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Course of the International Normalized Ratio in response to oral vitamin K_1 in patients overanticoagulated with phenprocoumon

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Summary. Oral vitamin K_1 is used for the treatment of excessive anticoagulation. Detailed information on changes in the International Normalized Ratio (INR) in response to vitamin K_1 is not available. We therefore measured the INR for the first 7 d following the oral intake of 1–5 mg of vitamin K_1 in 24 patients routinely treated with phenprocoumon who had an INR $\geq$6·0 at presentation. On the first 2 d after administration of vitamin K_1, the mean INR decreased by 40% and 23% respectively. After day 2, the day-to-day proportional change in the mean INR depended on the dose of vitamin K_1 and varied from a decrease of 12% to an increase of 21%. On day 7 the mean INR was higher than on day 2 in three out of five treatment groups. Between day 2 and day 7, in general, 32% of the patients had an INR value within the target zone, 25% had an INR value $\geq$6·0 and 8% had an INR value <2·0. These findings suggest that our routine treatment of overanticoagulation in patients on phenprocoumon should be intensified to improve its efficacy.

Keywords: overanticoagulation, coumarin anticoagulants, vitamin K_1, International Normalized Ratio, efficacy.

Oral anticoagulants have a narrow therapeutic index (Rosendaal, 1996). The optimal therapeutic range of oral anticoagulant therapy, as recommended by the Federation of Dutch Thrombosis Centres, lies between 2·5 and 3·5 International Normalized Ratio (INR) or between 3·0 and 4·0 INR (Cannegieter *et al*, 1995; The SPIRIT Study Group, 1997), depending on the indication for treatment. When the INR is >6·0 the risk of bleeding, the most common adverse reaction to oral anticoagulants, sharply increases (Cannegieter *et al*, 1995). Therefore such an excess anticoagulant effect should be treated promptly and adequately.

In the absence of life-threatening haemorrhagic complications, the usual way to achieve a reduction in anticoagulant effect is to discontinue the drug for 2 or more days and, depending on the intensity of the INR value, administer 1–10 mg of vitamin K_1 orally (Federatie van Nederlandse Trombosediensten, 1987). Detailed information on changes in the International Normalized Ratio in response to vitamin K_1 is not available since INR values are usually not measured daily, but only after a week. The literature provides limited information: two studies have been performed on the response of the INR to oral vitamin K_1 (Weibert *et al*, 1997; Pengo *et al*, 1993). In one (Weibert *et al*, 1997) the INR was measured twice: 1 or 2 d after administration of vitamin K_1 and 4–7 d after warfarin therapy was resumed. In the other study (Pengo *et al*, 1993) the INR value was determined after 1, 2 and 9 d. These studies both focused on efficacy and expressed the results in the number of patients with an INR below or above 5·0. No data were given on changes in INR over time. Harrell & Kline (1995) reported on five patients in whom oral vitamin K_1 was used to treat overanticoagulation. After 1 or 2 d the INR had decreased by 58% to 89%.

To obtain detailed insight into the course of the INR after oral administration of vitamin K_1 and to test the efficacy of

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our routine treatment of overanticoagulation, we determined the INR value over 7 consecutive days in patients on phenprocoumon who had an INR >6·0 at presentation.

SUBJECTS AND METHODS

Patients treated with phenprocoumon (Marcoumar®) by the regional Red Cross anticoagulant clinic The Hague who were prescribed oral vitamin K_1 because of an INR value $\geq 6{\cdot}0$ between 9 June 1997 and 27 June 1997, were asked to participate in this prospective study. Patients treated with vitamin K_1 because of a subsequent medical intervention or whose prothrombin time had to be checked within 7 d were excluded.

On day 0 patients suspended phenprocoumon therapy and took an oral dose of vitamin K_1 (Konakion® Cremophor EL-based drop solution 20 mg/ml). This dose was determined by the INR value and the target zone of anticoagulation, according to an algorithm employed at the anticoagulant clinic (Table I). Because of individual factors, the algorithm could be deviated from. The required number of drops were taken with about half a cup of water. The day at which the patient restarted phenprocoumon, as well as the adjustment of the dosage, depended on the patient's individual circumstances: standard practice was to restart phenprocoumon on day 2 and to lower the dosage by about 15%.

