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CASE REPORT

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Effect of S-1 on blood levels of phenobarbital and phenytoin: A case report

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Abstract

Drug-drug interaction of fluorinated pyrimidine anticancer agents with phenytoin is well known, but interaction with phenobarbital is limited. We describe a case showing increases in plasma phenobarbital as well as phenytoin concentrations during preoperative S-1 (tegafur/gimeracil/oteracil) and radiation therapy for rectal cancer.

KEYWORDS

drug-drug interaction, phenobarbital, phenytoin, S-1, therapeutic drug monitoring

1 | INTRODUCTION

Drug-drug interactions are an essential factor that clinicians should consider in treating patients. The interaction between fluorinated pyrimidine anticancer agents and phenytoin (PHT) is well known.[1-5] However, the interaction between fluorinated pyrimidine anticancer drugs and phenobarbital (PB) is limited.[6] Here, we describe a case showing increases in plasma PB as well as PHT concentrations during preoperative S-1 (tegafur/gimeracil/oteracil) and radiation therapy for rectal cancer in a patient taking PHT/PB combination tablets.

2 | CASE DESCRIPTION

A 59-year-old male patient (height 164.2 cm, weight 53.4 kg, body surface area 1.57 m^2, with a history of drinking and smoking) was admitted to the Department of Gastroenterological and Pediatric Surgery in Oita University Hospital in February 201X to receive preoperative chemoradiation therapy (CRT) for rectal cancer (cT3N2M0 stage IIIb). S-1 (120 mg/day) and radiation therapy (1.8 Gy/fr, a total of 45 Gy/25 fr) were started on the 5th day of admission. The CRT was administered daily for five days during weekdays and off for two days during weekend, based on the results of a clinical trial conducted at Oita University Hospital.[7]

The patient had a history of epilepsy and was taking eight tablets of Hydantol® F (PHT 200 mg, PB 66.7 mg, sodium caffeine benzoate 133.3 mg) daily. No epileptic seizures occurred for many years, and no apparent adverse events due to Hydantol® F were observed. We performed therapeutic drug monitoring (TDM) to confirm the plasma concentrations of PHT and PB. Plasma PHT and PB concentrations were measured by the latex agglutination inhibition method using Dimension® Xpand Plus (SIEMENS). When TDM

was performed on the 9th hospital day, the concentrations of PHT and PB were 2.5 and 6.9 μg/mL (9.9 and 29.7 μmol/L), respectively. Because of the known interaction between S-1 and PHT, we planned to perform TDM once a week. Figure 1 shows the changes in plasma concentrations of PHT and PB. As expected, plasma levels of PHT tended to increase with the initiation of S-1, but PB also showed an increasing trend. On the 37th hospital day, which was the last day of S-1 administration, plasma concentrations of PHT and PB increased to 19.2 and 13.9 μg/mL (76.1 and 59.9 μmol/L), respectively. Thus, plasma concentrations of PHT and PB increased approximately eightfold and twofold, respectively, compared to the concentrations shortly after starting S-1.

Regarding adverse drug reactions, myelosuppression associated with the CRT was the only adverse event observed, with no significant changes in renal and hepatic function, as shown in Table 1. Because the therapeutic ranges for PHT and PB are 10-20 and 10-40 μg/mL (39.6-79.3 and 43.1-172.2 μmol/L),[8-10] respectively, the increases in plasma concentrations of PHT and PB in this patient did not cause adverse effects such as dizziness and somnolence. Other oral medications that the patient took during CRT were magnesium oxide, esomeprazole, loxoprofen, and teprenone, and no injection drug was used. When the patient was readmitted for surgery on the 106th hospital day counting from the first admission day, the increased plasma concentrations of PHT and PB had declined to the same levels as shortly after starting CRT.

3 | DISCUSSION

The interaction of fluorinated pyrimidine anticancer drugs with PHT is widely known,[1-5] while the report on the interaction with PB is limited.[6] The package insert or the interview form of S-1 contains a description of the interaction with PHT, but no mention of the interaction with PB. Previous reports show that fluorinated pyrimidine anticancer drugs inhibit CYP2C9.[5,11] In the present case, other drugs that the patient took during CRT were magnesium oxide, esomeprazole, loxoprofen, and teprenone. It is unlikely that these drugs caused the increases in plasma concentrations of PHT and PB. As shown in Table 1, no hepatic or renal disorders such as decreased metabolism of PHT and PB and excretion of S-1 were observed during CRT. The increases in plasma PHT and PB concentrations were suspected to be caused by tegafur in S-1, which inhibits the activity of CYP2C9.

