Chinese Medicine, **2011, 2, 58-61**
doi:10.4236/cm.2011.22011 Published Online June 2011 (http://www.SciRP.org/journal/cm)

Rikkunshi-to Partially Reverses Cancer Chemotherapy-Induced Decrease in Plasma Valproic Acid Concentration in a Patient with Malignant Lymphoma

Masashi Ishihara[1], Kiyoyuki Kitaichi[1], Katsuhiko Matsuura[1], Hiroshi Nakamura[2], Hisashi Tsurumi[2], Hisataka Moriwaki[2], Yoshinori Itoh[1*]
[1]*Department of Pharmacy, Gifu University Hospital, Gifu, Japan*
[2]*First Department of Internal Medicine, Gifu University Graduate School of Medicine, Gifu, Japan*
E-mail: *yositou@gifu-u.ac.jp*
Received April 6, 2011; *revised April* 28, 2011; *accepted April* 29, 2011

Abstract

A fifty-five-year-old male patient with malignant lymphoma who took oral valproic acid (VPA) tablets and itraconazole (ITZ) capsles received 3 courses of cancer chemotherapy, including 2 courses of a combination of rituximab/methotrexate/ifosphamide/etoposide/carboplatin/ methylpredonisolon (R-IMVP16/CBDCA regimen) and subsequent one course of a combination of rituximab/ranimustine/citara bine/etoposide/merphalan (R-MEAM regimen). Plasma concentration of VPA dramatically decreased below the therapeutic concentration after the first and second chemotherapy and seizures appeared in both cases. Plasma concentration of ITZ was also lowered after the second chemotherapy course. At the third chemotherapy, Rikkunshi-to, a Japanese herbal medicine, was prescribed for 14 days. Plasma VPA concentration decreased, though to a lesser extent, after chemotherapy, in which the level was near the border of therapeutic concentration. No convulsion was observed. Therefore, care should be taken to monitor plasma drug concentration during cancer chemotherapy. Rikkunshi-to may be useful to alleviate the chemotherapy-induced decrease in plasma concentrations of orally administered drugs.

Keywords: Cancer Chemotherapy, Malignant Lymphoma, Valproic Acid, Therapeutic Drug Monitoring, Convulsion, Rikkunshi-to

1. Introduction

Valproic acid (VPA) has a broad spectrum of inhibitory activity in various types of epilepsy. Furthermore, the compound is used as a therapeutic agent for manic state of the bipolar disorder. However, there are individual differences in the absorption, distribution, metabolism, excretion, and thus pharmacokinetic parameters, including the maximum drug concentration time and half-life, of VPA. Therefore, individual monitoring of plasma concentration of VPA is required to determine the dosing schedule of VPA [1,2]. The effective plasma concentration of VPA is reported to be 50 - 100 μg/ml [3,4] or 40 - 120 μg/ml, according to the manufacturer's instruction. When the plasma concentration exceeds 100 μg/ml, the incidence of the hepatic dysfunction is heightened [3]. Thus, it is important to maintain the optimal plasma concentration of VPA.

It has been reported that several compounds exhibit pharmacokinetic interactions with VPA, which includes carbapenem antibiotics [5-8], lamotrigine [9], salicylic acid [10,11], benzodiazepines [12] and anticancer drugs [13]. Ikeda *et al.* [13] reported a reduction of plasma concentration of VPA in a patient who received cancer chemotherapy regimen including cisplatin.

We reported here a case of marked decrease in plasma VPA concentration after combination cancer chemotherapy with episodes of epileptic seizures. In addition, the usefulness of a herbal medicine Rikkunshi-to was subsequently discussed.

2. Methods

A male fifty-five-year-old patient who had recurrent CD20- positive diffuse large B-cell lymphoma (DLBCL) was a subject of the present study. Data were obtained

from the record of pharmaceutical practices in hematology ward and electric medical record.

