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LETTER TO THE EDITORS

Effects of voriconazole co-administration on oxycodone-induced adverse events: a case in the retrospective survey

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Letter to the editor

Oxycodone, a semisynthetic μ-opioid receptor agonist, is widely used for acute and chronic pain [1]. Because oxycodone is a substrate of cytochrome P450 (CYP) 2D6 and 3A4 [2–4], pharmacokinetic drug interaction may occur under concomitant use of CYP inhibitors, such as azole antifungals. Hagelberg et al. recently reported a drug interaction between oxycodone and voriconazole, an antifungal agent with potent CYP3A4 inhibitory activity, in a pharmacokinetic study employing healthy individuals, where the area under the drug concentration-time curve for oxycodone increased by 2.7–5.6 fold under co-administration of voriconazole [5]. This finding suggests that voriconazole potentially enhances both the efficacy of and the occurrence of related adverse events when both drugs are used concomitantly. To assess the clinical impact of this drug interaction, we present a typical case and clinical survey of nine cancer patients who were treated simultaneously with oxycodone and voriconazole. The study was approved by the Ethical Committee of Tsukuba University Hospital (Tsukuba, Japan).

A 41-year-old man (63.6 kg) with Burkitt's lymphoma received oxycodone per os for his thigh pain. Dosage was maintained at 20 mg d^{-1} after admission. As he was feverish due to possible *Aspergillosis*, with positive *Aspergillus* antigen, voriconazole iv was administered for 5 days (700 mg d^{-1}; day 7, 400 mg d^{-1}; day 8–11). The fever gradually declined, and serum *Aspergillus* antigen turned negative on day 13. The patient complained of nausea and vomited just after starting voriconazole (on days 8 and 9). A sudden reduction in heart rate was also observed on day 9. Although he had required additional oxycodone (rapid-release preparation) as the rescue dose (2.5–5.0 mg d^{-1}) both before starting and after stopping voriconazole, he needed no rescue dose during voriconazole co-administration (Fig. 1). These observations suggested that voriconazole co-administration enhanced both the efficacy of and the adverse symptoms relating to oxycodone, resulting in no need for a rescue dose of oxycodone but inducing nausea and vomiting while both drugs were used concomitantly. The dosing schedule for other drugs (omeprazole, gabapentin, zolpidem, magnesia oxide) was unchanged before and after voriconazole administration. Liver and kidney function (aspartate aminotransferase, 52 IU L^{-1}; alanine aminotransferase, 97 IU L^{-1}; blood urea nitrogen, 6.5 mg dl^{-1}; serum creatinine 0.49 mg dl^{-1}), and other laboratory data were also unchanged throughout the study.

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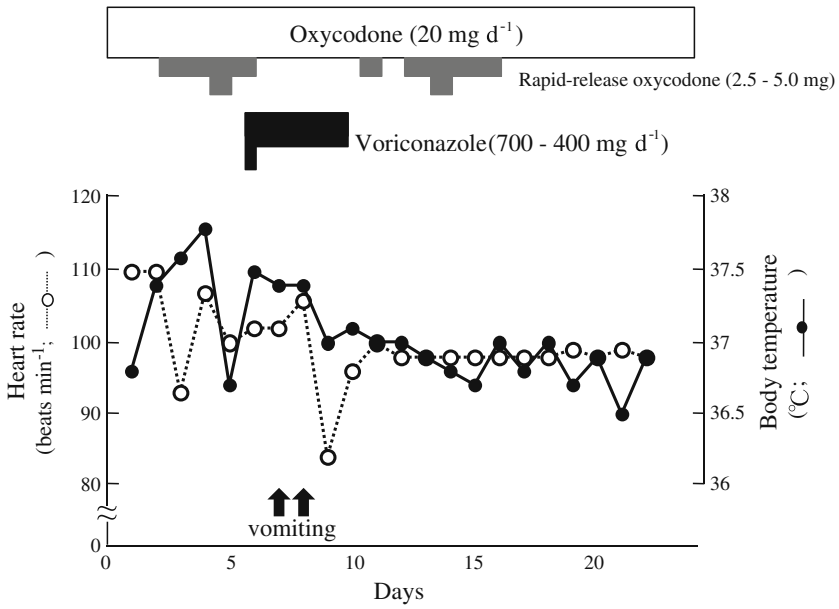

