence that older age increases the risk and severity of bleeding

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during VKA therapy.[2-7] Compared with younger patients, elderly patients require lower dosages and are more prone to anticoagulation instability, as they often have comorbidities and use drugs that interact with VKAs. The risk of major bleeding increases sharply when international normalized ratio (INR) is >5.0 and remains above the therapeutic range for a prolonged period.[8] Therefore, optimal reversal of overanticoagulation may contribute to decreasing the bleeding risk, especially in the elderly.[9,10]

In patients on VKA presenting with major bleeding, prothrombin complex concentrates (PCC) and vitamin K1 (vitK1) usually are given to reverse anticoagulation. In patients with high INRs but no significant bleeding, the usual strategy is VKA dose omission with or without vitK1 administration.[11-15] In patients with INRs between 5 and 6, the treatment is controversial, as some guidelines recommend the use of vitK1,[9] whereas others suggest that merely omitting the VKA is sufficient to restore the INR to the target range.[16] However, none of the available recommendations for anticoagulation reversal are based on studies that focused specifically on elderly patients, so it is not clearly established whether they apply to this population. We are aware of a single retrospective cohort study, conducted in older outpatients with INRs >6.0 (239 patients ≥75 years) and designed to determine the predictors of INR normalization after withholding 2 warfarin doses.[14] Advanced age was an independent risk factor for a prolonged time to INR normalization, with the odds of having an INR ≥4.0 after 2 warfarin dose omissions increased by 18% for each decade of age.[14] The patients at highest risk for a prolonged time to INR normalization were those aged ≥80 years who were taking 15 mg or less of warfarin per week.[14]

Ensuring optimal anticoagulant therapy in the elderly has received close attention in our teaching hospital for many years.[17-20] In addition to recommendations on anticoagulant therapy, we implemented guidelines for managing overanticoagulation in elderly inpatients based on American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy recommendations.[21] To evaluate these guidelines for managing overanticoagulation (INR ≥5.0) in elderly hospitalized patients receiving VKA therapy, we conducted a cohort study in which we assessed the 24-hour INR response. We also analyzed factors influencing the vitK1 response and, specifically, comedications, because polypharmacy is very frequent in this population.

CLINICAL SIGNIFICANCE

- In hospitalized patients aged 75 years or older receiving vitamin K antagonist therapy who have an international normalized ratio in the range of 5-9 without signs of bleeding, low-dose oral vitamin K (1-2 mg) should be administered to correct overanticoagulation.
- In hospitalized patients aged 75 years or older receiving vitamin K antagonist therapy who have an international normalized ratio of 9 or higher without signs of bleeding, vitamin K doses of 5 mg or less may be more appropriate than doses >5 mg in order to avoid over-correction.

MATERIALS AND METHODS

Setting, Patients, and Study Design

We conducted an observational study at the geriatric Charles Foix-Teaching Hospital in the Paris metropolis, France. Over a 2.5-year period (June 2006-December 2008), consecutive hospitalized patients aged ≥75 years who were taking warfarin or fluindione with a target INR of 2.0-3.0 and who experienced overanticoagulation defined as INR ≥5 were included in the study.

The primary outcome was to evaluate whether guidelines based on ACCP recommendations for the management of overanticoagulation (INR ≥5.0) allowed INRs to return to the 1.8-3.2 range in elderly inpatients. The secondary outcomes were to evaluate whether these guidelines allowed return of INRs to the 1.5-4.5 range and to analyze factors that influenced the response to vitK1.

The guidelines for managing VKA overdosage in elderly hospitalized patients, based on the 7th ACCP Conference recommendations,[21] are as follows: in patients with INR ≥5.0 and no serious bleeding, the VKA is withheld, vitK1 is given in a dose that depends on the INR (Table 1), and the INR is determined on the next day. In patients presenting with serious bleeding, the VKA is withheld, 10 mg vitK1 (Vitamine K1, Roche, Basel, Switzerland) is given by slow intravenous infusion supplemented with PCC. To enhance physician adherence to the guidelines, we supplied each physician with a pocket-sized card listing the recommendations. The physician adherence to guidelines was assessed based on the following: omission of the VKA dose, administration of vitK1 (time, dosage, route); INR measurement on Day 1; and administration of PCC in patients with severe bleeding.

