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A single dose of oral vitamin K effectively reverses oral anticoagulation with phenprocoumon during heart catheterisation

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Summary

Question under study: To investigate the effectiveness of a single adjusted dose of oral vitamin K to temporarily reverse oral anticoagulation with phenprocoumon (Marcoumar®) for heart catheterisation.

Methods: Patients under stable oral anticoagulation with phenprocoumon routinely scheduled for heart catheterizstion were given a single adjusted dose of oral vitamin K a day prior to the intervention. The customary anticoagulation scheme was kept unchanged with the exception of taking the double usual dose of phenprocoumon the evening after the intervention. The primary outcome was the achieved international normalised ratio (INR) immediately before the intervention. Secondary outcomes were the INR after one and four weeks, changes in phenprocoumon and coagulation factors II and VII and adverse events.

Results: 38 patients at a median age of 71 (63–74) years scheduled for heart catheterisation were included. The median INR changed from 2.2 (1.9–2.6) the day before to 1.5 (1.4–1.7) immediately before the intervention. An INR ≤1.5 respectively ≤1.8 was achieved in 61% and 95% of the patients. The INR values after one respectively four weeks were comparable to preintervention values. No thromboembolic or bleeding adverse events occurred during the study.

Conclusion: A single adjusted oral dose of vitamin K given a day prior to heart catheterisation combined with a doubled phenprocoumon dose on the procedure day seems to be an easy applicable, safe and effective way to temporary reverse oral anticoagulation with phenprocoumon.

Key words: oral anticoagulation; reversal; coumadins; phenprocoumon; vitamin K

Background

Patients on long-term oral anticoagulation with coumadins often need a safe short-term reversal of their anticoagulation for invasive medical procedures such as heart catheterisation. By lowering the international normalised ratio (INR) however, patients are at risk for thrombotic complications during and after the intervention, with the risk depending on the indication of the anticoagulation (atrial fibrillation, pulmonary embolism, valvular or dilatative cardiopathy). Treating physicians face the dilemma to safely decrease the INR during the intervention with the least possible destabilisation of the anticoagulation therapy in order to prevent thromboembolic events or bleeding [1, 2].

Most recommendations for reversal of an oral anticoagulation therapy are established for 4-hydroxy-coumarin (Warfarin®), which is mainly used in America and Great Britain and has a short half-live of 36 hours. In German speaking countries, many patients are treated with phenprocoumon (Marcoumar®), which allows a more stable long-term anticoagulation due to its long half-live of 168 hours [2–9]. Recommendations for short-term antagonism of phenprocoumon have not been prospectively validated so far. We therefore intended to validate a simple scheme (table 1) using a single adjusted dose of oral vitamin K (Kanavit®) 24 hours prior to invasive medical procedures in order to decrease the INR below 1.5, a value widely accepted as being safe for most medical procedures and some surgeries, or below 1.8, the threshold we considered as safe for heart catheterisations, where bleeding complications can be better controlled due to the facility of external pressure haemostasis [1, 2]. The present scheme was historically intro-

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duced and has been used by many clinicians so far, but it has never been prospectively validated. The rational behind the scheme is the expected rapid increase of carboxylated factor VII, due to its short half-life, together with a more stable behaviour of factor II, due to its longer half-life, after vitamin K intake. Similarly, by adding the double dose of phenprocoumon after the intervention, factor VII levels are expected to decrease rapidly due to their short half-life, whereas factor II levels are expected to remain more stable.