Table I. Algorithm for the administration of vitamin K_1 in patients on phenprocoumon.

	Target zone of anticoagulation	
INR value	2·0–3·5 INR	2·5–4·0 INR
6·0–7·9	Optional	Optional
8·0–8·9	2 mg	1 mg
9·0–11·9	3 mg	2 mg
12·0–14·9	5 mg	4 mg

On the next 7 d after taking vitamin K_1, day 1 to day 7, venous blood samples were collected in 3·2% sodium citrate Vacutainer tubes. The patients were visited at home between 8.00 and 12.30 a.m. Within 5 h after collection the blood samples were centrifuged at 3000 rpm for 10 min and plasma was frozen at −20°C. Prothrombin times were measured after the 1-week follow-up in order not to affect treatment. All measurements were done at the same time on an automatic coagulation analyser (Electra 1600C). The thromboplastin used was a human recombinant tissue factor (Ortho® RecombiPlasTin) with an international sensitivity index of 1·05 (batch RTF-159).

To confirm the assumption of no effect of freezing on the prothrombin time measurement, two blood samples were taken on day 7. Of one of these samples plasma was frozen and the prothrombin time was measured afterwards. Of the other sample the prothrombin time was measured directly. The mean difference in the INR value between both samples was −0·1, 95% CI [−0·5; 0·3], indicating that freezing did not affect prothrombin time measurement.

To control for other factors that may affect the INR, patients were asked about their health and changes in co-medication and alcohol intake during the study period. In addition, the intake of vitamin K_1 and phenprocoumon were verified by questionnaire.

The course of the INR is described in terms of the proportional change in the mean INR between 2 consecutive days. Baseline INR and dose of vitamin K_1 are highly correlated: more vitamin K_1 is prescribed when the INR is higher (Table I). Therefore we also analysed patients separately according to the dose of vitamin K_1 (1, 2, 3, 4 or 5 mg), starting from the patients being compliant. To test the efficacy of the routine treatment of overanticoagulation, the frequency of INR values $\geq 6{\cdot}0$, INR values within the target zone (2·0–3·5 INR or 2·5–4·0 INR) and INR values <2·0 was calculated.

RESULTS

The number of patients treated with vitamin K_1 and fulfilling the inclusion criteria in the 3-week study period was 41. Of the 34 patients we were able to contact, 24 (71%) were willing to participate, 10 men and 14 women. One patient was lost to follow-up after day 2. The mean age of the patients was 70 years (range 42–87 years). They had been using phenprocoumon for 3 d to 19 years, with a median duration of use of 2 years and 4 months. Indications for anticoagulant

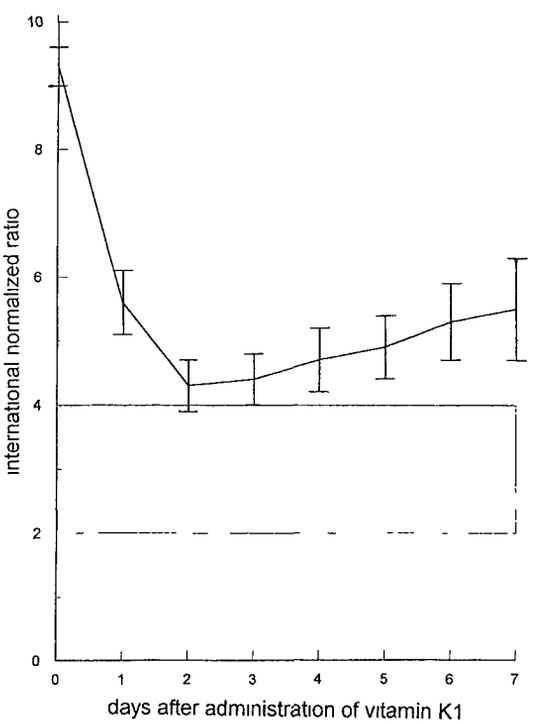

Fig 1. Course of the INR (mean ± SE) during the first week after administration of vitamin K_1 in patients overanticoagulated with phenprocoumon. The grey area indicates the target zone.

