

Severe over-anticoagulation despite standard phenprocoumon initiation protocol after aortic valve replacement in two paediatric patients

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Introduction: Vitamin K antagonists (VKA) are loaded routinely with standard clinically-based initiation protocols in children early after mechanical valve implantation, as this allows patients to reach target international normalised ratio (INR) rapidly without prolonged hospitalisation.

Cases: We present two boys aged 7 (patient 1 (P1), body weight 18 kg) and 16 years (patient 2 (P2), body weight 61 kg) who underwent mechanical aortic valve replacement. Postoperatively, overlapping with unfractionated heparin, we began oral anticoagulation with phenprocoumon using a standard body weight-based dosing algorithm. Target INR was 2.5 – 3.0. After only two doses of phenprocoumon (on day 1/day 2: P1 4.5 mg/1.5 mg, P2 9 mg/6 mg) both patients demonstrated an INR >7 in venous blood samples. Due to the significant risk of bleeding we administered vitamin K to both and fresh frozen plasma to P2. Hereafter, both patients required unusually low phenprocoumon doses of under 15 % of normal (P1: 0.1 mg every three days, P2: 0.75 mg per day) to reach target INR. We performed sequencing of the vitamin K epoxide reductase complex 1 (VKORC1), cytochrome P450 2C9 (CYP2C9), and cytochrome P450 4F2 (CYP4F2) genes and found a homozygous VKORC1:c.-1639AA haplotype and a heterozygous CYP4F2 wild type (CYP4F2*1*1) haplotype in both patients, as well as a heterozygous CYP2C9*1*2 haplotype in P2. This confirmed enhanced sensitivity to VKA in both patients, leading to severely reduced phenprocoumon dose requirement.

Conclusions: Aside from age-related factors, genetic variations in VKORC1, CYP2C9, and CYP4F2 have been associated with significant inter-individual VKA dosing variability. Although infrequent, these variations may pose a significant risk for over-anticoagulation in children. Therefore, when using a standard clinically-driven loading protocol, patients with increased VKA sensitivity due to unknown mutations are at risk for bleeding. On the other hand, a low-dose initiation protocol would lead to prolonged hospitalisation in the majority of the children, who are unaffected by these genetic variations.

The routine application of a genotype-guided algorithm for phenprocoumon initiation therapy remains unrealistic in daily paediatric cardiac surgery. Therefore, it is even more crucial to be aware of this potential risk and to interpret the daily blood samples with care.