Methods

All ambulatory patients on oral anticoagulation therapy with phenprocoumon (Marcoumar®), who were routinely scheduled for invasive medical procedures at our institution, such as diagnostic heart catheterisation or endoscopy, and who were seen by their ward physician at least 24 hours prior to the study were eligible for the study. Patients were informed and asked for written consent by their ward physician. Patients willing to participate received adjusted doses of oral vitamin K (Kanavit®) 24 hours prior to the intervention as depicted in table 1. They were advised to continue their daily phenprocoumon doses as prescribed by their treating physician with the exception of taking the double usual dose (calculated as average daily dose from the preceding week) the evening after the intervention (see table 1). All other medications were continued as accustomed and most patients left the hospital the day after the intervention, ensuring stable dietary habits and vitamin K intake. Patients recorded their phenprocoumon doses and INR values as usual in their pocket books. The international normalised ratio (INR), the coagulation factors II and VII and the phenprocoumon serum level were assessed 24 hours before and after the intervention, and immediately (1–2 hours) before the intervention. The INR was also assessed 7 (6–8) and 30 (28–32) days after the intervention. The stability of the oral anticoagulation was assessed by reviewing the INR values recorded in the patient's anticoagulation booklets during the 6 months before the intervention. Adverse events (bleeding, thromboembolic events) were obtained from involved physicians (specialist and family doctors), patients and the medical records from the hospital stay. The main outcome of the study was the INR value, obtained immediately before the intervention, which was required to be ≤1.8 for heart catheterisation. Secondary outcomes were the stability of the INR assessed 7 and 30 days after the intervention, the concentration of the coagulation factors II and VII, the phenprocoumon serum level and adverse events (bleeding, thromboembolism). The study was approved by the local ethical review board of the University Hospital of Zurich. INR values, factor VII and factor II were measured by standardised and validated laboratory methods used in the coagulation laboratory and the institute of clinical chemistry of the University Hospital of Zurich. Phenprocoumon was quantified using HPLC with mass spectrometric detection as described previously by our Institute for Clinical Chemistry [10].

SPSS version 12.0 for Windows and Excel were used for data analysing and presenting. All values are given as medians and interquartile range (IQR).

Results

Patients' characteristics: 38 patients (16 female) at a median age of 71 (63–74) years were included in the study. The indications for oral anticoagulation therapy were pulmonary hypertension (29 patients) or atrial fibrillation (9 patients). The intervention was either diagnostic or therapeutic heart catheterisation in all patients.

Anticoagulation before the intervention: 24 hours prior to the intervention, 24 (64%) patients had an INR within the therapeutic range (INR 2–3),

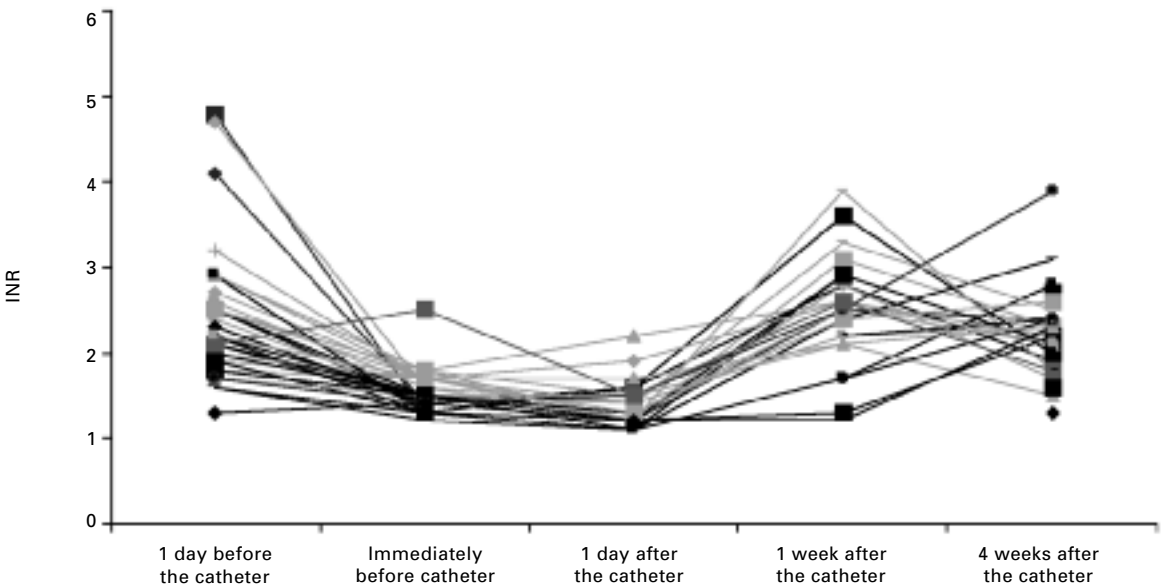

Figure 1

Every line depicts the course of the INR of an individual patient. Black and orange lines are used for patients who achieved an INR ≤1.5 or ≤1.8 respectively, immediately before heart catheterisation. A red line is used for the patient who did not achieve an INR ≤1.8.

