A severe case of warfarin-canrenoate interaction: a role for genetic predisposition?

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The interindividual variability in warfarin response is generally attributed to dietary vitamin K intake, drug interactions, demographic and genetic factors (D'Andrea *et al*, 2008). Many drugs are known to modify international normalized ratio (INR) values in warfarin-treated patients both for pharmacodynamic and pharmacokinetic interactions. We report an unusual case of interaction between potassium canrenoate (PC) and warfarin in a 77-year-old Caucasian female with atrial fibrillation, heart failure (New York Heart Association class II) and hypertension. During the previous 5 years, the patient had been effectively anticoagulated with warfarin 35·0 mg/week with a very stable INR (Fig 1); in the last 10 months drug therapy also included furosemide, bisoprolol and ramipril. Two weeks after PC addition (50 mg/d) to control a slight hypokalaemia, she suddenly developed an extensive facial and neck haematoma after a mild lesion of the internal jowl, followed by analogous limb lesions as consequences of mild traumas. Blood examinations revealed a marked INR increase (10·8), requiring warfarin discontinuation and vitamin K administration. Warfarin treatment was suspended until INR reached 1·0; subsequent titrations after warfarin reintroduction eventually resulted in a stable INR within the therapeutic range (2·0–3·0) with a final regimen of 22·5 mg/week (about 66% of the previous dose); PC was never withdrawn. Any other possible factor able to interfere with warfarin therapy was excluded, including: recent illness, changes in dietary vitamin K intake, over-the-counter products, fruit-juices, herbal products, alcohol, tobacco. The patient and her relatives confirmed adherence to drug therapy.

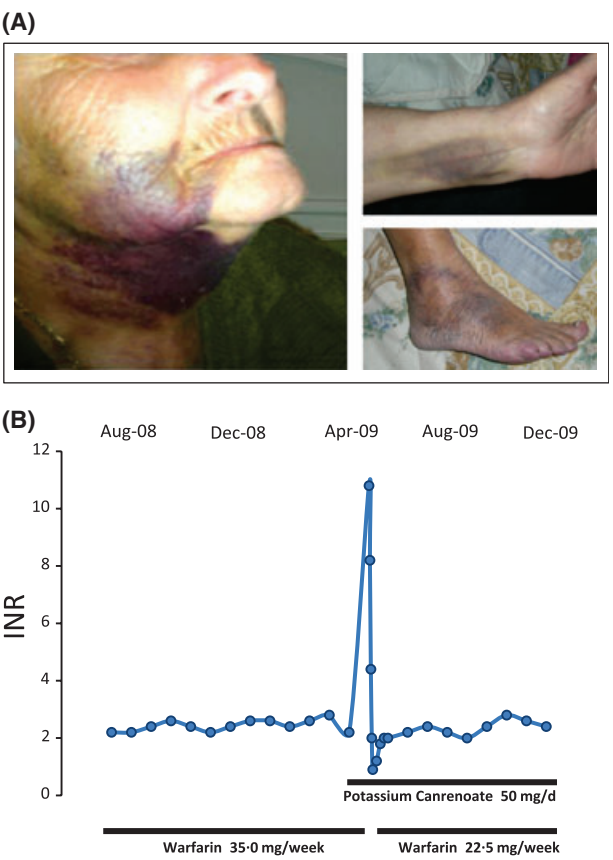

Fig 1. Clinical manifestations of the patient. (A) Patient's lesions. (B) Patient's INR.

Warfarin inhibits the synthesis of vitamin K-dependent clotting factors via inhibition of the vitamin K epoxide reductase complex 1 (vkorc1) and is primarily metabolized via cytochrome P450 2C9 (cyp2c9). The patient was genotypized for three warfarin-related SNPs, *CYP2C9*2*, *CYP2C9*3* and *VKORC1 -1639G>A* (rs9923231, minor allele frequency 0·432 in Caucasian population) (D'Andrea *et al*, 2008). The Taqman Drug Metabolism Genotyping Assay (Applied Biosystems, Foster City, CA) was used. The patient was found to be homozygous wild-type for both *CYP2C9* loci and homozygous -1639AA (low dose required) for *VKORC1*. Both PC and warfarin are highly bound to human serum albumin (HSA), and PC was previously shown to competitively displace warfarin from HSA to a significantly higher extent than spironolactone (the latter was, on the contrary, reported to decrease the anticoagulant effect of warfarin by means of clotting factors concentration) (O'Reilly, 1980; Takamura *et al*, 1997). This interaction may increase warfarin bioavailability, taking also into account that both R-Warfarin and PC undergo extensive hepatic metabolism via CYP3A (Cook *et al*, 1993; D'Andrea *et al*, 2008).

To date, this is the first clinically relevant interaction between warfarin and PC. Its imputability was graded as 'probable' according to the objective causality assessment performed by our Pharmacovigilance Unit. As the combination of warfarin and PC might be quite common in cardiovascular therapy (e.g. 2042 out of 58 831 – 3·5% – warfarin users have at least a coexistent prescription of PC within a time window of 1–3 months according to recent prescription data of Tuscany), we hypothesize that the increase in warfarin serum concentration afforded by PC pharmacokinetic interactions may lead to a clinically relevant bleeding syndrome only in subjects with a warfarin-sensitive genotype (e.g. *VKORC1* -1639AA as in the present case).

bjh British Journal of Haematology

Acknowledgements

We thank Dr Roberto Berni, Dr Emiliano Sessa and Dr Rosa Gini (Regional Authority for Healthcare Services of Tuscany) for their help in obtaining prescription data from Tuscan County.

Funding

None.

Conflict of interest

None.

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Keywords: warfarin, potassium canrenoate, drug interactions, bleeding, pharmacogenetics.

First published online 10 June 2010
doi:10.1111/j.1365-2141.2010.08232.x

Paroxysmal nocturnal haemoglobinuria clones in children with acquired aplastic anaemia: a prospective single centre study

Previous studies in adults with acquired aplastic anaemia (AA) found a high incidence of paroxysmal nocturnal haemoglobinuria (PNH) minor clones at diagnosis, associated with a better response to immunosuppressive therapy (IST) (Maciejewski *et al*, 2001; Ishiyama *et al*, 2003; Sugimori *et al*, 2006). Few studies exist regarding the origin and changes over time of PNH clones in children with AA. In a previous study (Timeus *et al*, 2005) the simultaneous flow cytometric analysis (FCA) of circulating $CD34^+$ cell absolute count and apoptotic rate (AR) in children with AA identified a typical pattern at diagnosis or relapse (low $CD34^+$ count and high AR) and at myelodysplastic transformation (high $CD34^+$ count and low AR). The present study aimed to assess the incidence of PNH^+ cells in AA children at diagnosis, during IST and off-therapy, and to evaluate its correlation with the functional state of circulating $CD34^+$ cells, response to IST and survival.

A cohort of 24 Caucasian children (median age 8·7 years, 14 males and 10 females) with AA diagnosed between 1990 and 2009 (18 severe or very severe and six non severe AA, according to Camitta *et al* (1976) criteria), was prospectively studied for the presence of PNH^+ cells by FCA, since 1998. All but four patients (Patients 5, 7, 14 and 16, Fig 1), who received related