To assess the return to the 1.8-3.2 and 1.5-4.5 ranges, we analyzed Day 0 (the day with the INR ≥5) and Day 1 (the following day) INRs. The mean ± SD (range) Day 0 and Day 1 INRs and the percentages of Day 1 INRs in the 1.8-3.2 range, in the 1.5-4.5 range, <1.8, <1.5, >3.2, and >4.5 were calculated. Excluded from the analysis were INRs ≥5 for which PCC was administered.

In order to analyze factors that may influence the response to vitK1 K, for each patient we recorded age, sex, indication and type of VKA therapy, the VKA daily dose, the number of comedications, and serious bleeding events on Day 0.[22] For each episode of overanticoagulation, we listed comedications known to interfere with VKA (amiodarone, antibiotics, systemic or topical azole antifungal

Table 1 Guidelines for Managing Elevated INRs or Bleeding in Patients Receiving Vitamin K Antagonist Therapy*

Condition	Description
INR ≥5.0 but <9.0, no significant bleeding	Omit dose and give vitamin K1 (1-2.5 mg orally). Monitor the next day and use additional vitamin K1 if necessary.
INR ≥9.0; no significant bleeding	Hold VKA therapy. Give higher-dose vitamin K1 (5-10 mg orally). Monitor the next day and use additional vitamin K1 if necessary. Resume therapy at lower dose when INR therapeutic.
Serious bleeding at any elevation of INR	Hold VKA therapy and supplement with prothrombin complex concentrates. Give vitamin K1 (10 mg by slow intravenous infusion). Vitamin K1 can be repeated every 12 hours.

INR = international normalized ratio; VKA = vitamin K antagonist.
*Based on 7th American College of Chest Physicians Conference recommendations.[21]

agents, acetaminophen >4 g/day for at least 4 days, proton-pump inhibitors, serotonin reuptake inhibitors, statins, L-thyroxine, allopurinol, colchicine) added or stopped (rifampicin) within 10 days before the episode.[23-25]

Data Source

All medications, the VKA daily dose, and the measures taken to reverse the overanticoagulation (VKA dose omission, vitK1, and PCC administration) were collected by searching the hospital pharmacy computer database. INRs, all centrally measured at the hospital laboratory using STA-Neoplastin CI from Diagnostica Stago (Asnières sur Seine, France) on a STAR with an International Sensitivity Index of about 1.6, were taken from the laboratory database. A permanent Patient Identification Number is assigned to every hospitalized patient; this unique number links to both databases and patient records. A standardized data collection form was used for each patient to record age, sex, indication of VKA therapy, and serious bleeding events on Day 0.[22]

This study was approved by the Comité pour la Protection des Personnes (CPP)-Ile-de-France-VI, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.

Statistical Analysis

Day 1 INRs were compared with Day 0 INRs using a 2-way unbalanced analysis of variance with patients as random effect and Day as fixed effect. We performed univariate then multivariable analyses to evaluate whether patient and treatment characteristics influenced the response to vitK1 administration, coded as a qualitative variable with 3 values: "INR <1.8," "1.8≤ INR ≤3.2," and "INR >3.2." The qualitative variables tested were sex, type of VKA (warfarin/fluindione), indication (atrial fibrillation, venous thromboembolism, or arterial thrombosis) of VKA, and addition or withdrawal of at least one VKA-interfering medication within 10 days before Day 0. The quantitative variables tested were age, Day 0 INR, vitK1 dose, VKA daily dose, number of comedications on Day 0, and of VKA-interfering medications added or withdrawn within 10 days before Day 0. In univariate analysis, unbalanced analyses of variance were used for quantitative variables and Fisher's exact tests for qualitative ones. Variables with P-values <.10 by univariate analysis were entered into a stepwise logistic regression analysis. The dependent variable for logistic regression was "INR <1.8." Variables with P-values <.05 using the Wald test were retained in the final logistic model. All the tests were 2-sided and P-values <.05 were considered significant. Computations were performed using the SAS V9.2 statistical package (SAS Institute, Cary, NC).