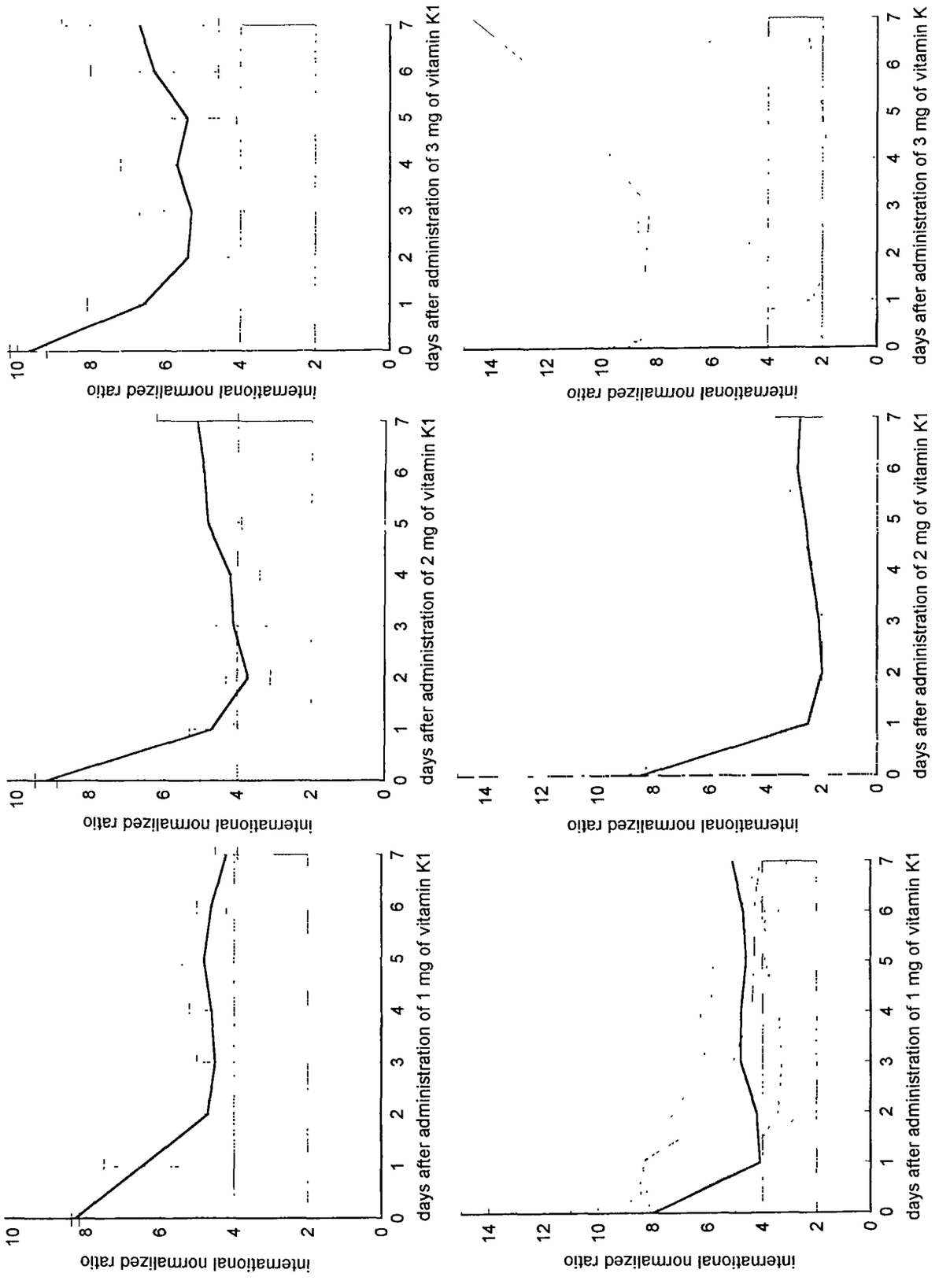

Fig 2. Course of the INR during the first week after administration of 1, 2 and 3 mg of vitamin K_1 in patients overanticoagulated with phenprocoumon (six, six and five patients respectively). The upper panel shows the mean INR ± SE. The bottom panel shows the course of the INR for the individual patients. The grey area indicates the target zone.

therapy were: cardiac disease (13 patients), cerebrovascular thromboembolism (four patients), peripheral arterial disease (three patients), venous embolism (two patients) and prophylactic venous treatment (two patients). The INR at presentation ranged from 7·3 to 14·2, with a mean of 9·3. The mean dose of vitamin K_1 prescribed was 2·7 mg (range 1–5 mg). In 17/24 patients the dose of vitamin K_1 was according to the algorithm; seven patients were prescribed a higher dose.

Fig 1 shows the course of the INR (mean ± SE) during the first week following administration of vitamin K_1 for all patients combined. On the first 2 d after administration of vitamin K_1, the INR decreased. On day 0, the mean INR was 9·3 ± 0·3. On day 1 and day 2, the mean values were 5·6 ± 0·5 and 4·3 ± 0·4 respectively. The proportional decrease in the mean INR was 40% on day 1 and 23% on day 2. After day 2, the mean INR did not decrease further, but slightly increased instead. The day-to-day proportional increase ranged from 2% to 8%. On day 7, the mean INR was 5·5 ± 0·8, 28% higher than the mean value on day 2. Remarkably, the mean INR did not reach the target zone on any of the 7 d.

The pattern of a decrease in the INR during the first 2 d following the intake of vitamin K_1, was observed for all doses of vitamin K_1 (Fig 2, upper panel) and for each of the patients (Fig 2, bottom panel). The extent of the response to oral vitamin K_1 varied greatly between patients: the range in INR values on day 0 was much smaller compared to the range on day 1 and day 2. In a few patients the INR did not decrease immediately but only after 1 d.

