Case Report

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Probable Acenocoumarol-Amoxycillin Interaction

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Abstract

We present the case of a woman undergoing treatment with acenocoumarol for deep vein thrombosis, who maintained an international normalized ratio (INR) of between 2.5 and 4 for 2 months. Seven days after the introduction of amoxycillin (500 mg/8 h) for a probable respiratory infection, the patient developed spontaneous bruising, with an INR of 7.1. Treatment with amoxycillin was discontinued, and 3 weeks later the INR had returned to previous values. In this case, the increase in the INR value with associated bruising after the addition of amoxycillin suggests a drug interaction between acenocoumarol and amoxycillin, other possible causes having been eliminated.

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Many factors can influence the response to oral anticoagulants and necessitate the modification or individualization of dosage. Oral anticoagulants are well known to have a number of clinically significant drug interactions that require close monitoring when patients are on a multiple-drug regimen [1]. Particularly noteworthy are interactions that enhance the effect of oral anticoagulants and increase the risk of bleeding.

In this report we discuss the case of an elderly woman, under treatment with acenocoumarol, who developed spontaneous bruising after 7 days of treatment with oral amoxycillin.

An 81-year-old woman was hospitalized for treatment of right osteoarthritis, and a hip prosthesis was inserted. During the immediate postoperative period, the patient suffered from deep vein thrombosis in both legs, for which anticoagulation was performed, first with a continuous intravenous infusion of sodium heparin, and 5 days later with the commencement of oral anticoagulant therapy

with acenocoumarol. After acenocoumarol had been administered at 4 mg/day for 3 days, the dosage was titrated to maintain an international normalized ratio (INR) of between 2.5 and 4. This patient suffered from chronic obstructive pulmonary disease and hyperuricemia and was treated with oral terbutaline (5 mg/6 h), amiloride (5 mg/day) and hydro-chlorothiazide (50 mg/day). Laboratory studies, including blood chemistry, complete blood count, urinalysis, and liver function tests were normal, except for mild hyperuricemia. The patient had a

comprehensive functional assessment for all activities of daily living and no cognitive disorders were observed.

Having made satisfactory progress, the patient was discharged 3 weeks later and returned to her geriatric residence. Tests carried out at that time showed a prothrombin time (PT) of 34 s (control 13 s), a partial thromboplastin time (PTT) of 62 s (control 31 s) and an INR of 3.8, when 3 mg/day acenocoumarol were being administered.

In the course of the next month, two further tests gave similar results and, therefore, neither the dose of acenocoumarol nor of concomitant drugs was changed.

Seven days later, the patient experienced coughing and increased expectoration without fever or change in chest roentgenogram and was treated with oral amoxycillin (500 mg/8 h) and fluid therapy.

A further 7 days later, bruising was observed on both buttocks, although no evidence of bleeding was observed. A test was requested and showed a PT of 57 s (control 13 s), a PTT of 81 s (control 34 s) and an INR of 7.1. Acenocoumarol was discontinued for 2 days and upon resumption was administered at 2 mg/day. Treatment with amoxycillin was also discontinued, although all concomitant drugs continued to be administered at the same dosages.

At this point, there was no indication of hepatic dysfunction, congestive heart failure, or gastrointestinal disorders. There were no signs of fever or change in diet intake.

Six days later, a new test was requested. This showed a PT of 19 s (control 13 s), a PTT of 35 s (control 29 s) and an INR of 1.6. Consequently, the dosage of acenocoumarol was increased to 3 mg/day.

Three weeks later, tests gave results similar to those registered when the patient had been discharged from hospital, and the same dose of acenocoumarol was administered until the next tests.

In this particular case, the well-documented time period between the addition of amoxycillin to the acenocoumarol regimen and the subsequent rise in PTT with associated bruising suggests a drug interaction. We believe it likely that the phenomena observed in this case are related to the administration of amoxycillin, since other possible causes, such as the appearance of intercurrent diseases and change in diet, can be discounted. Any misunderstanding on the part of the patient as to the correct dosage to be taken, or the intake of nonprescribed drugs can also be discounted, because the drugs were always administered under the direct supervision of nurses.

In the medical literature, various reports of interactions between oral anticoagulants and antibiotics have discussed an increase in metabolic rate, for example, with rifampin [2], and nafcillin [3], or inhibition of the metabolic pathway, for example with chloramphenicol [4], metronidazole [5], erythromycin [6], and trimethoprim-sulfamethoxazole [7].

Moreover, other pharmacodynamic interactions have been reported with the second- and third-generation cephalosporins which augment the anticoagulant effect by inhibiting the cyclic interconversion of vitamin K [8], and

with large doses of penicillins [9] and moxalactam [10], since these inhibit platelet function, and thus prolong bleeding.

Likewise, with the use of sulphonamides and a large number of broad-spectrum antibiotics (neomycin, tetracyclines) hypoprothrombinemia with prolongation of the PT has been reported

in patients being treated with oral anticoagulants [11,12]. This is probably due to the elimination of bacterial flora in the gut and the suppression of synthesized vitamin K, which thus enhances the anti-vitamin K effect of oral anticoagulants. Such an effect, however, is not normally observed unless there is a dietary deficiency of vitamin K.

In the case reported here, the interaction between acenocoumarol and amoxycillin was probably produced either by an alteration in the intestinal microflora by amoxycillin (although in this patient the dietary intake of vitamin K was normal), or by inhibition by the antibiotic of the hepatic metabolism of acenocoumarol, since amoxycillin is poorly bound to plasmatic albumin and, therefore, displacement of acenocoumarol from plasma albumin (with an increase in the free fraction) is very unlikely.

In conclusion, both oral anticoagulant drugs and antibiotics of the penicillin group have been widely used, and so far there have been no reports of any interaction. However, this newly discovered interaction between amoxycillin and acenocoumarol may be clinically important in elderly patients who need concomitant administration of such drugs.

Additional controlled studies and epidemiologic data are needed to identify patients at risk and to determine the possible mechanisms of this interaction.

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