RESULTS

Patient and Treatment Characteristics

Over the 2.5-year study period, 239 patients (aged 86.1 ± 6.5 years) experienced 385 INRs ≥5. The main patient and treatment characteristics are shown in Table 2. Most patients (71%) were treated with warfarin and the main indication was atrial fibrillation. The mean number of comedications was 8.4 ± 3.3 (0-18), their distribution is depicted in Figure 1. In 34% of excessive anticoagulation episodes, one or more VKA-potentiating drugs were added

Table 2 Characteristics of 239 Patients Receiving Vitamin K Antagonist

Patients, n	239
Age (years), mean ± SD (range)	86.1 ± 6.5 (75-101)
Females, n (%)	177 (74)
VKA	
Warfarin, n (%)	170 (71)
Fluindione, n (%)	69 (29)
VKA daily dose (mg)	
Warfarin, mean ± SD (range)	2.9 ± 1.5 (0.3-7.5)
Fluindione, mean ± SD (range)	13.8 ± 7.9 (2.5-40)
Indications for VKA (therapeutic INR range, 2.0-3.0)	
Atrial fibrillation, n (%)	174 (73)
Venous thromboembolism, n (%)	60 (25)
Arterial thrombosis, n (%)	5 (2)
INR ≥5, n	385
5 ≥ INR ≤6, n	228
6 < INR <9, n	116
INR ≥9, n	41
Number of concomitant medications on the day overanticoagulation was diagnosed, mean ± SD (range)	8.4 ± 3.3 (0-18)

INR = international normalized ratio; VKA = vitamin K antagonist.

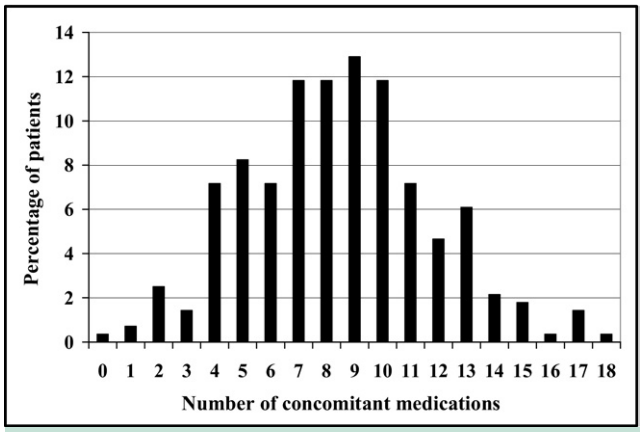

Figure 1 Distribution of concomitant medications (number/patient).

within 10 days before the episode, with antibiotics being the most frequent (Table 3). No patient had VKA-inhibiting drugs discontinued within 10 days before Day 0.

Day 1 INR response

On Day 0, the mean INR value (n = 385) was 6.6 ± 2.4 (5.0-20.0), 343 (89%) INRs were within the 5.0-9.0 range, and 42 (11%) INRs were ≥9.0. For 220 (57%) of these 385 Day 0 INRs ≥5.0, all criteria of physician adherence with guidelines were fulfilled: the VKA dose was omitted, vitK1 was administered on Day 0, the dosage and route of vitK1 administration (orally or intravenously) were in agreement with the guidelines (Table 1), and the INR was checked on Day 1. Three patients with serious bleeding (including 2 of them with intracerebral bleeding) received PCC and 10 mg of intravenous vitK1, according to the guidelines. They all had an INR >10. No other serious bleeding events were recorded on Day 0. Among the 165 INRs that were not managed according to recommendations, for 48 values between 5.0 and 6.0, VKA dose was omitted and vitK1 was not administered but the INR was checked on Day 1. In 11 cases, the appropriate vitK1 dose was given but the INR could not be measured the next day because the patients were discharged from the hospital in the interval. In the remaining 106 INRs ≥5, the guidelines were not followed for at least one reason: vitK1 was not administered (n = 51) despite an INR >6.0, vitK1 was not administered on Day 0 (n = 14), the vitK1 dose was inappropriate (n = 16), or the INR was not checked on Day 1 (n = 79).

In the subgroup of patients for whom INRs were managed with VKA dose omission and vitK1 administration according to guidelines, without PCC, the mean INR value decreased from 6.8 ± 2.4 (Range: 5.0-20.0) on Day 0 to 2.7 ± 1.3 (Range: 1.1-10.1) on Day 1 (Figure 2) ($P < .0001$) (n = 217). Of these 217 values, 119 (55%) Day 1 INRs were in the 1.8-3.2 range; 44 (20%) were <1.8, 54 (25%) were >3.2; 186 (86%) were in the 1.5-4.5 range, 14 (6%) were <1.5 (marked overcorrection), and 17 (8%) were >4.5 (marked undercorrection).

