Letter to the Editors

The effect of omeprazole and esomeprazole on the maintenance dose of phenprocoumon

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The response to vitamin K antagonists (VKAs) is determined by many different factors like age, weight, height, vitamin K intake and genetic polymorphisms [1]. The proton pump inhibitors (PPIs) omeprazole and esomeprazole may enhance the effect of VKAs by inhibition of the hepatic metabolism of coumarins [2]. Some isolated cases have been reported of clinically significant elevated INRs in patients concomitantly using omeprazole and phenprocoumon, a VKA frequently used in Europe [3]. Practical experience suggests an interaction between omeprazole or esomeprazole and phenprocoumon, but scientific evidence is still lacking.

Van Schie *et al.* developed a dosing algorithm including age, gender, height, weight, CYP2C9 and VKORC1 genotypes and amiodarone use and a dosing algorithm without the genotypes to predict the phenprocoumon maintenance dose [4]. Given the possibility that omeprazole use affects the stable phenprocoumon maintenance dose, we examined whether information about its use would improve the predictive value of a dosing algorithm.

Data from the pre-EU-PACT study were used to study the effect of omeprazole and esomeprazole on the stable phenprocoumon maintenance dose [4]. More details about this study can be found elsewhere [4]. The main outcome measure of the present study was the mean stable phenprocoumon maintenance dose in mg day⁻¹ in the first stable period after initiation of phenprocoumon therapy. Only patients who reached a stable dose within 1 year were included in the analyses. Multiple linear regression analysis was used to develop a genotype-guided algorithm and a non-genotype-guided algorithm to estimate the square root of the weekly phenprocoumon maintenance dose. We included the same predictive variables used by van Schie *et al.* [4], but added an extra variable for omeprazole or esomeprazole use.

A stable maintenance dose was reached within 1 year by 597 patients. Of these, 46 patients used omeprazole and 18 patients used esomeprazole. On average, non-users required 2.27 mg (SD 0.90) phenprocoumon day⁻¹, significantly higher than the average dose seen in both omeprazole users (1.78 mg day⁻¹, SD 0.73, 95% CI of the difference 0.22, 0.75) and esomeprazole users (1.88 mg day⁻¹, SD 0.52, 95% CI of the difference 0.12, 0.66). Since the phenprocoumon dose was not significantly different between omeprazole and esomeprazole users (95% CI of the difference -0.47, 0.28), we combined them into one group for inclusion in the algorithm. Five hundred and eighty-seven phenprocoumon users were included in the analysis of the non-genotype-guided algorithm and 559 for the genotype-guided algorithm. Omeprazole/esomeprazole use significantly influenced the phenprocoumon maintenance dose in the genotype-guided algorithm ($P = 0.002$) and the non-genotype-guided algorithm ($P = 0.001$) (Table 1). The genotype-guided algorithm was as follows:

$\text{SQRT (maintenance dose (mg week}^{-1}\text{))} = 2.870 - 0.254$
(if CYP2C9*1/*2) - 0.356 (if CYP2C9*1/*3) - 0.431 (if CYP2C9*2/*2) - 0.708 (if CYP2C9*2/*3) - 0.693 (if CYP2C9*3/*3) - 0.594 (if VKORC1 CT) - 1.371 (if VKORC1 TT)
- 0.015 × Age (years) + 0.034 (if female) + 0.009 × Weight (kg) + 0.011 × Height (cm) - 0.315 (if amiodarone use) - 0.234 (if omeprazole/esomeprazole use).

With this genotype-guided algorithm, 56.7% of dose variation could be explained, 0.8% more than in the study of van Schie *et al.* [4]. With our non-genotype-guided algorithm, the predictive value was 18.9%, 1.6% more than the algorithm of van Schie *et al.* [4].

The information obtained in this study could help physicians determine the right phenprocoumon dose for patients. If a patient is already using omeprazole or

Table 1

Algorithms to predict stable phenprocoumon maintenance dose

	Genotype-guided algorithm	P value	Non-genotype-guided algorithm	P value	Univariate r^2
Intercept	2.870		1.659		
CYP2C9 genotype		<0.001		—	5.1
*1/*1	0		—		
*1/*2	−0.254		—		
*1/*3	−0.356		—		
*2/*2	−0.431		—		
*2/*3	−0.708		—		
*3/*3	−0.693		—		
VKORC1 genotype		<0.001		—	34.3
CC	0		—		
CT	−0.594		—		
TT	−1.371		—		
Age (years)	−0.015	<0.001	−0.010	0.001	8.3
Gender, if female	0.034	0.579	0.109	0.174	2.3
Height (cm)	0.011	0.001	0.011	0.020	7.2
Weight (kg)	0.009	<0.001	0.013	<0.001	13.1
Amiodarone use, if yes	−0.315	0.003	−0.304	0.032	0.4
Omeprazole/esomeprazole use, if yes	−0.234	0.002	−0.323	0.001	2.5
Unadjusted r^2 of the algorithm	56.7%		18.9%		

NB, Dependent variable is the square root of the stable maintenance dose of phenprocoumon.

esomeprazole when phenprocoumon treatment is started, the dosing algorithm can be used to predict the required dose. If a patient starts using omeprazole or esomeprazole during phenprocoumon treatment the dose of phenprocoumon should be lowered. This could help prevent over-anticoagulation and thereby reduce the risk of bleeding events when phenprocoumon and omeprazole or esomeprazole are used simultaneously.

In this study we observed a lower phenprocoumon dose requirement in omeprazole and esomeprazole users and developed a dosing algorithm using this information. We only demonstrated the effect of omeprazole and esomeprazole. An interaction between phenprocoumon and other PPIs should be investigated in future research.

Competing Interests

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