Inflammatory response mediated increase in vitamin K antagonist associated anticoagulation

Karl A. Nowak[1], Patrick Richter[2], Ali Sigaroudi[2]
[1]Klinik für Klinische Pharmakologie und Toxikologie, Universitätsspital Zürich
[2] Praxis am Bahnhof AG, Rüti ZH

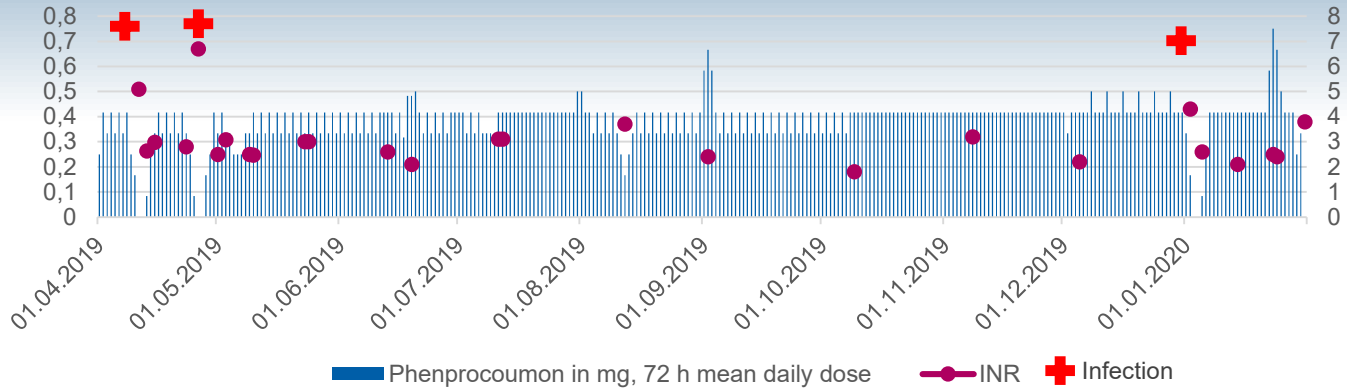
Learning objectives

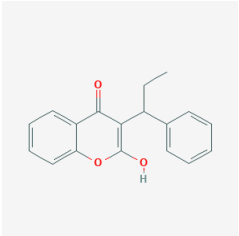
- To consider the need for dose adjustments and close therapeutic drug monitoring in inflammatory conditions
- Highlighting non drug-drug interaction mediated pharmacokinetik alterations in Vitamin K Antagonist (VKA) response

Background

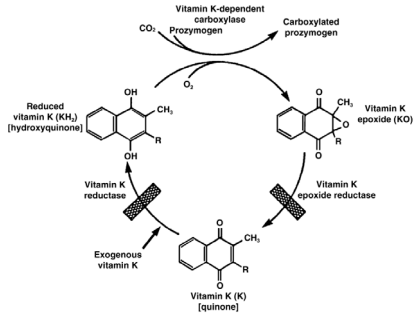
Oral anticoagulants are a common sight in the clinical and ambulatory setting, with VKA being one of the oldest substances approved in the prevention and therapy of arterial and venous thrombotic conditions. Due to Phenprocoumones mechanism of action inhibiting the synthesis of procoagulatory as well as anticoagulatory factors via disrupted recuperation of Vitamin K, its long half-life, metabolism via cytochrome p450 (CYP) 2C9 and 3A4 and narrow therapeutic range, strategic foresighted considerations are recommended in drug dosing and monitoring.