Table 1

Temporal anticoagulation reversal scheme to be validated in the present study.

Dosage of oral Vitamin K *		Evening doses of phenprocoumon (Marcoumar)		
INR 24 hours prior to intervention	**Kanavit®* 21–23 hours prior to intervention**	**Day before the intervention**	**Intervention day**	**Following days**
<1.5	none	As prescribed by treating physicians	Double usual daily dosage (calculated from the preceding week)	As prescribed by treating physicians
1.5–2	3 mg			
2–3	5 mg			
>3	10 mg			

*Kanavit® = vitamin K, 1 drop = 1 mg

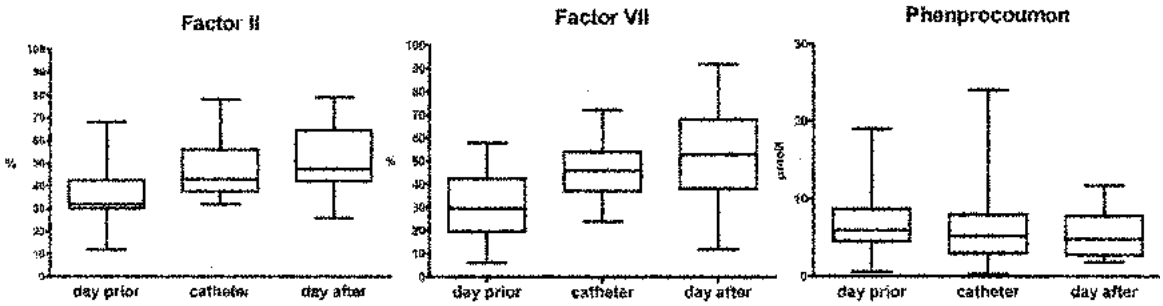

Figure 2

The courses of the serum levels of the coagulation factors II and VII and phenprocoumon are shown for the analyses 21–23 hours prior to the intervention "day prior", immediately before the heart catheterisation ("catheter") and the values obtained 22–26 hours after the catheter ("day after").

whereby the median INR of all patients studied was 2.2 (1.9–2.6) (figure 1). The majority of patients received 5 mg of oral vitamin K (n = 22), 6 and 9 patients received 10 mg and 3 mg vitamin K respectively, and one patient did not receive vitamin K due to an INR level of 1.3 (see scheme table 1). For logistical reason, the adjusted vitamin K dose was given between 21–23 hours before the planned catheter, as the adjusted dose could only be given after having obtained an actual INR value. Long-term anticoagulation was assessed by reviewing patients INR pocket booklets. This could be obtained from half of the patients, whereby an average of 8.3 INR values per patient was retrieved during 6 months, of which the calculated median INR value was 2.35 (2.2–2.6). The median levels of the coagulation factors II and VII 24 hours prior to the intervention were 32 (30–42) and 30 (21–39) %, respectively. The median phenprocoumon serum level was 5.9 (4.6–8.6) µmol/L (therapeutic range 2.2–18 µmol/l) (figure 2).

