

Case report

Drug interaction: Omeprazole and PhenprocoumonChrista Enderle¹, Willi Müller² and Ulrich Grass^{*3}Address: ¹Hospitalstr. 31, 88499 Riedlingen, ²Bahnhofstr. 33, 31737 Rinteln and ³Oberhof 18, 78351 Bodman-LudwigshafenE-mail: Ulrich Grass* - grass.akupunktur@t-online.de

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Abstract

Background: Oral anticoagulants like the coumarin derivatives are characterised by a particularly narrow therapeutic range. Any interfering co-medication can pose a challenge to establishing a stable anticoagulant dosage regimen and thus present a serious risk for the patient. Here we describe two cases of patients on anticoagulant therapy that suggest possible drug interactions between phenprocoumon and the proton pump inhibitor omeprazole.

Results: In both patients, the International Normalised Ratio (INR) increased beyond the therapeutic range after they were given omeprazole for the treatment of gastrointestinal symptoms. The INR returned to therapeutic levels after the phenprocoumon dose was reduced (Case 1) and omeprazole discontinued (Case 2).

Conclusions: The increased anticoagulant activity of phenprocoumon observed in the two described cases and the known interaction potential of omeprazole suggest that the clearance of phenprocoumon may have been reduced due to competitive inhibition of its degradation by omeprazole. Drug interactions may be one of the reasons for the difficulties encountered with some patients in establishing a stable anticoagulant therapy. Physicians should carefully review any concurrently used medication and if possible opt for drugs with a low interaction potential.

Background

Oral anticoagulants like the coumarin derivatives are characterised by a particularly narrow therapeutic range. Concurrently taken drugs such as alcohol, barbiturates, and anti-inflammatory agents potentially interact with coumarin derivatives and can seriously affect anticoagulant activity. Any interfering comedication can pose a challenge to establishing a stable anticoagulant dosage regimen and thus present a serious risk for the patient [1,2]. Here we describe two cases of possible drug interactions between phenprocoumon and the proton pump inhibitor omeprazole, requiring adjustment of the anticoagulant dose.

Case 1

A 68-year-old woman (height: 160 cm; body weight: 60 kg) with a history of recurring tachyarrhythmia, hypertension and severe hyperlipaemia was treated with phenprocoumon (Marcumar, Roche) since December 1998. After an initial phasing-in period of about 5 months, the required dosage for maintaining the patient's International Normalised Ratio (INR) between 2.1 and 2.7 had stabilised at 5^{1/2} to 6^{1/2} tablets of phenprocoumon (3 mg/tablet) per week. At this stage, the INR was determined every 3 to 4 weeks to monitor anticoagulation therapy.

Concurrently the patient was treated with β -acetyldigoxin (Novodigal 0.2: 1 \times 1/day), sotalol hydrochloride (So-

talex 80: $2 \times 1/\text{day}$), pirtanide (Arelix mite: $1 \times 1/\text{day}$), hydrochlorothiazide (Esidrix: $1 \times 1/\text{day}$), irbesartan (Aprovel 150: $1 \times 1/\text{day}$), potassium chloride (Rekawan: $1 \times 1/\text{day}$), and simethicone (Enzym-Lefax: $3 \times 1/\text{day}$).

On October 15th 1999, a gastroscopy was performed to investigate the patient's persistent upper abdominal complaints. This revealed the presence of a large hiatus hernia as well as histological evidence of reflux esophagitis. After commencing (October 15th) treatment with omeprazole (Antra MUPS $1 \times 20 \text{ mg}/\text{day}$), the patient's INR increased from initially 2.15 (determined on October 6th) to 3.34 (November 3rd), although the phenprocoumon dosing regimen and all other medication had been continued without changes. For the following weeks, the phenprocoumon dose was therefore reduced to $5^{1/2}$ tablets per week, compared to 6 tablets per week just prior to omeprazole treatment. At the next check-up (November 17th), the INR had returned to 2.28, a value well within the targeted range.

Case 2

The second case concerns a 72-year-old diabetic woman with advanced arthropathy which had immobilised her for a considerable period of time. Her condition led to a bilateral pulmonary embolism which was scintigraphically confirmed on April 9th 1999. A thrombosis in her left leg was phlebographically confirmed six days later and on April 16th the patient was put on a loading schedule of phenprocoumon commencing with 4 tablets on day 1, 3 on day 2, 1 on day 3, and further as required. At the same time, the patient was given omeprazole ($1 \times 20 \text{ mg}$ before bedtime) to treat a minimal antrum gastritis. Other co-medications were enalapril (Xanef: $1 \times 1/\text{day}$), glyburide (Euglucon: $1 \times 1/\text{day}$), and dipyrone (Novalgin: $3 \times 20 \text{ drops}/\text{day}$).

