

## Phenprocoumon dose requirements and genetic polymorphisms in chronic thromboembolic pulmonary hypertension

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### Background:

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by large fibrotic thrombus in the pulmonary arteries, likely originating from pulmonary embolism. Inadequate anticoagulation is one of the suspected mechanisms of disease in CTEPH.

The aim of our study was to assess phenprocoumon dosing in relation to genetic polymorphisms of vitamin K epoxide reductase complex subunit 1 (VKORC 1) and cytochrome P-450 2C9 (CYP2C9).

### Patients and Methods:

The ratio of weekly mean phenprocoumon dose in relation to mean INR levels was assessed in CTEPH patients on phenprocoumon oral anticoagulation for at least 6 months, compared with PAH patients. VKORC 1 (-1639, -3730) and CYP2C9 (\*2, \*3) single nucleotide polymorphisms (SNPs) were determined by polymerase chain reaction (PCR).

### Results:

In 72 consecutive patients were observed (46 CTEPH, 26 PAH; mean treatment duration  $51.7 \pm 44.7$  months, mean age  $63.4 \pm 12.2$  years (63% female). Mean dose of phenprocoumon per week was 15.8 mg (4.5 mg to 42 mg). The mean ratio of weekly phenprocoumon dose and INR levels showed statistically significant differences between CTEPH (mean ratio  $6.58 \pm 3.3$ ) and PAH (mean ratio  $4.87 \pm 1.7$ ;  $P=0.013$ ). As expected, patients with CTEPH and VKORC1 -1639 GG homozygous wild type required significantly higher phenprocoumon doses compared with VKORC1 -1639 AA homozygous mutants ( $P<0.05$ ). The distribution of the two subsets of CYP2C9 (\*2, \*3) was not different from the normal population.

### Conclusions:

CTEPH patients require more phenprocoumon in relation to INR levels than PAH patients. Unmet phenprocoumon dosing requirements may be one mechanism of disease in CTEPH.