The course of the INR after day 2 was not consistent. The day-to-day proportional change in the mean INR depended on the dose of vitamin K_1 and varied from a decrease of 12% to an increase of 21%. On day 7, the mean INR was lower than on day 2 in the 1 mg and the 5 mg group and was higher than on day 2 in the 2, 3 and 4 mg group.

In addition to determining the effect of vitamin K_1 administration on the time-course of the INR, we also looked at its effectiveness in reducing the excess anticoagulant effect to lower and safer levels, preferably in the target zone. Of 24 patients with an INR ≥6·0 on day 0 who received 1–5 mg of vitamin K_1, eight (33%) still had an INR ≥6·0 on day 1, five (21%) on day 2, 3 and 4, seven (29%) on day 5 and day 6 and six (25%) on day 7. This concerned 12 individual patients, five of whom had an INR ≥6·0 on at least 5 d. All patients had taken <5 mg of vitamin K_1.

The number of patients with an INR value within the target zone was five (21%) on day 1, eight (33%) on day 2 and day 6, seven (29%) on day 3, day 4 and day 7, and nine (38%) on day 5. 12 different patients were involved; in three of them the INR was in the target zone for only 1 or 2 d.

An INR value <2·0 occurred in two patients (8%) on day 2, 3 and 4.

DISCUSSION

To obtain detailed insight into the course of the INR after oral administration of vitamin K_1 in doses of 1–5 mg, we measured the INR value for 7 consecutive days in patients on phenprocoumon with an INR ≥6·0 at presentation. The first 2 d after administration of vitamin K_1 the mean INR decreased; afterwards it slightly increased again. On all days the mean INR was above the target zone. After a week 25% of the patients were still overanticoagulated (INR ≥6·0), only 29% had an INR within the target zone and none were underanticoagulated.