Before anticoagulation was initiated, the patient's INR value was 1.02. On the third and fourth day of anticoagulation therapy it had increased to 2.02 and 3.28, respectively. Because the patient responded so strongly, she received no further phenprocoumon during the following days. However, surprisingly the INR value remained at the high level throughout the following 9 days. It was suspected that this unusually long persistence of anticoagulant activity was caused by interference of omeprazole with the metabolism (and thus elimination) of phenprocoumon. Consequently, omeprazole was discontinued on April 29th. Four days later the INR value had decreased to 1.5 and anticoagulation therapy with phenprocoumon was successfully resumed using initially $5^{1/2}$ tablets per week. By mid July, the required dose for maintaining the INR within the therapeutic range had stabilised at 3 to $3^{1/2}$ tablets/week.

In December 1999, the patient had to undergo minor surgery and, thus, phenprocoumon was withheld for three weeks. Within 7 days the INR value had dropped to below 1.5, and no problems were encountered when anticoagulation therapy was resumed with a loading schedule similar to the one used in April. This observation lent further support to the notion that indeed omeprazole may have been responsible for the problems with the anticoagulation regimen encountered in April.

Discussion

In both patients the INR increased beyond the therapeutic range in correlation with omeprazole treatment. In case 1, the INR returned to therapeutic levels after reducing the dosage of phenprocoumon. In case 2, even after phenprocoumon was discontinued the INR remained above therapeutic levels and decreased only after omeprazole was also discontinued; when phenprocoumon was subsequently resumed there were no difficulties in adjusting this patient's INR to the desired level. Nor were any such difficulties encountered at a later stage when phenprocoumon was first withheld from the same patient in preparation for surgery and then subsequently reintroduced with the usual loading schedule. In neither case were any of the other co-medications adjusted. Throughout the observation period both patients continued with the routine of their other co-medications. Collectively, above observations suggest that our difficulties in adjusting the anticoagulation level may be due to some interference from omeprazole. Unfortunately, neither phenprocoumon nor omeprazole levels were measured in our two patients and on the basis of the available evidence any suggestions about the possible mechanism(s) of interference remain speculative.

Omeprazole is known for its high potential to interact with other drugs [3,4]. One of the reasons is the relatively high affinity of omeprazole for certain isoenzymes, or CYP isoforms, of the cytochrome P450 enzyme system. This system has a key function in hepatic oxidative drug metabolism [5] including the degradation of coumarin derivatives [6,7], and common metabolic pathways together with the limited metabolic capacity of the involved CYP isoenzymes are the major reason why so many drug-drug interactions occur.

However, based on currently available evidence, omeprazole and phenprocoumon do not seem to be metabolised via the same CYP isoforms. Omeprazole is primarily metabolised via CYP2C19 and to a lesser extent by CYP3A4 [3,8], whereas phenprocoumon is metabolised via CYP2C9 and possibly also other, as yet to be identified isoforms [9]. In vitro experiments with human liver microsomes indicate that omeprazole can actually inhibit CYP2C9, but it can do so only at relatively high concen-

trations [8]. This would seem to preclude any clinically significant interaction of omeprazole and phenprocoumon at the metabolic level. However, CYP2C19 is polymorphically expressed, resulting in substantial interindividual variation in the metabolic rate of drugs eliminated via this isoform [3,4,8]. Some individuals are deficient in CYP2C19 and consequently metabolise omeprazole via alternative but less efficient pathways. In such slow metabolisers the serum concentration of omeprazole has been reported to reach levels that are on average fivefold higher [10,11], and the area under the serum concentration *versus* time curve to be on average tenfold [10] or even 20-fold [11] greater than in normal rate metabolisers. At those concentration levels it is possible that omeprazole could effectively compete with phenprocoumon for binding sites on CYP2C9, thus resulting in competitive inhibition of phenprocoumon metabolism. This would explain the increased anticoagulant activity of phenprocoumon which was evident in the two described cases during co-medication with omeprazole. Unfortunately, we do not know the CYP2C19 genotype of our two patients described here.

Similar cases, involving the coumarin derivatives acenocoumarol and warfarin, have been reported also by others [[12–14]]. But systematic studies on the interaction potential of omeprazole with coumarin derivatives in slow *versus* normal rate metabolisers are still lacking.

Drug interactions may be one of the reasons for the difficulties encountered with some patients in establishing a stable anticoagulant therapy. Physicians should carefully review any concurrently used medication and if possible opt for drugs that are known to have a low interaction potential.

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