

## Highly probable interaction between acenocoumarol and valproic acid

Manuel Vélez<sup>1</sup>, Professor Covadonga Pérez<sup>1</sup>, Alegría R Dominguez<sup>2</sup>, Professor Teresa Bermejo<sup>1</sup>

### ABSTRACT

**Study objectives:** To report a highly probable interaction between acenocoumarol and valproic acid (VPA), resulting in increased international normalised ratio (INR) values.

**Methods:** A 77 year-old Caucasian male was admitted to the hospital with a diagnosis of epileptic seizure due to low VPA levels of 42.4 mg/L. He had been on anticoagulation therapy with acenocoumarol for four years due to atrial fibrillation. He also carried a VDD pacemaker. Upon admission, his INR was inside the therapeutic range at 2.9. He required an infusion of 1600 mg of VPA and his dose was adjusted to 500 mg/8 hours. On day six, having maintained previous acenocoumarol dosages, his INR increased to 5.6 and acenocoumarol was suspended. On day nine, VPA levels were still infra-therapeutic (38.3 mg/L) and neurologists decided to increase the dosage to 1,000 mg twice daily while haematologists re-introduced acenocoumarol at low doses. On day 11, his INR value elevated again reaching 3.9. During hospitalisation he had no major bleeding complications and was discharged 11 days after admission, maintaining VPA 1,000 mg twice daily and the same weekly dosages of acenocoumarol he had been receiving before admission (23.5–25 mg/week).

**Discussion:** VPA may increase acenocoumarol's anticoagulant effect by displacing acenocoumarol from protein-binding sites. Other causes, e.g. nonadherence, other relevant interactions, of the patient's increased INR were excluded in this case. Using the Drug Interaction Probability Scale, acenocoumarol–VPA interaction appeared to be highly probable.

**Conclusion:** Healthcare professionals should be aware of the possible rise in INR value, and the risk of bleeding after making an increase in VPA dosage in patients under treatment with acenocoumarol.

### KEYWORDS

Acenocoumarol, atrial fibrillation, epilepsy, interaction, international normalised ratio, valproic acid

### INTRODUCTION

Acenocoumarol, an anticoagulant, is the most commonly used 4-hydroxy coumarin derivate in our clinical practice. Coumarins are mainly used for the prevention and treatment of venous thromboembolism, as well as for stroke prophylaxis in patients with cardiac arrhythmias, particularly atrial fibrillation [1]. Maintaining adequate international normalised ratios (INRs) in the appropriate therapeutic range is challenging [1, 2]. When treating atrial fibrillation benefits appear within range 2.0–3.0 [3]. The use of coumarins is complicated because of their narrow

therapeutic window and high interpatient variability in response [4]. Due to the pharmacokinetics and pharmacodynamics of acenocoumarol, many drug–drug interactions have been reported [5].

Valproic acid (VPA) is a simple branched-chain fatty acid with anticonvulsant activity. It is commonly prescribed for treatment of various forms of epilepsy. Numerous VPA interactions have been described due to its ability to inhibit several hepatic enzymes, the ability of other agents to induce its hepatic metabolism and due to its high serum protein-binding ratio (> 90%) [6, 7].

In this paper, we present a case of acenocoumarol–VPA interaction, which resulted in an elevated INR.

### Case Report

A 77 year-old Caucasian male under treatment with VPA 500 mg twice daily for three years to control his epileptic seizures was followed up by neurologists. The patient was also taking acenocoumarol as anticoagulation therapy due to atrial fibrillation, with a pacemaker implanted four years ago to treat a bifascicular block. The goal was to maintain his INR value between 2–3, with monthly controls. Dosages from 23.50–25.00 mg per week had kept his INR value

### CONTACT FOR CORRESPONDENCE:

Manuel Vélez

<sup>1</sup>Pharmacy Department

Hospital Universitario Ramón y Cajal

Carreterra Colmenar, KM9, 100

ES-28034 Madrid, Spain

Tel: +34 91 3368057

Fax: +34 91 3369026

rebotado@hotmail.com

<sup>2</sup>Department of Internal Medicine, Hospital Universitario Ramón y Cajal, Madrid, Spain

stable (average 2.61) in the last twelve laboratory tests. His medical history was also significant for hypertension and hypercholesterolaemia. The dosages of concomitant drugs remained stable for the previous three years and included bisoprolol 1.25 mg/day, enalapril 5 mg/day, atorvastatine 10 mg/day, and omeprazole 20 mg/day.