Validation of the presented scheme: In 37 (95%) patients, INR values ≤1.8 immediately before heart catheterisation were achieved and the intervention could thus be performed without delay. An INR ≤1.5, a value considered safe for other invasive medical procedures, was measured in 23 patients (61%). The median INR of all 38 patients under the present anticoagulation reversal scheme immediately before the intervention was 1.5 (1.4–1.7). The INR the day after the intervention (45–47 hours after oral vitamin K intake) was still ≤1.5 in 32 (83%) of the studied patients and ≤1.8 in (36) 94% of the studied patients (median INR 1.3 [1.2–1.5]). After 7 days, the INR was back within the therapeutic range under usual phenprocoumon dosage in 20 (53%) patients (median INR 2.6 [2.1–2.9]). At the end of the study period (a month after the catheter), the INR was therapeutic in 26 patients (68%) with an overall median value of 2.2 (1.9–2.4). The median levels of both coagulation factors measured significantly rose after vitamin K intake: after 21–23 hours to 43 (38–55) and 46 (37–53) %, for factor II and VII respectively, and after 45–47 hours to 48 (42–63) and 53 (41–68) % respectively (figure 2). The measured serum levels of phenprocoumon decreased to 5.2 (3.4–7.2) µmol/l after 21–23 hours and 4.8 (3.2–7.5) µmol/l after 45–47 hours. None of the patients reported having received prophylactic low molecular weight heparin after the intervention.

Adverse events: No bleeding complications during the heart catheterisations and the observational period were reported. And, despite the observed slightly prolonged reversal of the anticoagulation, no thromboembolic or other adverse events related to the anticoagulation were reported until the study ended a month after the catheter.

Discussion

This study demonstrates that a single adjusted dose of oral vitamin K given at least 21 hours prior to a scheduled heart catheterisation sufficiently decreases the INR in 95% of patients orally anticoagulated with phenprocoumon (Marcoumar®) to enable the intervention. We found a baseline therapeutic INR level within the range of 2–3 in only about two third of the patients on oral anticoagulation with phenprocoumon. These findings are comparable to other investigated cohorts on vitamin K antagonists [11, 12]. The presently investigated oral anticoagulation reversal scheme was designed to include all patients, not only those with therapeutic INRs, in order to investigate a clini-

cally representative cohort of the population under oral anticoagulation with phenprocoumon. With our simple regimen of oral vitamin K intake 21–23 hours prior to heart catheterisation, an INR ≤1.8 was achieved in all but one patient, and an INR ≤1.5, a threshold considered safe for most medical procedures and some surgeries, in two third of the patients [2, 13]. Our norm of a safe INR level (ie ≤1.8) for cardiac catheterisation is confirmed by this, albeit small, study cohort by the absence of bleeding episodes.

For logistical reasons, the adjusted oral vitamin K dose could not be given until 21–23 hours before the intervention. The observation of a persisting low INR the day following the intervention alerts that this time interval is probably too short. Previous studies on reversal of the oral anticoagulation and pharmacokinetic data showed that vitamin K application maximally lowers the INR after 24–48 hours [3–5, 7, 14–20]. We have learned from the present validation study that the best time point for oral vitamin K intake to temporary reverse oral anticoagulation is around 36–48 hours prior to the intervention. Hence we expect, that a future prospective evaluation of a slightly modified scheme with an extended time frame between the application of oral vitamin K1 and the intervention (36–48 hours) might optimise results; first observations in few patients after the end of this study already look encouraging.

Appling our temporary anticoagulation reversal scheme, the INR of most patients had returned within or close to the therapeutic range after one week and remained there until the end of the study in the majority of patients. The fact that none of the investigated patients suffered from a thromboembolic adverse event or bleeding complication during the observational period encourages the use of a single oral vitamin K dose to achieve a short-term decrease of the INR for heart catheterisation in patients under oral anticoagulation therapy due to pulmonary hypertension or atrial fibrillation. If this reversal scheme would prove to be safe also in the management of high risk patients or during other interventions remains to be evaluated in future trials, designed not only to address the peri-catheter values but also the course of the INR, coagulation factors and events until a week after the intervention. These assessments were unfortunately not obtained in the present study for logistical reasons, as we addressed patients only very shortly hospitalised and mainly managed by their treating physicians. As anticipated, there was no appreciable change in phenprocoumon level following the double mean dose of phenprocoumon the evening after the procedure (figure 2).

