Letter to the Editor

Thromboembolism and coumarin overdosage in a 19-year-old female: impact of pharmacogenetics

To the Editor:

Individualized therapies based on the patients’ unique pharmacogenomics and pharmacogenetics will become an all-important topic in various medical disciplines within the forthcoming years. The clinical case presented here underlines the need for future individualized and genotype-adapted medical treatment. Written consent to publish this report has been obtained from the patient.

In 2009, a 19-year-old female patient was admitted from another hospital with bilateral pulmonary embolism as a result of deep venous thrombosis after an arthroscopy of the right talocalcaneal joint a few weeks ago. Under initiated phenprocoumon therapy with a cumulative dose of 16.5 mg over 3 days and overlapping administration of heparin (Table 1), the patient had developed a progressive bilateral pelvic thrombosis.

On admission to our hospital, physical examination showed a massively swollen right leg without affecting esthesia or motor function. There was also no evidence of a compartment syndrome. Oxygenation was uncomplicated, although echocardiography indicated a moderate right ventricular strain. The CT scan showed a complete occlusion of the infrarenal caval vein and both common iliac veins (Fig. 1a) but no hint of malignancy. Laboratory tests showed an INR of 4.0 that rose to more than 6.9 (therapeutic target INR 2.0–3.0) during the following days without further administration of phenprocoumon (Table 1). As a result of the uncontrolled...

Table 1. INR course after the administration of 9, 6 and 1.5 mg of phenprocoumon on day 2, 3 and 4 of hospitalization

| Day of hospitalization | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10–18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
|------------------------|---|---|---|---|---|---|---|---|---|-------|----|----|----|----|----|----|----|----|----|----|----|----|
| INR (laboratory reference INR 0.8–1.2, therapeutic target INR 2.0–3.0) | 1.1 | 1.1 | 1.3 | 1.7 | 3.0 | 4.0 | 4.7 | 5.1 | 5.0 | Ø 6.5 | 5.2 | 3.9 | 3.6 | 2.7 | 2.6 | 2.1 | 2.1 | 2.6 | 2.2 |
| Applied dose of phenprocoumon (mg) | – | 9 | 6 | 1.5 | – | – | – | – | – | – | – | – | – | – | – | – | 1 | 1 | 1 | 1 |
| aPTT (s) due to overlapping heparinization (laboratory reference aPTT 26–36 s, therapeutic target aPTT 60–80 s) | 28–75 | 36–44 | 43–60 | 42–60 | 78–81 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Functional protein C level (%) (laboratory reference 70–140%) | | | | | | | | | | | | | | | | | | | | 30 |
| Free protein S level (%) (laboratory reference 58–113%) | | | | | | | | | | | | | | | | | | | | 16 |

*Reduced maintenance dose of 1 mg phenprocoumon per day (starting on day 25) after spontaneous normalization of INR. Therapeutic target INR 2.0–3.0 (rows 2 and 3). Inadequate overlapping administration of unfractionated heparin. The target aPTT (60–80 s) is hardly reached during the initiation of coumarin therapy. Heparin therapy was performed from day 1 to day 5 of hospitalization (row 4). Pharmacologically suppressed levels of proteins C and S under coumarin therapy (rows 5 and 6).
blood coagulation and the hemodynamic stability present, no thrombolysis was performed.

Besides the use of oral contraceptives, a positive paternal family history for thromboembolism was identified as a predisposing risk factor (Fig. 1b). The genetic screening revealed a heterozygous prothrombin 20210G>A mutation, associated with a threefold increased risk for thrombotic episodes (1). Although her mother also reported a history of thrombosis, neither the factor V leiden mutation, which frequently is combined with the prothrombin mutation, nor an antithrombin III deficiency or a persistent lupus anticoagulant could be detected in the patient.

Yet, the rise of the INR to excessively high levels after the administration of only a standard starting dose of phenprocoumon and its lacking reduction within several days despite cessation of this medication remained unclear. Eventually, a pharmacogenetic screening for variants in the CYP2C9 and VKORC1 genes shed light on the questions. These genes account for up to 50% of the variability in dosing of vitamin K antagonists. CYP2C9 revealed a heterozygous *1*3 genotype which causes an Ile359Leu amino acid substitution and is associated with decreased coumarin degradation (2). Also VKORC1, which is the target molecule of all vitamin K antagonists and necessary for the recycling of vitamin K epoxide to vitamin K, additionally showed a homozygous AA haplotype. This genotype does not lead to a change in the amino acid sequence but mainly as a result of reduced gene promotor activity causes a decreased VCORK1 expression. The combination
of both genetic variants led to a high coumarin sensitivity in the patient and therefore to an excessive inhibition of blood coagulation.

For therapy, the patient was analgized and immobilized as long as free-floating thrombi were detectable. Legs were treated with compression bandages. The INR normalized after 16 days without substitution of coagulation factors or vitamin K and finally a dose of 1 mg phenprocoumon per day was sufficient to maintain a stable therapeutic anticoagulation level. As a result of spontaneous recanalization of the inferior caval vein, no surgical intervention was performed. We recommended the patient a life-long coumarin therapy.

Regarding the pathophysiologic mechanism, the patient’s primarily unknown hypercoagulatory state and thus an unadjusted perioperative thrombosis prophylaxis promoted the initial development of a deep venous thrombosis. The subsequent treatment with unfractionated heparin was switched to phenprocoumon on the second day of hospitalization (Table 1). Yet, during the initial phase of coumarin therapy the vitamin K-dependent synthesis of both anticoagulatory proteins C and S is reduced temporally before the inhibition of the coagulation factors II, VII, IX and X which leads to a transient hypercoagulative state requiring an overlapping heparinization. The genetic variants in VCORK1 and CYP2C9 increase this coumarin effect and therefore presumably potentiated the inhibition of protein C and S synthesis. In combination with a subtherapeutic overlapping administration of heparin (administered dose of 500 IE/h, measured aPTT below 60 s) (see Table 1 for details) during the first 3 days of coumarin therapy, this supposedly facilitated the formation of the huge thrombus described in the patient. Unfortunately, because of the undetermined blood levels of proteins C and S during initiation of coumarin therapy this assumption cannot be proven.

In this case, several genetic variants have contributed to the occurrence of a thromboembolic event and thereafter may have complicated its medical treatment. As prevalence of heterozygous prothrombin mutation reaches 19% in patients with hereditary thrombophilia and as 25% of the worldwide population carry either the VKORC1 haplotype A or the CYP2C9*3 allele and therefore bear a relevant risk for coumarin overdosage, the knowledge about the respective genotypes may have contributed to risk reduction for thrombosis and phenprocoumon overdosage in the patient (3). In future, decreasing costs for whole genome sequencing will put the vision of the preventive and individualized medicine into practice. For now, genetic screening should at least be provided for those at risk.

Competing interest

All authors declare the absence of any conflicts of interest.

C Brennera, B Hubera, A Beckera, H Ostermannb, C Beckerc, G Steinbecka and W-M Franzad

aDepartment of Internal Medicine I, Cardiology, Pneumology and Nephrology,
bDepartment of Internal Medicine III, Hematology and Oncology, and
cDepartment of Radiology, University of Munich, Campus Grosshadern, Munich, Germany

References


Correspondence:
Wolfgang-M.Franz, M.D
Klinikum der Universität München - Campus Grosshadern
Medizinische Klinik und Poliklinik I
Marchioninistr. 15
81377 München
Germany
Tel.: +49 89 7095 3094; fax: +49 89 7095 6094;
Email: Wolfgang.Franz@med.uni-muenchen.de