Daily phenprocoumon dose vs INR





Phenprocoumon
99% Protein bound
Substrate of CYP2C9 + 3A4
T1/2 160 h
Excretion ~35% via kidneys
Partial enterohepatic recycling



Case

Patient characteristics
53 years old male
68 kg, 180 cm
Caucasian
Discontinued history of nicotine (20 PY) and heroine abuse

Current Diagnoses
Mechanical aortic valve composite graft
COPD GOLD D, IV
- Past lung volume reduction
Chron. Hepatitis C, Genotype 4
- Successfulreatment with Epclusa (Sofosbuvir, Velpatasvir
- HCV-RNA below threshold

Daily Medication
Phenprocoumon - as indicated
Nebivolol 5 mg
Roflumilast 0.5 mg
Methadone 60 mg bid
Salbutamol/Ipratropium
Indacetarol/Gylcopyrronium

Medical history
The 53 year old male patient with a 7 year old mechanical aortic valve prosthesis under stable dosing regime with VKA Phenprocoumon, Nebivolol, Roflumilast, Salbutamol/Ipratropiumbromide, Indacetarol/Glycopyrronium and opioid substitution with Methadone, presented with three distinct episodes of respiratory infection. Clinical examination revealed elevated body temperature, symptoms of upper and lower respiratory tract infection including sore throat, rhinitis, dyspnea. Laboratory results confirmed viral and bacterial colonization, elevated C-reactive protein (CRP) and concomitant elevated supratherapeutic INR prior to treatment or change in medication.

Episode 1
March-April 2019: Viral infection
T 38,0 °C, CRP 49.9 mg/l, INR 5.0

Episode 2
End of April 2019: Staph. aureus
T >38.0 °C, CRP 150 mg/l, INR 6.7

Episode 3
January 2020: Viral infection
T >38.0 °C, CRP 38.7 mg/l, INR 4.3

Inflammatory response mediated increase in vitamin K antagonist associated anticoagulation

Karl A. Nowak[1], Patrick Richter[2], Ali Sigaroudi[2]
[1]Klinik für Klinische Pharmakologie und Toxikologie, Universitätsspital Zürich
[2] Praxis am Bahnhof AG, Rüti ZH

Discussion

Given the unchanged medication, dosing and plausibly excluded changes in lifestyle factors, food intake and drug behavior, causality of INR response under maintained VKA is in this case very likely attributable to changes in our patients physiological response.

Phenprocoumon is metabolized mainly via Phase-1 Enzymes CYP2C9 and CYP3A4, the efflux transport protein P-glycoprotein plays only a minor role in drug elimination.

Variations in drug-drug interactions during the mentioned episodes could be ruled out. No concomitantly used substance is known to have a significant effect on the metabolism of Phenprocoumon via phase 1 enzymes or the efflux transport protein P-glycoprotein.

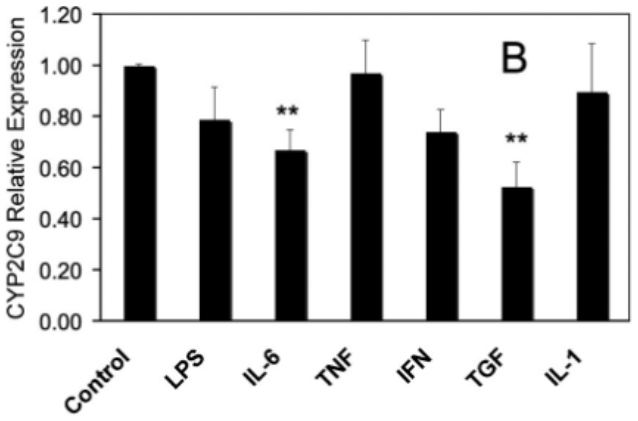
In vitro studies utilizing human hepatocytes could elucidate the gene-specific effect of cytokines. Expression of CYP2C9 was significantly reduced in response to Interleukin 6 (IL-6) and transforming growth factor-β (TGF), thus reasonably explaining modified drug response in inflammatory states.

Past studies with healthy subjects demonstrated inhibition as well as in some cases induction of hepatic enzymes after induced inflammatory responses (bacterial lipopolysaccharids), though clinical data in sparse and cases rarely reported.

