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Interaction between Levothyroxine and Phenprocoumon: a case report

Case Report

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Abstract: Several case reports have associated the combined use of thyroid drugs and oral anticoagulants, like coumarin, with overanticoagulation. However, this effect has never been described for phenprocoumon, a coumarin derivate that is widely prescribed in continental European countries and in Latin America. We describe a 62-year-old female who had an unexpectedly labile anticoagulation profile when levothyroxine (Puran T4®) was added to her drug therapy regimen, which included phenprocoumon (Marcoumar®). This resulted in an elevated international normalized ratio (INR) that was unrecordable and bleeding (macroscopic hematuria) that required hospitalization and treatment with vitamin K. The patient had been taking phenprocoumon for almost ten years for systemic embolism prophylaxis because of her history of mechanical bileaflet mitral valve prosthesis. One month before the events described, the patient was prescribed sodium levothyroxine (50 mcg daily) to treat hypothyroidism (TSH = 40 μU/mL; reference range, 0.40-4.0 μU/mL). Approximately 3 weeks prior to initiation of levothyroxine treatment, her INR was 2.8. A drug interaction was therefore suspected. The Horn Drug Interaction Probability Scale (DIPS) indicated a probable interaction between oral phenprocoumon and levothyroxine in this case. Clinicians should be aware that levothyroxine may interact with oral phenprocoumon, resulting in overanticoagulation.

Keywords: *Drug-drug interaction • Levothyroxine • Phenprocoumon • Overanticoagulation • Oral anticoagulants*

1. Introduction

Phenprocoumon is a coumarin-type oral anticoagulant (OAC), or vitamin K antagonist (VKA), that is widely prescribed in continental European and Latin American countries for the prophylaxis and treatment of thromboembolic events. The most common complication of this OAC is bleeding, with major bleeding events occurring in 1%–3% of patients annually. Because of the narrow therapeutic range of this drug, many patients experience bleeding of variable severity or recurrent thrombotic events [1-5]. Monitoring of international normalized ratio (INR) and dose adjustments are frequently required during OAC therapy and are influenced by changes in concomitant medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors [6].

Phenprocoumon is rapidly absorbed after oral administration, is highly protein-bound to albumin (99%), and is eliminated almost exclusively through hepatic metabolism via the cytochrome P450 system (CYP). Compared to warfarin and acenocoumarol, phenprocoumon metabolism is less dependent on the polymorphic CYP2C9 enzyme, but may be more liable to CYP3A4-mediated drug interactions [7,8]. Phenprocoumon consists of 2 isomers: R and S. S-phenprocoumon is 1.5–2.5 times more potent than R-phenoprocoumon and the half-life of racemic phenprocoumon is 156–172 h [2].

OACs are frequently used concomitantly with thyroid hormones such as levothyroxine [9]. Some medical textbooks [10,11] and electronic databases [12] point out the potential for an interaction between thyroid hormones and coumarin anticoagulants, resulting in overanticoagulation. However, this effect has never been described for phenprocoumon. Because phenprocoumon metabolism differs somewhat from that of other OACs, it is important to investigate the occurrence of drug interactions between phenprocoumon and levothyroxine.

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In this case report, we describe an adult woman who had an unexpectedly labile anticoagulation profile when levothyroxine was added to her drug therapy regimen, which included phenprocoumon.