The patient was admitted to hospital due to an epileptic seizure secondary to low VPA levels (42.4 mg/L). On admission, his INR value was 2.9. The patient received an IV VPA infusion of 1,600 mg over 20 hours in the emergency room. The following day, medication was adjusted orally and he received 1,200 mg (500-200-500) and on day two, 500 mg/8 hours, in an attempt to reach therapeutic levels. He was hospitalised in the Neurology Department on day three. The patient continued taking acenocoumarol with the same dosages as he did at home and, until day six, no other analysis was made, when he showed an INR value of 5.6, treatment with coumarin was suspended by the haematologist. On day nine, neurologists decided to increase the dose of VPA to 1,000 mg twice daily, because his VPA plasma levels were still infratherapeutic (38.3 mg/L), and haematologists re-introduced acenocoumarol at low dosages. Two days after this new increase in VPA dosage (day 11), he reached VPA therapeutic levels (77.8 mg/L) but his INR value again increased and reached 3.9, at which point the haematologists decided to suspend acenocoumarol once more. The patient was discharged the same day and, one week later, he continued with the anticoagulant therapy at the same weekly dosages he had been receiving previously (23.50–25.00 mg/week), keeping the INR value within therapeutic range. He continued treatment with VPA 1000 mg twice daily.

## DISCUSSION

Interactions are one of the main factors that alter INR during anticoagulant treatment. Approximately 250 drugs are currently known to interact with warfarin and, for the majority of them, the mechanism is not clearly established [8]. Published data for oral anticoagulants is based mainly on warfarin research [9] and there is not much information available for acenocoumarol.

To our knowledge, there is only one reported case in which an interaction between warfarin and VPA is suggested [10]. We could not identify any published case reports describing an acenocoumarol–VPA interaction.

VPA is an acidic molecule, which binds extensively to plasma proteins, and is saturable within the usual therapeutic dose range [7]. Saturation of plasma protein-binding sites may explain the minimal increase in total VPA concentration

seen in our patient after our attempts to increase VPA dose to obtain the therapeutic levels, as it has been reported by Guthrie et al. [10]. VPA is also an enzyme inhibitor, capable of reducing the rate of metabolism of a co-administered drug, usually via the *CYP2C9* isoform of cytochrome P450 [6].

Acenocoumarol is mainly metabolised by *CYP2C9* [11], and interaction with VPA could be explained by the inhibition of this isoform. This mechanism provides a possible explanation for the interaction because, in general, the onset of effect for inhibitors is quicker than for inducers and may occur after only several doses of the inhibitor [12]. However, we think that this is not the mechanism that explains the interaction in our case because we need to consider at least three factors: the half-life of acenocoumarol (8–11 hours), the rates of synthesis of clotting factors and the amount of time required for depleting liver stores of vitamin K [13]. Consequently, the onset of coagulopathy can take some days after introducing the implicated drug and this did not happen in our patient, because in the second VPA dose adjustment INR elevated only two days afterwards. An inhibition mechanism is also unlikely because, when the patient was discharged, he continued with the same weekly acenocoumarol dosages he had been receiving previously, although his VPA dosage had doubled.

Acenocoumarol is also an acidic compound with extensive binding to plasma albumin (~ 99%). VPA and coumarins both have high affinity for the same binding site on albumin [14]. A competition for albumin-binding sites, between VPA and acenocoumarol, could result in the displacement of acenocoumarol from albumin-binding sites, and a transitory increase in its effect when VPA dosages are increased, as Guthrie et al. suggested with warfarin [10]. There is *in vitro* evidence of this fact and it was suggested that VPA and its unsaturated metabolites might displace warfarin from plasma-binding sites [15]. Drug clearance is also increased with higher levels of unbound drug, so the displacement produced by VPA is expected to balance out over time, resulting in little or no net effect on anticoagulant pharmacokinetics in the long term. All this could explain why INR was in range after discharge with the same weekly acenocoumarol dosage as before admission.