In the subgroup of patients with INRs between 5.0 and 6.0 who were managed with VKA dose omission but no vitK1, mean INR decreased slightly but not significantly, from 5.3 ± 0.3 (5.0-6.0) on Day 0 to 5.0 ± 1.6 (2.3-10.0) on Day 1 ($P = .149$) (n = 48) (Figure 2). Of these 48 Day 1 INRs, 4 (8%) were in the 1.8-3.2 range, 44 (92%) were >3.2, 29 (60%) were >4.5, and none were <1.8. In comparison, in the subgroup managed according to guidelines, 121 Day 0 INRs were in the 5.0-6.0 range, with the mean INR decreasing from 5.5 ± 0.3 (5.0-6.0) on Day 0 to 2.7 ± 1.3 (1.2-5.6) on Day 1 ($P < .0001$) after oral administration of 1 mg vitK1 (Figure 2). Of these 121 Day 1 INRs, 68 (56%) were in the 1.8-3.2 range, 30 (25%) were >3.2, 23 (19%) <1.8, 107 (88%) were in the 1.5-4.5 range, 7 (6%) were >4.5, and 7 (6%) <1.5.

Factors Influencing vitK1 Response

Among the study variables, none influenced the return of INRs to the 1.8-3.2 range or to values >3.2 on Day 1; only the vitK1 dose and Day 0 INR value were significantly associated with Day 1 INRs <1.8 in the univariate analysis. By multivariate analysis, only the vitK1 dose that is closely linked to Day 0 INR value remained significant, with higher doses of vitK1 associated with Day 1 INRs <1.8 (odds ratio = 1.31, 95% confidence interval, 1.15-1.49, $P < .0001$).

When we analyzed the INR response to vitK1 according to the dose in the group of INRs managed according to recommendations (Table 4), we found that doses of 1-1.5 mg and of 2-2.5 mg produced similar proportions of Day 1 INRs in the 1.8-3.2 range, <1.8, and >3.2. With these vitK1 doses, fewer than 15% of Day 1 INRs were <1.5 or >4.5. In patients given 5 mg of vitK1, more than half the Day 1 INRs were in the 1.8-3.2 range, 45% were <1.8, and all were in the 1.5-4.5 range. Finally, in patients given more than 5 mg of vitK1, more than half the Day 1 INRs were <1.8, one third were <1.5, and none were >4.5.

DISCUSSION

This study is the first to address the management of overanticoagulation in very elderly inpatients (n = 239, mean

Table 3 Vitamin K Antagonist-potentiating Drugs Added within 10 days before the Episode of Overanticoagulation

Potentiating Drugs	n (%)
Antibiotics	60 (68)
Systemic/topical azole antifungal agents	13 (15)
Proton-pump inhibitors	11 (13)
Amiodarone	7 (8)
Serotonin reuptake inhibitors	4 (5)
Statins	8 (9)
L-thyroxin	2 (2)
Colchicine	2 (2)
Tramadol	1 (1)

