Poster

[P27-4] P27-4: Cardiovascular drugs (1)

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[P27-4-1] A case of significantly prolonged PT-INR after use of miconazole gelled preparation during warfarin therapy

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Background

Recently, several cases have been reported that warfarin's effect is enhanced by concomitant use of miconazole, one of azole antifungal drugs and have CYP inhibitory activity, however the its mechanism have not been clarified . We experienced a case of significantly prolonged PT-INR after use of miconazole gelled preparation (MCZgp) during warfarin therapy and measured the plasma concentration of warfarin, miconazole, and vitamin K to clarify the cause of significant prolongation of PT-INR in this case.

Methods

A 44-year-old man treated with cisplatin and doxorubicin for squamous cell skin cancer started warfarin therapy for deep vein thrombosis (day 1) 9 days after chemotherapy and MCZgp for oral candidiasis (day 4 - 6). PT-INR was measured at day 5, and prolonged value of PT-INR, over the measurement upper limit value, was found. Then, warfarin and MCZgp was discontinued on the same day and day 6, respectively. Because the prolongation of PT-INR continued, vitamin K2 was administered intravenously on day 8, and PT-INR returned to 1.07 next day. Plasma samples used for clinical test were collected and used for the analysis of plasma concentrations of warfarin enantiomers, miconazole and vitamin K (K1: phylloquinone, K2: menaquinone 4 (MK 4) and menaquinone 7 (MK 7)).

Results

The plasma concentrations of S- and R-warfarin at 12 hours after administration were within common therapeutic range (0.1 - 0.4 g/mL), and the concentration of miconazole was less than lower limit of detection (10 ng/mL). On the other hand, although MK4 level was within the normal range (around 0.8 ng/mL), VK1 and MK-7 were very low level (less than 0.10 ng/mL and 0.13 - 0.36 ng/mL, respectively) after day 5.

Conclusions

In this case, no increase in plasma concentrations of warfarin and miconazole were found. It was considered that the abnormally prolonged PT-INR was not due to pharmacokinetic interaction between those drugs. Extremely low Vitamin K concentration might be caused by decrease of food intake due to chemotherapy and is considered to be one of cause of prolongation of PT-INR.