2. Case report

A 62-year-old woman (weight 46 kg, height 1.53 m) was admitted to the hospital because of macroscopic hematuria during 5 days after and an unrecordable INR. She denied chest pain and shortness of breath. Ten years ago, she had received a mechanical bileaflet mitral valve prosthesis because of severe mitral valve insufficiency. The patient had a history of atrial fibrillation and chronic heart failure. She was receiving long-term phenprocoumon (Marcoumar®) therapy and was maintaining a stable INR within the therapeutic range (target INR: 2.5–3.5). Fifteen days before starting levothyroxine (Puran T4®; 50 mcg daily) treatment for hypothyroidism, her INR was 2.8. Twenty-six days after starting oral levothyroxine, the patient's INR rose to an unrecordable value and she began experiencing macroscopic hematuria. She was admitted to the hospital 5 days after the onset of macroscopic hematuria. On admission, there were no symptoms of any intercurrent illness and laboratory results, including liver function tests, were normal (Table 1). A chest X-ray radiograph showed borderline cardiomegaly. Medications taken by the patient as part of a chronic therapy regimen were as follows: phenprocoumon (3 mg/day), which the patient stopped taking after the onset of macroscopic hematuria and resumed on the day of admission; carvedilol (6.25 mg/day); captopril (50 mg/day); furosemide (40 mg/day) spironolactone (25 mg/day); levothyroxine (50 mcg/day); and digoxin (0.125 mg/day). A thorough history did not identify any change in diet, concomitant medication, food supplements, or drug therapy compliance. On the day of admission, the concomitant medication regimen remained unchanged, but phenprocoumon was discontinued immediately, and she was given vitamin K (10 mg, intravenously) and fresh frozen plasma. Twenty-four hours later, her INR decreased to 2.14 (Figure 1). Hemoglobin concentration was considered satisfactory and the hematuria spontaneously resolved several hours after admission. Anticoagulation with phenprocoumon was resumed 5 days after the hematuria resolved, but at a lower dose of 1.5 mg daily. The patient's INR rose 3 days after resuming phenprocoumon therapy to 6.79. This INR increase was smaller than that observed with higher doses of phenprocoumon. Phenprocoumon was stopped on the 8th day of hospitalization and levothyroxine was stopped on the 10th day of hospitalization. The patient was discharged 17 days after hospital admission. At discharge, the patient had an INR of 5.0 and a TSH value of 12 (reference range: 0.40–4.0 μU/mL). The patient was taking the same medications at the time of discharge as at the time of admission, with the exception of phenprocoumon and levothyroxine. The Horn Drug Interaction Probability Scale (DIPS) indicated a probable interaction between oral phenprocoumon and levothyroxine in this case [13].

Table 1. Laboratory results on hospital admission.

Laboratory test	Normal value	Patient
Hemoglobin (g/dL)	11.5–16.0	11.5
Eosinophils	1–6 % (180–1,080/mm^3)	3
Typical lymphocytes (%)	25–33	28
Atypical lymphocytes (%)	0	0
Leukocytes (x 1,000/mm^3)	4 - 10	6,3
Monocytes	150-1,350/mm^3	600
Platelet count (x 1,000/mm^3)	150–450	200
AST (U/L)	15–37	20
ALT (U/L)	30–65	30
GammaGT (U/L)	5–85	80
Alkaline phosphatase (U/L)	50–136	130
Total cholesterol mmol/L	< 11.1	11.0
LDL cholesterol mmol/L	< 7.2	7.1
Triglycerides mmol/L	< 8.8	8.8
Fasting glucose mmol/L	3.9 – 5.9	5.5
Sodium mmol/L	130 – 145	136
Potassium mmol/L	3.5 – 5.5	4.3
Creatinine mmol/L	0.03 – 0.07	0.06
Urea mmol/L	0.8 – 2.2	2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GammaGT. gamma-glutamyl transpeptidase; LDL low-density lipoprotein.

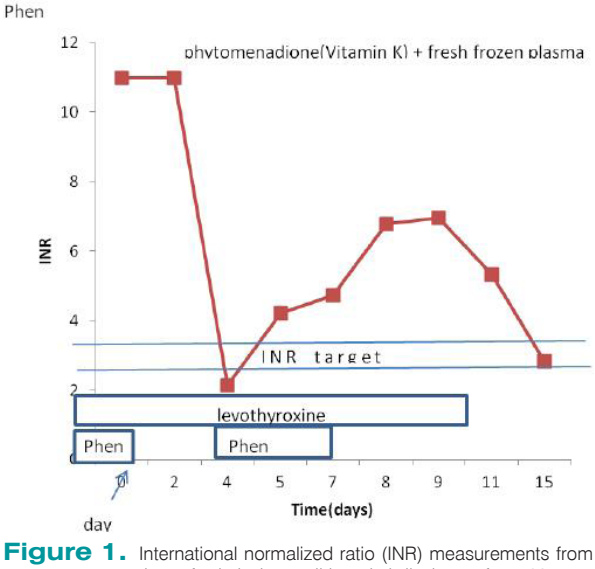

Figure 1. International normalized ratio (INR) measurements from time of admission until hospital discharge for a 62-year-old female patient experiencing a suspected interaction between phenprocoumon (Phen) and levothyroxine. Boxes indicate days on which the respective drugs were administered.