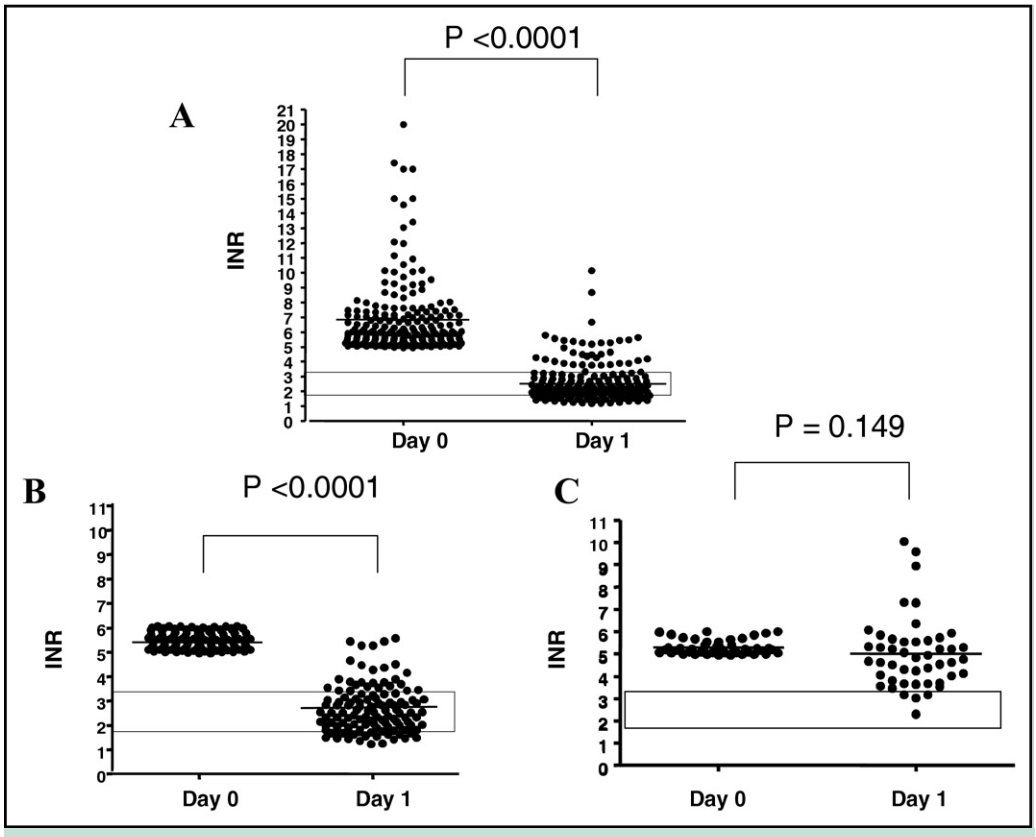

Figure 2 Day 0 and Day 1 international normalized ratios (INRs), and *P* values for the difference: (**A**) 217 Day 0 INRs managed according to recommendations.
(**B**) 121 Day 0 INRs between 5.0 and 6.0 managed with VKA dose omission and vitamin K1 administration according to recommendations.
(**C**) 48 Day 0 INRs between 5.0 and 6.0 managed with VKA dose omission but no vitamin K1 administration.
The therapeutic range 1.8-3.2 is represented by the rectangle.

age 86 years) with a substantial number of comedications. We found that the guidelines based on the grade 2C (observational studies) ACCP recommendations were effective in returning most INRs to the therapeutic range within 24 hours.[21] Indeed, after vitK1 administration according to the guidelines, 86% of Day 1 INRs were in the 1.5-4.5 range, and 55% were within the narrower and safer 1.8-3.2 range. We then specifically focused on Day 0 INRs between 5.0 and 6.0. When the VKA dose was omitted without vitK1 administration, only 8% of Day 1 INRs were in the 1.8-3.2 range and 92% were >3.2; in contrast, when low-dose vitK1 was given orally (1 mg) according to recommendations, 56% of Day 1 INRs were between 1.8 and 3.2, and 88% between 1.5 and 4.5.

Table 4 Day 1 INRs (n, %) Within Various Ranges on the Day after Recommended Vitamin K1 Administration, According to the Vitamin K1 Dose

		Vitamin K1 (mg)			
		1-1.5*	2-2.5†	5‡	>5§
	n	170	22	11	14
INR ranges	1.8-3.2	97 (57%)	11 (50%)	6 (56%)	5 (36%)
	>3.2	46 (27%)	7 (32%)	0	1 (7%)
	<1.8	27 (16%)	4 (18%)	5 (45%)	8 (57%)
	1.5-4.5	148 (87%)	17 (77%)	11 (100%)	10 (71%)
	>4.5	14 (8%)	3 (14%)	0	0
	<1.5	8 (5%)	2 (9%)	0	4 (29%)

Day 0 INR values:
*5.8 ± 0.7 ; †6.6 ± 1.1 ; ‡10.1 ± 0.9 ; §13.8 ± 3.

Most studies evaluating the effectiveness of vitK1 to reduce elevated INRs were conducted in nonelderly outpatients. The results are difficult to interpret, given the wide range of vitK1 doses tested and target INR ranges after vitK1 administration.[15,26] In studies evaluating 24-hour INR outcomes, patients with baseline INRs between 4.0 and 10.0 were usually analyzed separately from those with baseline INRs >10.0.

A meta-analysis including 8 randomized controlled trials showed that among 321 patients with baseline INRs between 4.0 and 10.0, 82% had INRs in the 1.8-4.0 range 24

hours after fixed-dose vitK1 therapy (0.5-2.5 mg).[26] In a recent retrospective study including a large number of patients (n = 1043), after oral administration of 2 mg vitK1 to patients with INRs between 5.0 and 10.0, 90% of INRs were below 4.5.[10] Finally, in a double-blind placebo-controlled trial in patients much younger than ours with INRs in the 4.5-10.0 range, the proportion of patients with INRs of 1.8-3.2 on Day 1 was 20% with the placebo and 56% with vitK1 (1 mg).[27] Our findings in elderly inpatients are in agreement with these results obtained in nonelderly outpatients showing that low-dose vitK1 was more effective in returning INRs to the treatment range than simply withholding warfarin.[26,27] This effect of vitK1 is valuable, as prolonged exposure to risky INRs may increase the risk of bleeding, especially in the elderly.[28] Of note, in the new ACCP guidelines issued in 2008, administration of oral vitK1 in patients with mild to moderately elevated INRs without significant bleeding is now a grade 1A recommendation (ie, strong recommendation, high-quality evidence).[9]

