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SPECIAL REPORT

Investigating unexpected INRs: in search of the culprit Adherence, interactions, genetics, and superwarfarin

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ABSTRACT

Treatment with coumarin derivatives is highly individualised due to high intra- and inter-individual variation in dose response and risks of severe bleeding or thromboembolic complications. Treatment focuses on reaching and maintaining a stable target international normalised ratio (INR). However, unexpected INRs that are not explained by noncompliance or vitamin K intake may occur. Here we describe seven cases of unexpected INRs, and provide clues that clarify the underlying mechanism.

KEYWORDS

Coumarin, CYP2C9, INR, superwarfarin, VKORC1

INTRODUCTION

Coumarin derivatives are known to have a small therapeutic range, with many factors implicated in this range.[1-3] Coumarins act as competitive inhibitors of the vitamin-K-epoxide-reductase (VKOR), which is essential in recycling vitamin K.[2-4] Inhibiting VKOR results in decreased production of vitamin K-dependent coagulation factors. In this article, we present seven cases of unexpected international normalised ratio (INR). These cases show that beside the traditional factors such as vitamin K intake, intercurrent comorbidity, and nonadherence, one should consider other factors such as comedication, genetic factors and superwarfarins.

CASE REPORTS

Patient A, a 79-year-old man, was treated with acenocoumarol. However, his target INR was not achieved.[5] Both raising the dosage to 8 mg/day and eventually changing to phenprocoumon 9 mg/day did not result in INR above 1.1. Nonadherence and absorption problems were excluded since serum concentration of phenprocoumon was 11 mg/l – the therapeutic range for elevation of INR is 1 to 3 mg/l – and vitamin K in serum was low, 0.6 nmol/l (reference 0.8 to 5.3 nmol/l). DNA prepared from blood was analysed for mutations in the vitamin K epoxide reductase C1 (*VKORC1*) coding region. We found a novel missense mutation leading to partial resistance to acenocoumarol and phenprocoumon.[6] Eventually, the patient's INR reached its target (2.5 to 3.5) with a daily dosage of 18 to 21 mg phenprocoumon.

Patient B, a 68-year-old man, was admitted to the intensive care unit with recurrent pulmonary embolism. He had been treated with phenprocoumon for a few years. It was not possible to find the correct dose in spite of dose adjustments. The INR showed fluctuating values. He was screened for mutations in cytochrome P450 enzyme subunit C9 (*CYP2C9*) and *VKORC1*. *CYP2C9* is known to be involved in metabolisation of coumarins.[7] No abnormalities were found in *CYP2C9* but a heterozygous mutation was found in the *VKORC1* gene (C1173T), resulting in increased sensitivity to coumarins. Such patients need prudent dosing.[8]

Patient C, an 87-year-old female, was prescribed acenocoumarol after the diagnosis atrial fibrillation. INR values were stable within the therapeutic range with a daily

dose of 1.7 to 1.8 mg acenocoumarol. After starting tube feeding for a deglutition complication, her INR was lower than before (<1.5). Target INR was reached by prescribing a higher dose of 3 mg acenocoumarol a day. The effect of tube feeding is known from the literature.[9,10]

Patient D, a 43-year-old female treated with acenocoumarol, showed strongly fluctuating INR values. During hospital admission she was treated with a list of drugs of which carbamazepine is known to cause induction of the hepatic metabolism of anticoagulants. Comedication with carbamazepine has been reported to cause decreased anticoagulant effects by inducing cytochrome P450 activity.[11,12] Acenocoumarol is then quickly metabolised and the effect on coagulation is lowered. In this case, serum concentration of acenocoumarol was beneath the lower limit of detection of 20 µg/l (the therapeutic concentration is 30 to 90 µg/l). Changing carbamazepine into valproate did not resolve the problem. Finally, intake under supervision resulted in target INR.

Patient E, a female, 63-year-old, was admitted to the hospital with anaemia and gastrointestinal bleeding with high INRs. Intoxication with coumarin derivatives was suspected and blood was analysed. However, acenocoumarol, phenprocoumon, and warfarin were all absent in her serum. Subsequently, a blood sample was sent to the Leiden University Medical Centre for superwarfarin screening. Both difenacoum and difethialone were detected in her blood. The patient was treated with vitamin K (10 mg per os per day) for several months until her INR returned to normal. Superwarfarins are rodenticides, which have a long-lasting effect and a high volume of distribution, even at low concentrations. In this case it is likely an autointoxication; in superwarfarin intoxications unintentional intake should be excluded. High dosages of vitamin K for a long period are the antidote.[13]

Patient F, an 18-year-old boy, was seen at the emergency room. He said he had taken 6 to 7 spoons of a brodifacoum containing rodenticide, which is equivalent to 0.007 g of brodifacoum. Treatment with activated charcoal was started immediately (4 x 50 g). Oral vitamin K (10 mg/day on first three days after intake) was prescribed. INR showed no elevations and the serum concentration of brodifacoum was 3 µg/l. Even a week after the suspected date of ingestion the INR was normal. Calculations on the basis of the suspected intake and 100% biological availability, however, would result in a much higher serum concentration of 100 µg/l. The patient had *pervasive developmental disorder not otherwise specified (*PDD NOS), thus we think that he strongly exaggerated the amount of poison he took. Because brodifacoum has a long half-life of elimination (20 to 60 days, half lives of acenocoumarol and phenprocoumon are 10 and 160 hours, respectively), in serious intoxications INR values have to be checked regularly, and long-lasting administration of vitamin K is needed.[14]