Usual causes of pathological enhancement of anticoagulant activity, such as changes in dietary intake of vitamin K, renal or cardiac arrest, or the addition of other drugs that alter INR, were studied and discarded. Non-adherence was excluded to explain these changes in INR value and patient's albumin remained in physiological range during his hospital stay (3.4–4.8 g/dL).

Although no haemorrhagic complications were reported in our patient, it is important to consider that, at INR values above 3.0, death caused by major bleeding increases rapidly [4] and, at INR values above 5.0, mortality is about 800 per 1,000 patient years. We would also like to emphasise that VPA alone inhibits the secondary phase of platelet aggregation and this can cause altered bleeding time, bruising, haematoma and thrombocytopenia with no changes in INR values [9]. Therefore, we conclude that there was a high risk of ongoing haemorrhage when the VPA doses were increased and analyses were not being conducted.

Using the Drug Interaction Probability Scale, acenocoumarol-VPA interaction appeared to be highly probable [16].

## CONCLUSION

To our knowledge, this is the first report of an interaction between acenocoumarol and VPA. Clinicians should be aware of the interaction risk associated with changes in VPA doses when acenocoumarol is a concomitant treatment. The patient's INR value should be monitored shortly after these changes in order to avoid the possibility of increasing haemorrhagic anticoagulant complications.

## REFERENCES

1. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest*. 2001;119(1 suppl):8S-21S.
2. Tang EO, Lai CS, Lee KK, Wong RS, Cheng G, Chan TY. Relationship between patients' warfarin knowledge and anticoagulation control. *Ann Pharmacother*. 2003;37(1):34-9.
3. Lip GY, Boos CJ. Antithrombotic treatment in atrial fibrillation. *Postgrad Med J*. 2008;84(991):252-8.
4. Odén A, Fahlén M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ*. 2002;325(7372):1073-5.
5. Rodríguez RM, Tuneu L. Interacciones de los anticoagulantes orales. *JANO*. 2006;1623:55-7.
6. Gunes A, Bilir E, Zengil H, Babaoglu MO, Bozkurt A, Yasar U. Inhibitory effect of valproic acid on cytochrome P450 2C9 activity in epilepsy patients. *Basic Clin Pharmacol Toxicol*. 2007;100(6):383-6.
7. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol*. 2006;61(3):246-55.
8. Myers SP. Interactions between complementary medicine and warfarin. *Aust Prescr*. 2002;25(3):54-6.
9. Baxter K. *Stockley's drug interactions*. 7th ed. London: Pharmaceutical Press: 2006.
10. Guthrie SK, Stoysich AM, Bader G, Hilleman DE. Hypothesized interaction between valproic acid and warfarin. *J Clin Psychopharmacol*. 1995;15(2):138-9.
11. Hermans JJ, Thijssen HH. Human liver microsomal metabolism of the enantiomers of warfarin and acenocoumarol: P450 isoenzyme diversity determines the differences in their pharmacokinetics. *Br J Pharmacol*. 1993;110(1):482-90.
12. Jaffer A, Bragg L. Practical tips for warfarin dosing and monitoring. *Cleve Clin J Med*. 2003;70(4):361-71.
13. Davydov L, Yermolnik M, Cuni LJ. Warfarin and amoxicillin/clavulanate drug interaction. *Ann Pharmacother*. 2003;37(3):367-70.
14. Sjöholm I, Ekman B, Kober A, Ljungstedt-Påhlman I, Seiving B, Sjödin T. Binding of drugs to human serum albumin: XI. The specificity of three binding sites as studied with albumin immobilized in microparticles. *Mol Pharmacol*. 1979;16(3):767-77.
15. Panjehshahin MR, Bowmer CJ, Yates MS. Effect of valproic acid, its unsaturated metabolites and some structurally related fatty acids on the binding of warfarin and dansylsarcosine to human albumin. *Biochem Pharmacol*. 1991;41(8):1227-33.
16. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*. 2007;41(4):674-80.