The serum levels of both measured coagulation factors II and VII significantly rose 21–23 and 45–47 hours after the oral vitamin K application (figure 2). Phytomenadion, the vitamin K applied in the present study, is a synthetically manufactured active vitamin K1 and has an identically active profile as the natural vitamin K1 (Phylloquinon) as it is encountered eg in leafy vegetables, milk, herbal oils and yolk. As its natural counterpart, phytomenadion in vivo is involved in the post-ribosomal carboxylation of different coagulation factors (factor II (prothrombin), VII, IX, X) and coagulation inhibitors (protein C S and Z) and is a potent antagonist of phenprocoumon and other orally applicable anticoagulants. A certain rise was therefore anticipated for both measured coagulation factors, but unexpectedly, the increase of factor II with a longer half-life (50 hours) was only slightly less pronounced than the one of factor VII with a shorter half-life (3 hours). Moreover, in the later we found a slightly higher variance. Possible explanations might be the small sample size or alimentary changes despite the short hospitalisation time compared to factor VII [21, 22].

The present study has several limitations. First, this study is a prospective validation study of a specific temporary oral anticoagulation reversal scheme (table 1), which was historically introduced by clinical experience. We did not compare our scheme with other current strategies in a randomised controlled manner. A randomised controlled trial facing this question would have been logistically much more extensive and thereby might have addressed only a restricted patient population. Second, the number of patients recruited is relatively small. In Switzerland the adjustment of the oral anticoagulation dosage is generally in the hand of family doctors and most patients scheduled for heart catheterisation are hospitalised only very shortly (often not more than a night). As a result the majority of potentially recruitable patients are not seen by the ward physician early enough (at least 24 hours prior to the procedure) to be included in the study. Third, we did not formally register a number of patients unwilling to participate after information, but personal experience and communication with ward physicians did not retrieve any denials. Forth, we did not include INR-values between the second and sixth day after the intervention. Lastly, all the included patients were scheduled for heart catheterisation. It is highly probable that the INR level would have behaved similarly for other procedures like minimal invasive surgery, endoscopic polypectomies or biopsies, but we do not know what the bleeding and thromboembolic complication would have been in these settings. Therefore the present findings can formally give evidence only for similar patients scheduled for heart catheterisation in a comparable setting.

Despite these limitations, we consider the data of this prospective validation study important for treating physicians (family doctors and specialists) as they reflect a common medical problem concerning patients on continuous oral anticoagulation with phenprocoumon, referred for heart catheterisation in Switzerland. The fact that none of the investigated patients suffered from a thromboembolic adverse event or bleeding complication during the observational period encourages the

use of a single oral vitamin K dose to achieve a short-term decrease of the INR for heart catheterisation in patients under oral anticoagulation therapy due to pulmonary hypertension or atrial fibrillation.

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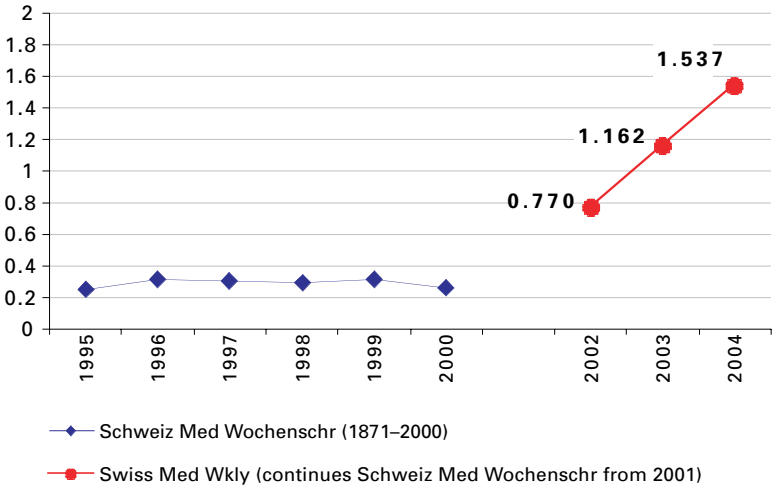

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