Most trials of vitK1 included few patients with INRs >10.0. In these patients, vitK1 allowed INRs to lower, however, the optimal dose required is unclear, as the doses tested vary across trials.[15,26] In the meta-analysis including only 42 patients from 4 randomized controlled trials and 63 from 5 nonrandomized trials, 24 hours after a vitK1 therapy (0.5-5 mg), 52% of patients with INRs >10.0 at baseline had INRs of 1.8-4.0, and 43% still had INRs >4.0.[26] In a retrospective study testing 3 mg of oral vitK1, among 104 patients with INRs >10.0, 86% had INRs below 4.5 on the following day.[29] In our study, among patients with baseline INRs ≥9.0, 29% of those given more than 5 mg of vitK1 had Day 1 INRs <1.5, indicating marked overcorrection, whereas all those given 5 mg of vitK1 had Day 1 INRs in the 1.5-4.5 range. Moreover, in our population, the only variable that independently influenced the Day 1 INR response in the multivariate analysis was the vitK1 dose, with higher doses of vitK1 associated with Day 1 INRs <1.8. Interestingly, in the new ACCP recommendations issued in 2008, vitK1 doses of only 2.5-5 mg are recommended for patients with baseline INRs ≥9.[9] Another protocol that involves giving 3 mg of vitK1 to patients with INRs ≥10 also may be appropriate in the elderly and deserves further investigation.[10] However, overcorrection of the INR might not be considered a major problem in hospitalized patients; in this situation, patients can transitorily receive heparin or low-molecular-weight heparin.

Few studies on overanticoagulation reversal have assessed concomitant medications as a potential cause contributing to the elevation of INR, which is an important issue in elderly patients with comedications.[10,14] In our study, we not only recorded the number of comedications on Day 0, but we also identified the VKA-potentiating or -inhibiting drugs that were added or stopped within 10 days before the overdosage episode. This may explain our higher proportion (34%) of overanticoagulation episodes possibly related to medications, compared with others.[10,15] Antibiotics are known to be strongly associated with overanticoagulation and were the most frequent VKA-potentiating drugs identified in our study.[25,30,31] Moreover, we found that neither VKA-potentiating drugs added before the event nor the number of comedications or the VKA dose influenced the Day 1 INR response.

As with other studies on overanticoagulation reversal, one limitation of our study is that it was neither designed nor sized to evaluate the effect of vitK1 on clinical outcomes such as bleeding and thromboembolic events. However, there is widespread agreement that anticoagulation control influences anticoagulation-related outcomes.[9,32] One multicenter, randomized, placebo-controlled trial concluded that low-dose oral vitK1 did not reduce bleeding in warfarin recipients with INRs of 4.5 and 10.0, despite a more rapid correction in INR after vitK1 administration than without vitK1.[11] Only a randomized study on a large number of patients will be able to assess the effect of vitK1 on clinical outcomes in the elderly. Another limitation of our study is that patients with baseline INRs between 5.0 and 6.0 were not randomized to receive or not vitK1, so that a possible bias could exist regarding our findings. However, this issue was not the main aim of our study; only a randomized study could definitely confirm our results. Finally, 30% of the study patients were on fluindione, a VKA used mainly in France. However, like warfarin, fluindione has a long half-life and we showed that the type of VKA (warfarin or fluindione) did not influence the Day 1 INR response.

In conclusion, our results suggest that in elderly inpatients with INR ≥5.0, VKA dose omission with vitK1 administration, according to recommendations, reversed overanticoagulation, allowing most INRs to return to the 1.8-3.2 range without excessive overcorrection. Thus, the ACCP recommendations for reversing overanticoagulation seem to be appropriate in elderly hospitalized patients, most notably those with INRs <9.0. In elderly patients with INRs ≥9.0, vitK1 doses ≤5 mg as suggested in the 8th edition ACCP recommendations[9] may be better, to avoid overcorrection. We are currently evaluating a vitK1 dosing regimen that is more closely tailored to individual needs.

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