Fig. 1 Clinical course for a case treated with oxycodone and voriconazole co-administration

We retrospectively surveyed the combined use of oxycodone and voriconazole in the medical records. Nine cases, including the one reported here (male:female 2:7; 59±15 years; 49.8±11.0 kg) were found and assessed (Table 1). The drugs were co-administered at 0.39 (0.23–2.07) and 6.51 (2.16–7.92) mg kg^{-1} d^{-1}, respectively, for 15 (2−42) days. Dosing schedule of drugs affecting oxycodone metabolism was unchanged during the study period. Possible adverse events of oxycodone were observed in seven patients 1–10 days after initiation of voriconazole co-administration (vomiting four, drowsiness and respiratory depression two, delirium and sweating one). One patient (case 3) required oxycodone dose reduction due to vomiting and sweating during voriconazole co-administration. Case 7 had difficulty with pain control 2 days after voriconazole co-administration ceased. This implies that oxycodone concentration in the blood might be high enough for pain relief during voriconazole co-administration. These observations supported the possibility that voriconazole co-administration enhances oxycodone-induced adverse events, at least in these seven cases. Occurrence of these adverse events was not associated with voriconazole administration route (iv or po) or oxycodone and voriconazole daily dose during co-administration. Cases 8 and 9, however, showed no difference in oxycodone-related events whether or not voriconazole was co-administered.

Drug interactions between oxycodone and azole antifungals, such as voriconazole and itraconazole, impact the proper use of oxycodone from the pharmacokinetic stand-

Table 1 Patient characteristics

Case	Sex	Age (years)	PS	Diagnosis	Body weight (kg)	Dose (mg kg^{-1} d^{-1})		Co-administration period (d)	Adverse events (Occurrence day)
						Oxycodone	Voriconazole		
1	Female	51	2	NHL	69.4	0.86	2.16	42	Drowsiness (2)
2	Female	64	4	DLBCL	38.5	2.07	2.59	2	Delirium (2), hypopnea (2)
3	Male	76	3	Maxillary tumor	40.2	0.50→0.25	4.98	4	Drowsiness (2), vomiting (2, 3), sweating (3), hypotension (4), hypopnea (4)
4	Female	39	1	Mycosis fungoides	50.9	0.39	7.86	10	Vomiting (10)
5	Female	71	2	AML	39.3	0.25	7.63	6	Vomiting (3)
6	Male	41	1	BL	63.6	0.31	6.29 (iv)	5	Vomiting (2, 3), uncontrolled pain (1)
7	Female	48	2	MM	50.5	0.79	7.92	20	Uncontrolled pain (1)
8	Female	82	2	AML	52.6	0.38	7.60 (iv)	32	–
9	Female	60	2	ALL	43.0	0.23	6.51	15	–

AML acute myelocytic leukemia, *DLBCL* diffuse large B-cell lymphoma, *BL* Burkitt's lymphoma, *NHL* non-Hodgkin's lymphoma, *MM* multiple myeloma, *ALL* acute lymphatic leukemia, *PS* performance status

point [5–7]. Our preliminary study confirmed that this drug interaction, at least the combination of oxycodone and voriconazole, was clinically important, because oxycodone-induced adverse events were observed in seven of nine patients treated concomitantly with both drugs. As most events were observed 1–4 days after either introducing or stopping voriconazole co-administration (Table 1), we recommend paying attention to possible drug interactions early when both drugs are used simultaneously.

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