He was 164.5 centimeters tall, 57 kilograms weighs and 1.619 m^2 body surface area. For the therapy of aggressive B cell lymphoma, 4 cycles of Rituximab and 6 cycles of THP-COP regimen (cyclophosphamide 650 mg/m^2, day 1+vincristine 14 mg/kg [max. 2.0 mg], day 1 + pirarubicin 50 mg/m^2, day 1 + prednisolone 100 mg/ body, days 1-5) was treated every 3 weeks. Complete remission was obtained, but thereafter, the tumor was relapsed. The patient was admitted to receive autologous stem cell transplantation after treatment with other chemotherapy regimen. The patients received R-IMVP16/CBDCA regimen (rituximab 375 mg/m^2, day 1 + methotrexate 30 mg/m^2, days 4-6 + ifosfamide 1,000 mg/m^2, days 4-8 + etoposide 80 mg/m^2, days 4-6 + carboplatin 300 mg/m^2, day 4 + methylprednisolone 1,000 mg/m^2, days 4-6 + mesna 250 mg/m^2 x3, days 4-8) every 3 weeks for 2 cycles, and subsequent R-MEAM regimen (rituximab 375 mg/m^2, day 1 + ranimustine 300 mg/m^2, day 3 + citarabine 200 mg/m^2, days 4-7 + etoposide 200 mg/m^2 days 4-7 + merphalan 300 mg/m^2 day 8 + hydrocortisone 100mg/body, days 4-7) every 3 weeks for one cycle.

The patients also received valproic acid (VPA: Depakene-R® tablets 1,200 mg/day) for the therapy of preexisting symptomatic epilepsia, thus therapeutic monitoring of (TDM) VPA was regularly conducted. Moreover, itraconazole (ITZ, Itrizole® capsle 200 mg × 2) was prescribed for the therapy of fungal infection.

3. Results

Before chemotherapy, plasma trough concentration of VPA was maintained within a range of therapeutic concentration. However, the VPA concentration decreased dramatically after receiving the chemotherapy, in which the concentration (28.2 μg/ml) was below the minimal therapeutic concentration (40 μg/ml) at day 8 (**Figure 1**). Unfortunately, an epileptic episode was elicited during the collection of blood for the TDM of VPA. The plasma VPA level gradually increased after day 8 and the level was within the therapeutic range at day 16. The second R-IMVP16/CBDCA regimen was carried out thereafter. Similar pronounced decrease in plasma VPA concentration was observed. The maximal reduction was observed at day 7 (27.5 μg/ml). The concentration of VPA gradually increased after the end of the chemotherapy regimen, and the concentration was almost recovered at day 14. Due to the decrease in platelet count, platelet transfusion was performed. Unfortunately, convulsion was induced during platelet transfusion. The symptoms were ameliorated by the systemic administration of diazepam.

Before treatment with the third chemotherapy regimen such as R-MEAM, Rikkunshi-to (Tsumura Rikkunshi-to extract granules, 7.5 g/day) was administered for 14 days starting from the beginning of the chemotherapy to prevent the chemotherapy-induced decrease in plasma VPA concentration. The plasma VPA concentration decreased, though to much lesser extent as those observed in the preceding two chemotherapies, in which the minimal concentration (38.7 μg/ml) was near the border of the therapeutic concentration. No episodes of epilepsy were observed. Then, the patient successfully received autologous peripheral blood stem cell transplantation.

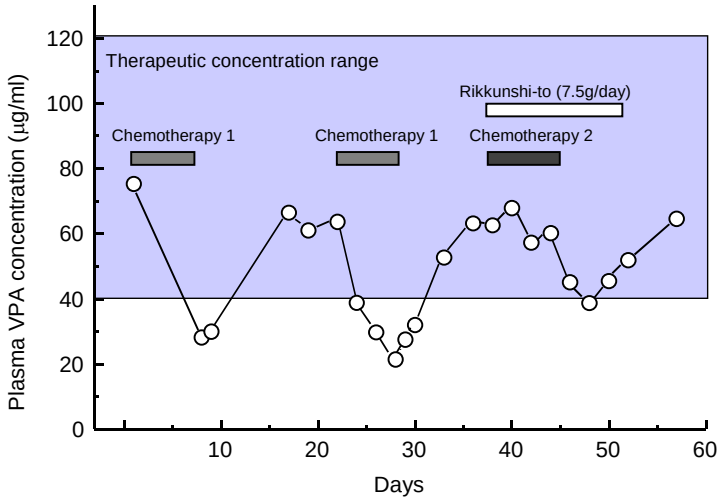

Figure 1. Time course of plasma VPA concentrations in a patient with malignant lymphoma who received cancer chemotherapy; 1. rituximab/methotrexate/ifosphamide/carboplatin (R-IMVP16/CBDCA regimen); chemotherapy; 2. rituximab/ranimustine/citarabine/etoposide/merphalan (R-MEAM regimen).