3. Discussion

In this case report we show a clinically significant increase in the INR of an adult female patient who had been stable while undergoing phenprocoumon therapy until levothyroxine was introduced into her treatment regimen. The INR rose when phenprocoumon was used concomitantly with levothyroxine, but lowered when this association was discontinued. No specific medical conditions were identified to explain this event, and apart from levothyroxine, none of the prescribed drugs were suspected to affect the anticoagulant effect of phenprocoumon. According to the DIPS [13], there was a probable interaction between oral phenprocoumon and levothyroxine. This is the first case report describing an interaction between phenprocoumon and levothyroxine. Coumarin derivatives act as competitive inhibitors of vitamin K epoxide reductase (VKORC1), which is responsible for regenerating reduced vitamin K from vitamin K epoxide after it has been consumed as a co-factor in the synthesis of coagulation factors II, VII, IX, and X [6]. While all OACs have a similar mechanism of action and a similar chemical structure, there are substantial differences in their clinical pharmacokinetics [8]. Therefore, while pharmacodynamic interactions may occur with all drugs of this group, the pharmacokinetics of the interactions should be observed separately for each drug.

An extensive review of clinical databases was performed to further investigate the potential mechanism of this interaction. The hypoprothrombinemic response to acenocoumarol and warfarin may be enhanced when thyroid hormone supplementation is added to patient drug therapy regimens. However, no significant effects are expected when acenocoumarol or warfarin is added to patients who are stable under thyroid replacement therapy [12]. The exact mechanism of the interaction among levothyroxine and OAC has not been established. Mechanisms of such interactions may include both pharmacokinetic and pharmacodynamic mechanisms, and may result in either hyper- or hypoprothrombinemia [14].

More than 40 years ago, sodium dextrothyroxine was reported to augment the anticoagulant effect of warfarin by increasing the rate of metabolism of coagulation factors [15]. A recent experimental study indicated that thyroxine treatment increased plasminogen activator activity in the kidney [16]. The plasma levels of vitamin K-dependent coagulation factors FII, FVII, FIX, and FX are significantly reduced under the influence of hormones in the hypothalamic-pituitary-thyroid axis [17]. Because pharmacodynamic interactions may occur with all OAC, the available literature suggests that a possible mechanism for the interaction between phenprocoumon and levothyroxine that results in an increased anticoagulant effect is a levothyroxine-induced increase in the rate of coagulation factor metabolism, as described for the interaction between acenocoumarol and thyroid hormones [18] and between warfarin and dextrothyroxine [15]. However, further validation is required.

The pharmacokinetic mechanism of this interaction is not clear. An increased absorption of phenprocoumon is an unlikely mechanism, because phenprocoumon is almost completely absorbed when administered alone. An interaction between these drugs due to protein displacement of phenprocoumon (plasma protein binding 98%–99%) by levothyroxine (plasma protein binding 99%) is likely because of the high rate of protein binding for levothyroxine [19]. However, the delayed onset of the clinical result raises some doubt about this mechanism. A change in the apparent volume of distribution is also unlikely because the patient was not edematous at any time and had normal serum creatinine. An interaction due to interference in the metabolism of phenprocoumon is not likely, as phenprocoumon is metabolized by CYP3A4 and CYP2C9, while levothyroxine is metabolized by deiodination.

In the case described here, the onset of overanticoagulation occurred 26 days after initiating the concomitant use of phenprocoumon and levothyroxine. This period of delay is similar to the delay that has been reported in other studies for the onset of adverse prothrombin time response (1 day–3 weeks) after the addition of other drugs to the pharmacotherapy regimen of patients taking phenprocoumon [20]. This delay may result from the long half-life of levothyroxine, as the peak therapeutic effect at a given dose of levothyroxine sodium may not be obtained for 4–6 weeks [19].

4. Conclusion

In this case report, an overanticoagulation effect due to a probable interaction between phenprocoumon and levothyroxine was described. Clinicians should be made aware of this potential interaction and adjust doses of phenprocoumon as necessary when initiating or discontinuing levothyroxine therapy. The complex response of coumarins to concomitant drug therapy makes it difficult to predict whether, and to what degree, anticoagulant control might deteriorate in individual patients. If levothyroxine is introduced into a drug therapy regimen that contains phenprocoumon, the patient INR should be monitored to guide adjustment of phenprocoumon and levothyroxine dosages. Patients exposed to this potential drug interaction should be advised when to seek medical attention, should symptoms of overanticoagulation occur.

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