Aprepitant does not alter prednisolone pharmacokinetics in patients treated with R-CHOP

Aprepitant, a neurokinin 1 receptor antagonist, is an effective antiemetic drug in the prevention of chemotherapy-induced nausea and vomiting. Aprepitant co-administration increases plasma concentrations of dexamethasone and methylprednisolone by inhibiting cytochrome P450 (CYP) 3A4 [1], whereas pharmacokinetics of cyclophosphamide, which is also metabolized by CYP enzymes including CYP3A4, is not significantly changed by aprepitant [2]. Thus, aprepitant co-administration provides different effects on pharmacokinetics of CYP substrates; however, it is unknown whether aprepitant affects pharmacokinetics of prednisolone, another CYP3A4 substrate. We aimed to evaluate the effect of aprepitant on pharmacokinetics of prednisolone, and the safety and efficacy of aprepitant when administered together with rituximab, cyclophosphamide (Shionogi, Osaka, Japan), doxorubicin (Adriamycin) (Sandoz, Tokyo, Japan), vincristine (Nippon Kayaku, Tokyo, Japan), and prednisolone (R-CHOP) in patients with non-Hodgkin’s lymphoma. We conducted a nonrandomized, open-label, single-group before/after design study between courses 1 and 2 of R-CHOP. This study was approved by the institutional review board of the University of Tsukuba Hospital. Patients received 100 mg of oral prednisolone from days 1–5 in divided doses of 60 mg at 8 am and 40 mg at 1 pm. Aprepitant was added orally for 3 days (125 mg on day 1, and 80 mg on days 2 and 3) at 7 am during the course 2. In each course, 3 mg of granisetron was given twice on day 1.

Ten patients (diffuse large B-cell lymphoma in seven and follicular lymphoma in three) completed the study. Antiemetic CR (defined as no emetic episodes and no use of rescue medication) without and with aprepitant was observed in 8 and 10 out of 10 patients, respectively. A series of serum prednisolone concentrations in eight patients were measured. The mean AUC of prednisolone from 0 to 5 h was not different between the courses 1 and 2 (2200 ± 490 and 2178 ± 794 ng h/ml, respectively; P = 0.932) (Figure 1), although areas under the curve of prednisolone were increased in four patients and decreased in other four patients by the co-administration of aprepitant. The median (range) T\textsubscript{max} [2 (0.5–2) and 2 (0.5–5) h, respectively] and the mean C\textsubscript{max} (646 ± 191 and 634 ± 285 ng/ml, respectively; P = 0.88) were not affected by aprepitant. There was no significant difference in blood glucose concentration and blood pressure level between the courses 1 and 2.

Previous studies have shown that CYP3A4 inhibitors, such as ketoconazole and itraconazole, do not affect the metabolism of prednisolone [3, 4], whereas they increase plasma concentration of dexamethasone and methylprednisolone [1]. Consistent with these reports, our results indicated that aprepitant had virtually no impact on prednisolone pharmacokinetics. Hepatic metabolism for prednisolone is different from those for dexamethasone and methylprednisolone, in that 11-β-hydroxysteroid dehydrogenase plays a role in addition to CYP3A4 only for prednisolone, through the conversion of the hydroxyl group to ketone on the 11th position of C-ring. Therefore, the contribution of CYP3A4 to the metabolism may be lower in prednisolone than in dexamethasone and methylprednisolone [5].

We concluded that aprepitant could be safely administered when strengthened antiemetic treatment is required, without serious drug interactions with prednisolone in R-CHOP.


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Figure 1. Prednisolone concentration (n = 8). Mean serum concentration profiles of prednisolone with or without aprepitant in eight patients. Blood samples were collected on day 3 after oral administration of prednisolone (60 mg at 0 h and 40 mg at 5 h). Aprepitant was administered orally for 3 days (125 mg on day 1, 80 mg on days 2 and 3) at −1 h of prednisolone. Error bars show standard deviations.
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disclosure

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references


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