Patient G, a 38-year-old man, started phenprocoumon after a pulmonary embolism. INR values ranged from 1.1 to 2.4, while target INR was 2.5 to 4.0. His serum phenprocoumon concentration was 0.3 mg/l (therapeutic concentration 1.0 to 3.0 mg/l). He was switched to acenocoumarol. Two weeks later we found acenocoumarol and phenprocoumon simultaneously in his blood. The acenocoumarol concentration was >180 µg/l, and the phenprocoumon concentration was 1.5 mg/l. It is peculiar, however, that the patient declared at that time he was not taking any coumarins at all.

DISCUSSION

When an unexpected high, low or strongly fluctuating INR is found, first of all technical failure in blood sampling, storage, or INR determination have to be excluded. We then advise to discuss compliance with the patient. Tablet intake under supervision and eventually measurement of serum concentrations may clear this issue. In addition, it is important to enquire about vitamin K intake, comorbidity, and check the patient's medication list for inducing or inhibiting drugs. A global blood screening is needed to confirm normal kidney and liver function. Finally, visually examine the tablets to rule out exchange of medication. A structured summary of potential causes and actions, in order of clinical relevance, is given in *table 1*.

Factitious behaviour is not easily diagnosed. In cases of sustained INR, we advise measuring blood concentrations of phenprocoumon and acenocoumarol, which can confirm intake. Detecting superwarfarins is possible, but relatively rare. The number of anticoagulant rodenticide intoxications registered at the Dutch Poison and Information Centre (NVIC) was 196 in 2006, and 224 in 2005. Coagulation defects are outside the scope of this article.

When all options mentioned above are excluded, we recommend screening for variations in *CYP2C9* and the *VKORC1* gene. *VKORC1* and *CYP2C9* genotype explain half of the inter-individual variability in anticoagulant maintenance dosages.[7,8] The *CYP2C9*2* and *CYP2C9*3* alleles, for instance, confer higher susceptibility to coumarins, with pharmacokinetic consequences. Lower dosages than in *CYP2C9* wild-type patients will give normal serum concentrations of the anticoagulant in patients carrying *CYP2C9*2* or *CYP2C9*3*. Allelic frequencies of *CYP2C9* *1, *2, and *3 in the Netherlands are 80%, 10 to 13%, and 7 to 10%, respectively.[7,8] Most *VKORC1* genetic variants correspond to an increased effect (prescribe lower dosages) of coumarins. The most abundant of these variations is 1173C>T, present in 40% of *VKORC1* alleles.[7,8] However, *VKORC1* variants exist that cause partial resistance, requiring very high dosages for therapeutic effect. In cases of partial resistance,

Table 1. *Action plan and factors to be considered to resolve INR problems (compare a measured INR with the target INR)*

INR within target
- No special action

INR above therapeutic target range

Lower the dosage

With several INRs above the target INR:
- Check adherence
- Concomitant disease
- Comedication (*CYP2C9* inhibitors, substrates)
- Stop of a *CYP2C9* inducer
- Alcoholabusus
- Low serum vitamin K
- Extremely sensitive: *CYP2C9* and *VKORC-1173*
- Superwarfarins

INR below therapeutic target range
- Elevate the dosage

When INR stays 1.0:
- Check for the right tablets
- Possible resistant → resistance genes

With several INRs under target INR:
- Adherence
- Recuperation
- Comedication (*CYP2C9* inducers)
- Stop a *CYP2C9* inhibitor or substrate
- High serum vitamin K
- Enteral feeding
- Measure serum levels of coumarin
- Resistance

Fluctuating INRs need a long time to achieve the therapeutic target range
- Adherence
- Being forgetful
- Concomitant disease
- Varying intake of vitamin K with nutrition or multivitamins
- Varying intake of interacting drugs
- In case of short-acting coumarin such as acenocoumarol:
- Standardise intake and blood sampling time. Choose a longer-acting coumarin such as phenprocoumon.
- Measure serum levels of anticoagulant
- *CYP2C9* and *VKORC1*-1173 status
- Poor quality of dose management

high serum levels of the anticoagulant are needed. So far, we detected three cases with a partial resistance to coumarins.

CONCLUSION

Broad testing of genetics in coumarin therapy has no additional value in settings where a good thrombosis service is available: it should be reserved for special cases only.[7,15,16] Genes do not change during a lifetime, so genetic analysis of *CYP2C9* and *VKORC1* only needs to be done once. The role of nonadherence in coumarin therapy is generally thought to be of great importance, although this could not be confirmed in adherence studies.[17,18] The influence of nonadherence is probably lower than genetic variation.

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