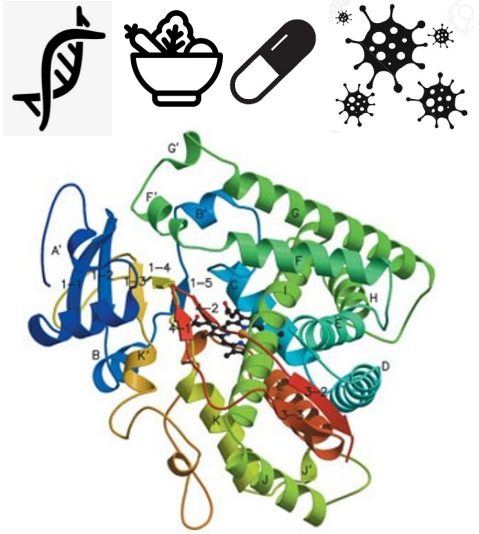
Our patient repeatedly and reliably demonstrates in three separate occasions an increased INR, independent of the cause of infection, indicating that plasma half-life and drug exposure of Phenprocoumon may indeed be increased due to inflammatory response alone.

The dosage of Phenprocoumon should be considered strategically and with foresight, since the elimination half-life of approx. 160 h is long, a possible accumulation of the active substance must not be neglected and the effect of a change in dose only occurs with a delay.

Furthermore, synergistic effects on the coagulation status due to vitamin K intake must be taken into account. In addition to a reduced vitamin K uptake due to the depletion of the symbiotic microbiota of the intestinal flora by broad-spectrum antibiotic treatment, it should be noted that an already established inflammatory process, by downregulating microsomal enzyme synthesis, influences the metabolism of vitamin K antagonists and the production of coagulation factors.



Effects of cytokines on P450 mRNA expression in human hepatocytes. Cells were treated with phosphate-buffered saline (1 µl/ml, Control), LPS (10 µg/ml), IL-6 (10 ng/ml)), TNF (10 ng/ml), IFN (10 ng/ml), TGF (10 ng/ml), or IL-1 (5 ng/ml) for 24 h and mRNA levels of CYP2C9. ** $p < 0.005$
Credits: Aitken, Alison E., 2007



Modifiers of Cytochrome p450 2C9 expression and function: genetics, food and supplements, drugs as well as cytokines (IL6 + TGFβ) in inflammatory response
Modified, Credits: Williams, Pamela A. 2003

References

1. Swissmedic Zugelassene Humanarzneiittel Stand 30.04.2021, available from: www.Swissmedic.ch
2. Falk, Volkmar, et al. "2017 ESC/EACTS Guidelines for the management of valvular heart disease." European Journal of Cardio-Thoracic Surgery 52.4 (2017): 616-664.
3. Abduljalil, Khaled, et al. "Quantifying the effect of covariates on concentrations and effects of steady-state phenprocoumon using a population pharmacokinetic/pharmacodynamic model." Clinical pharmacokinetics 52.5 (2013): 359-371.
4. Ferland, G. (2012). The discovery of vitamin K and its clinical applications. Annals of Nutrition and Metabolism, 61(3), 213-218.
5. Bovill, Edwin G., Mark Fung, and Mary Cushman. "Vitamin K and oral anticoagulation: thought for food." The American journal of medicine 116.10 (2004): 711-713.
6. Pineo, Graham F., and Russell D. Hull. "Vitamin K antagonists and direct thrombin inhibitors: present and future." Hematology/Oncology Clinics 19.1 (2005): 69-85.
7. Williams, Pamela A., et al. "Crystal structure of human cytochrome P450 2C9 with bound warfarin." Nature 424.6947 (2003): 464-468..
8. Christensen, Hege, and Monica Hermann. "Immunological response as a source to variability in drug metabolism and transport." Frontiers in pharmacology 3 (2012): 8.
9. Aitken, Alison E., and Edward T. Morgan. "Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes." Drug Metabolism and Disposition 35.9 (2007): 1687-1693.