PHT and PB are mainly metabolized by CYP2C9 and 2C19.[12,13] Although we were not able to perform detailed in vitro study, we hypothesize that the difference of increase in plasma concentration between the two drugs is due to the different ratios of metabolism of PHT and PB by CYP2C9 and 2C19. Previous reports indicate that approximately 80% of PHT is metabolized by CYP2C9,[14-16] while 20%-30% of PB is metabolized by CYP2C9 or 2C19.[13,17,18] In this patient, plasma PHT and PB concentrations increased approximately eightfold (2.5 → 19.2 μg/mL) and twofold (6.9 → 13.9 μg/mL), respectively, during CRT. This result suggests that compared to PB, PHT is metabolized by CYP2C9 approximately four times greater, and is almost consistent with previous reports.[13-18] Although the degree of the effect was smaller than PHT, this is the first report that plasma PB concentration also increases due to S-1, similar to PHT. In this patient, preoperative chemoradiotherapy by short-term intermittent oral administration of S-1 did not elevate the plasma concentrations of PHT and PB to levels that cause toxicity. However, we suspect that a typical schedule of S-1, such as oral administration for 28 consecutive days, may raise plasma concentrations of PHT and PB to levels that cause adverse effects and the dose of PHT and PB needs to be reduced. Tegafur contained in S-1 is mainly metabolized to 5-FU by CYP2A6, but there are no reports that PHT and PB cause induction of CYP2A6. Furthermore, there are no reports that PHT or PB induces or inhibits the metabolism of DPD, which is involved

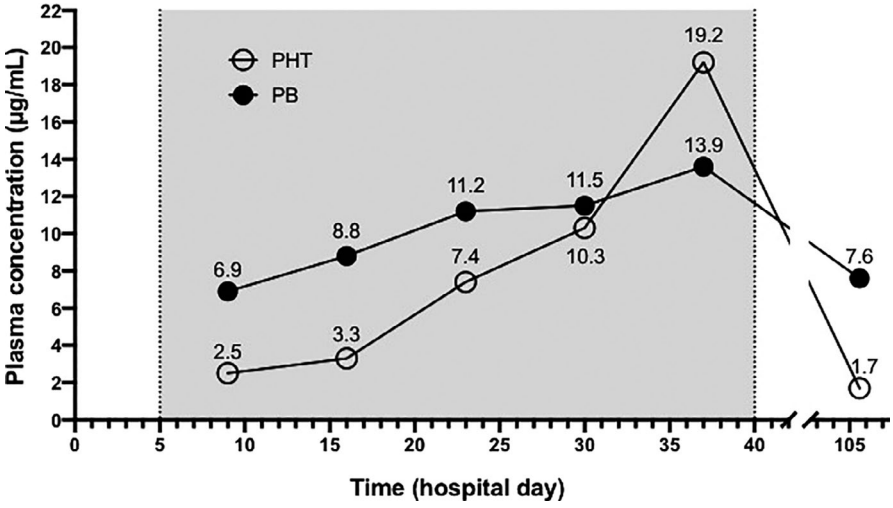

FIGURE 1 Time courses of plasma concentrations for PHT and PB. Time courses of plasma concentrations for PHT and PB are shown in Figure 1. White dots (○) and black dots (●) are shown for PHT and PB, respectively. The first day on the x-axis is the day of admission for CRT. The period highlighted in gray indicates the period during CRT was being performed

TABLE 1 Changes in blood test data during hospitalization

	Day 2	Day 23	Day 37
White blood cells ($\times 10^3/\mu L$)	7.9	3.7	2.2
Neutrophil (%)	75.5	74.1	69.5
Hemoglobin (g/dL)	12.3	11.4	12.6
Platelet ($\times 10^3/\mu L$)	333	173	167
Aspartate aminotransferase (U/L)	12.5	14.5	15.8
Alanine aminotransferase (U/L)	12.6	11.2	11.6
Total bilirubin (mg/dL)	0.35	0.29	0.48
Albumin (g/dL)	3.28	3.55	4.27
Serum creatinine (mg/dL)	0.66	0.69	0.74
Creatinine clearance (mL/min)[a]	91.0	87.1	81.2

[a]Calculated by Cockcroft-Gault formula.

in the degradation of 5-FU. Therefore, it is considered that the increase in plasma concentration of PHT and PB does not cause the increase in plasma concentration of S-1 and does not interfere with the treatment of S-1.

A similar increase in plasma concentration of PHT was observed when used in combination with UFT and capecitabine, which are also fluorinated pyrimidine anticancer agents as S-1.[4,5] Thus, this interaction is not specific to S-1 and is likely due to conversion of tegafur or capecitabine to 5-FU. To support this, there is a report that the blood levels of PHT and PB increased when 5-FU, PHT, and PB were used in combination.[6] However, in the report by Wakisaka et al,[4] plasma PB concentration was not increased when used in combination with UFT. These results suggest that the increase in plasma concentration of PB is more affected by indirect inhibition than by direct inhibition with fluorinated pyrimidine anticancer drugs. In other words, the plasma concentration of PHT increased by the metabolic inhibition caused by the fluorinated pyrimidine anticancer drugs, and an increase of the plasma PB concentration was caused by competitive inhibition by elevated PHT. Therefore, elevated plasma levels of PB may require the presence of not only fluorinated pyrimidine anticancer drugs but also drugs such as PHT that cause competitive inhibition of CYP2C9.

This case highlights the need to be careful about increases in plasma concentrations of PHT and PB when these drugs are used in combination with fluorinated pyrimidine anticancer agents. Therefore, we recommend performing TDM to confirm the plasma concentrations of PHT and PB when these drugs are used in combination with fluorinated pyrimidine anticancer agents.

ETHICS STATEMENT

Written consent was obtained from the patient for submission of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

KS, HO, RTanaka, RTatsuta, and HI: collected the data and wrote the manuscript. AF, TH, and MI: performed medical examination, chemoradiotherapy, and surgery. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are included in this case report. Details are available on request from the corresponding author.

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