The routine treatment of overanticoagulation employed at the anticoagulant clinic has not been tested extensively before and is an empirical one. Therefore one aim of this study was to test its efficacy. Starting from a duration of effect of oral vitamin K_1 of 2 d, as discussed below, the efficacy of the treatment can be judged on the INR value between day 2 and day 7. Overall, just 32% of the patients had an INR value within the target zone, 25% had an INR value ≥6·0 and consequently were at increased risk of bleeding. An INR value <2·0, and so an increased risk of thromboembolism, only occurred on day 2, 3 and 4 in two patients (8%). These figures indicate that the treatment is not sufficiently intense and an adjustment is recommended. Increasing the dosage of vitamin K_1 is one possibility. Another option would be to administer an additional small dose of vitamin K_1 on day 1 or day 2.

Although this study was only performed at the anticoagulant clinic of The Hague, the conclusion regarding the efficacy of the treatment of overanticoagulation in patients on phenprocoumon may also apply to many of the other anticoagulant clinics. Most clinics prescribe comparable doses of vitamin K_1, and some even lower doses.

This study was performed in a setting of routine medical care. As a consequence, in six patients, three of whom had just started oral anticoagulant therapy, the standard practice of restarting phenprocoumon on day 2 and lowering the dosage by about 15% was deviated from. However, the course of the INR in these patients was comparable with that observed in the patients in whom the standard practice was applied.

The greatest effect of vitamin K_1 was seen in the first 2 d. Considering the half-life of vitamin K_1 of approximately 1·5–3 h (Park *et al*, 1984a, b), a duration of effect of 2 d is plausible.

The extent of the response to oral vitamin K_1 varied greatly between patients. A difference in the degree of overanticoagulation is a plausible explanation. However, serum levels of phenprocoumon were not determined. The difference between the dose of phenprocoumon at presentation and the dose in a stable condition at a later time, as a proxy of the degree of overanticoagulation, was available for only a limited number of patients. We did not find a relationship between the dose of vitamin K_1 and the proportional decrease in INR between day 0 and day 2. Sex and age also were not related to this decrease.

Other factors that may affect the INR were not substantially present and cannot have had an appreciable effect on the results.

Our study was restricted to patients on phenprocoumon, since at the anticoagulant clinic of The Hague vitamin K_1 is only incidentally prescribed to patients on acenocoumarol, namely when the INR is >15·0. Because of a difference in half-life between oral anticoagulants, the course of the INR

in response to oral vitamin K_1 would be different for other anticoagulants This aspect should be taken into account when comparing our study with those of Weibert *et al* (1997) Pengo *et al* (1993) and Harrell & Kline (1995) which were performed in patients on warfarin The former two studies both focused on efficacy and gave no data on changes in INR over time In the study of Pengo *et al* (1993) nearly all patients had an INR <5 0 on days 1 2 and 9 The INR at presentation however was much lower than in our study Weibert *et al* (1997) found that 1 or 2 d after administration of vitamin K_1 73% of the INR values fell within the target zone 10% exceeded 5 0 and 17% was <2 0 4–7 d after warfarin therapy was resumed these percentages were 83% 1% and 16% respectively So compared to our study fewer patients had an INR above the target zone but more patients had an INR below this zone A higher dosage of vitamin K_1 in proportion to the INR at presentation by Weibert *et al* (1997) is a plausible explanation

In a report on five patients by Harrell & Kline (1995) the INR had decreased by 58% to 89% after 1 or 2 d In our study the maximum decrease in INR on an individual patient level was 77% on day 1 and 43% on day 2

In conclusion in this study among 24 patients on phenprocoumon with an INR ⩾6 0 the INR decreased during the first 2 d after administration of 1–5 mg of oral vitamin K_1 but slightly increased again afterwards Only one third of the patients had an INR value within the target zone between day 2 and day 7 To improve its efficacy the routine treatment of overanticoagulation in patients on phenprocoumon should be intensified

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