4. Discussions

We reported here a case of the reduction in plasma VPA concentration after high-dose chemotherapy such as R-IMVP16/CBDCA regimen and R-MEAM regimen. A number of literatures have reported the metabolic interactions between VAP and a variety of drugs, in which carbapenem antibiotics are the representative agents that cause a reduction in plasma VPA concentration [14,15]. Carbapenems facilitate glucuronidation of VPA [7], inhibit the transporter Mrp4 that mediates the efflux of VPA from erythrocytes to plasma [6,8], and suppress the intestinal transporter for VPA absorption [5]. On the other hand, there have been only a few reports on the pharmacokinetic interactions between anticancer drugs and VPA. Ikeda *et al.* [13] reported in patients with testicular tumor who undertook the combination chemotherapy such as BEP regimen (bleomycin, etoposide, and cisplatin) or TIP regimen (paclitaxel, ifosfamide, and cisplatin) that a severe reduction in plasma VPA concentration occur with the concomitant seizures.

Although the precise mechanisms underlying the decrease in plasma VPA concentration induced by the cancer chemotherapy, several possibilities can be raised: 1) facilitation of VPA glucuronidation are unclear, 2) inhibition of transporters that mediates the efflux of VPA from erythrocytes to plasma, 3) alteration of body fluid volume by transfusion, 4) decrease in the absorption of VPA from intestinal tracts.

In the present case, it is unlikely that the glucuronidation of VPA was enhanced by the cancer chemotherapy, since plasma concentrations of ITZ, which is metabolized by hepatic cytochrome P450 enzyme 3A4 [16], and its major metabolite OH-ITZ were also found to be lowered by R-IMVP16/CBDCA regimen, in which the concentrations of ITZ and OH-ITZ were 1,330 μg/ml and 1,288 μg/ml, respectively, before chemotherapy, while the values were 405 μg/ml and 372 μg/ml, respectively, at 7 days after the chemotherapy. Moreover, the possibility of inhibition of transporters that mediates the efflux of VPA from erythrocytes to plasma, as mentioned above, may be excluded.

The distribution volume of VPA is considered to be 12.5 l under food-deprived condition. Urine volume was maintained constant in the present patient. Moreover, the no changes in body weight was observed after the escalating dose of infusion, indicating no marked changes in fluid volume in this patient. Therefore, a possibility of the alteration of body fluid volume by transfusion, as mentioned above can be ruled out.

The chemotherapy agent that was used in common with both chemotherapy regimens was only etoposide. Etoposide causes dose-dependently myelosuppression, alopecia, stomatitis and diarrhea [17]. Etoposide-induced diarrhea results from the disintegration of the epithelial cells in lower intestinal tracts. Therefore, it is assumed that the reduction of the absorption of VPA from the intestinal tract due to the incidence of the injury of intestinal epithelial cells contributes at least in part to the decrease in plasma VPA concentration, although no diarrhea or dysfunction of the upper intestinal tract such as vomiting appeared in the present patient.

Based on the assumption that cancer chemotherapy may cause an injury of intestinal epithelial cells, which reduces plasma VPA concentration by the inhibition of the absorption of orally administered VPA, any agents that improve the intestinal dysfunction can be useful for prevention of chemotherapy-induced decline in plasma VPA concentration.

Rikkunshi-to is a kampo preparation that contains *Atractylodis Lanceae Rhizoma Pulveratum*, *Poria*, *Ginseng Radix*, *Pinelliae Tuber*, *Aurantii Nobilis Pericarpium*, *Zizyphii Fructus*, *Zingiberis Rhizoma*, and *Glycyrrhizae Radix*. This herbal medicine is used to alleviate gastritis, dyspepsia, appetite poor, nausea and vomiting. Takeda *et al.* [18] have shown in rats that hesperidin and iso-liquiritigenin, both of which are ingredients of Rikkunshi-to, reverse cisplatin-induced decrease in food intake by antagonizing cisplatin-induced decrease in plasma acylated-ghrelin concentration through blockade of 5-HT_{2B} and 5-HT_{2C} receptors.

In the present report, the chemotherapy-induced decrease in plasma VPA concentration was not marked and no seizure episodes were observed, when Rikkunshi-to was administered during and after cancer chemotherapy. Therefore, Rikkunshi-to may be useful to attenuate the malabsorption caused by cancer chemotherapy, although we could not rule out a possibility that R-MEAM regimen itself produced less marked decrease in the absorption of orally administered drugs than R-IMVP16/CBDCA regimen.

In conclusion, marked decrease in plasma VPA concentration appeared in a patient with diffuse large B-cell lymphoma who received high-dose cancer chemotherapy. However, no marked decrease in plasma VPA concentration was observed after chemotherapy, when Rikkunshi- to was administered before, during and after chemotherapy.

Therefore, this herbal medicine may be useful to alleviate the decline in plasma VPA concentration in patients receiving high-dose chemotherapy.

5. References

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