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Letters to the Editor

Nimorazole may increase the effect of phenprocoumon

Nimorazole may be administrated concomitantly with radiotherapy as a hypoxic radiosensitizer for the treatment of head and neck cancer [1]. This 5-nitroimidazole is closely related to metronidazole in structure and activity. Metronidazole inhibits CYP2C9, which may lead to clinically relevant interactions with warfarin, which also is degraded by the enzyme [2,3] and this risk is extrapolated to phenprocoumon. Because of its similarity with metronidazole, nimorazole given concomitantly with either warfarin or phenprocoumon may theoretically cause interaction too.

A 66-aged man was diagnosed with stage II squamous cell carcinoma of the glottis. He was referred to radiotherapy, 66 Gy in 33 fractions, 6 fractions per week with 2500 mg nimorazole given 1½ h before each fraction. Fifteen years previously he had had a mitral valve prosthesis inserted and since then had received phenprocoumon 1.5 mg 6 days per week with stable INR-values around 2.5. At the 16th nimorazole dose, he had hemoptysis, and on the 17th dose he noted continuous hematuria with no pain. At the 22nd dose INR was 7.5 and he was admitted to hospital. Phenprocoumon was discontinued and phytomenadion 2 mg was given. Apart from nimorazole, he was treated with two drugs, which could interact with phenprocoumon: fluconazole [4] 50 mg once daily and acetaminophen 1 g q.i.d. Fluconazole had only been given for 4 days, thus after the first symptoms of excessive bleeding. Acetaminophen was deemed an unlikely cause, since no clinically relevance is associated with the interaction [5]. Thus, the most likely explanation was an interaction with nimorazole, which was discontinued.

When the patient had recovered and re-started phenprocoumon, only 5 days remained of the planned radiation regimen during which the patient agreed to a nimorazole re-challenge. During the following 12 days—while phenprocoumon regimen was continued—the patient increased from 3.7 to 5.3 in INR, a change of 40% exceeding the least significant increase in INR, which had been estimated to 23%, being based on the laboratory's CV% at 8% for INR during therapy. This re-challenge observation supports the possibility of interaction.

It is a limitation, that only one case was observed. Moreover, another cause for hypocoagulation may exist. However, it is unlikely that reduced food intake due to irradiation therapy would lead to a decrease in vitamin K intake that could result in the severe INR-elevation observed. Also, no clinical or laboratory findings in the patient gave indications of underlying disease, which would have caused the hypocoagulatory state. Evaluation of the patient's CYP2C9 gene showed CYP2C9*1, which is the wildtype enzyme with normal activity. Other polymorphisms (*2 and *3) are known to cause insufficient metabolism of warfarin [6].

In conclusion, we observed a possible clinically important interaction between nimorazole and phenprocoumon. It is likely to be based on the similarities between nimorazole and metronidazole on the one hand and between phenprocoumon and warfarin on the other. Care for patients in treatment with a vitamin K antagonist for whom nimorazole therapy is indicated requires attention with regard to risk of hypocoagulation.

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