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ORIGINAL ARTICLE

The first case of phenytoin intoxication associated with the concomitant use of phenytoin and TS-1, a combination preparation of tegafur, gimeracil, and oteracil potassium

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Abstract
Purpose We reported the first case of phenytoin intoxication due to the concomitant use of phenytoin and TS-1, together with a review of the literature regarding the occurrence of phenytoin intoxication due to the concomitant use of phenytoin and fluoropyrimidine antitumor drugs such as fluorouracil (5-FU) and tegafur (FT).
Methods We showed the clinical course of our patient. Reports of phenytoin intoxication due to the concomitant use of phenytoin and fluoropyrimidine antitumor drugs in the English and Japanese language literature up to 2007 were identified by searching Medline and ICHUSHI Web (Japana Centra Revuo Medicina).
Results A patient taking phenytoin and TS-1, a combination preparation of tegafur, gimeracil, and oteracil potassium, experienced lightheadedness and repeated falls associated with an increase in serum phenytoin concentration (32.8 μg/ml) at 1 month after the start of TS-1 treatment. The time lag between initiation of combined treatment and onset of adverse symptoms suggests the presence of an indirect mechanism, rather than direct inhibition of drug-metabolizing enzymes by drugs in TS-1 or their active metabolites.
Conclusions Plasma phenytoin concentration should be closely monitored in patients receiving TS-1 and phenytoin concomitantly.

Keywords TS-1 · Phenytoin · Drug-interaction · Adverse event

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Introduction

Several cases of phenytoin intoxication due to the concomitant use of phenytoin and fluoropyrimidine antitumor drugs such as fluorouracil (5-FU) and tegafur (FT), a prodrug of 5-FU, have been reported [2, 5–7, 9, 12, 15, 19–22]. However, neither antitumor drugs nor anticonvulsants, which are necessary for patients with tumor and seizures, can be discontinued even when combined treatment may cause adverse reactions. Thus, serum phenytoin concentration should be closely monitored when these drugs are used concomitantly.

Due to the following reasons, it is difficult to predict quantitatively the incidence of adverse events associated with the concomitant use of FT/5-FU and phenytoin and to avoid such events by reducing the initial doses, etc.; (1) the presence of genetic polymorphisms of CYP2C9 and CYP2C19, which play principal roles in phenytoin metabolism [11]; (2) the non-linear pharmacokinetics of phenytoin [14]; and (3) the complex relationships among factors affecting metabolism of 5-FU and phenytoin [4, 10, 16].

TS-1 capsules (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is a combination preparation of the following three drugs: (1) tegafur, a prodrug of 5-FU, (2) gimeracil, which reversibly inhibits dihydropyrimidine dehydrogenase, an enzyme which metabolizes 5-FU, and (3) oteracil potassium, which inhibits phosphorylation of 5-FU to prevent gastrointestinal toxicity, in a molar ratio of 1:0.4:1[8]. Patients receiving TS-1 have more factors possibly affecting interaction between phenytoin and 5-FU than patients receiving 5-FU alone. In addition to the genetic polymorphism of CYP2A6, which is involved in the bioactivation of tegafur to 5-FU [16], individual differences in renal function, which determine the rate of elimination of gimeracil, may significantly affect serum 5-FU concentration [4].

In this article, we have described a patient with lightheadedness, falls, and increased serum phenytoin concentration (up to 32.8 μg/ml) that developed immediately after the discontinuation of the TS-1 treatment. We have also included a literature-based discussion.

Case report

The patient was a 70-year-old man, 163 cm in height, who weighed 81.3 kg and had a body surface area of 1.87 m^2 (DuBois method) with normal renal function (mean serum creatinine level 0.97 mg/dl and mean creatinine clearance 97 ml/min). He had received phenytoin 100 mg (Aleviatin 10% powder, Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) and clonazepam 1 mg (Landsen fine granule 0.1, Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) three times daily after meals for several years for the treatment of myoclonic seizures. He had also received pantethine 200 mg (Pantosin powder 20%, Daiichi Pharmaceutical Co., Ltd. Tokyo, Japan), teprenone 50 mg (Selbex capsules, Eisai Co., Ltd. Tokyo, Japan), trimebutine maleate 200 mg (Cerekinon tablets, Tanabe Seiyaku Co., Ltd., Osaka, Japan), "Magen Milttel" 1.3 g (an in-hospital preparation containing sodium bicarbonate 2.93 g, Alumiweis 0.97 g, l-menthol 0.02 g, and medicinal charcoal 0.64 g) three times daily after meals, tamsulosin hydrochloride 0.2 mg (Harnal D tablets, Astellas Pharma Inc., Tokyo, Japan) once daily after breakfast, ranitidine hydrochloride 150 mg (Zantac tablets, GlaxoSmithKline K.K., Tokyo, Japan) twice daily after breakfast and supper, and disopyramide 100 mg (Rythmodan capsules, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) and diltiazem hydrochloride 30 mg (Herbesser tablets, Tanabe Seiyaku Co., Ltd., Osaka, Japan) four times daily after meals and before sleep. During treatment with these drugs, serum phenytoin concentration was stably maintained between 9.4 and 11.2 μg/ml.

On August 30, 2005, the patient was diagnosed with gastric cancer. He declined surgical treatment and began to receive TS-1 capsules 40 mg twice daily after breakfast and supper. On September 2, 2005, he was discharged from the hospital. Since interaction between TS-1 and phenytoin was expected, the patient was informed about the possibility of occurrence of symptoms due to increase in serum phenytoin concentration (e.g., nausea/vomiting, photopsia, and difficulty in bodily movement), and was instructed to visit the hospital if such symptoms developed.

On September 26, 2005, he complained of lightheadedness and repeated falls and unstable walking, especially while climbing stairs at the scheduled hospital visit at the end of the first course of TS-1 treatment. Magnetic resonance imaging (MRI) revealed no abnormal findings. With no evidence of new abnormality, he returned home. However, he visited the hospital again 3 days later without improvement of symptoms, and was hospitalized. On September 29, 2005, since phenytoin toxicity was suspected, a blood sample was obtained at 17:00 hours after supper before drug treatment (he had received the morning and lunchtime doses as usual) for determination of serum phenytoin level in a commercial laboratory. TS-1 treatment was discontinued after conclusion of the first cycle. Although phenytoin concentration could not be determined immediately after his report of symptoms because of the lack of availability of real-time therapeutic drug monitoring (TDM) in the hospital; increase in serum phenytoin concentration (to 32.8 μg/ml, therapeutic range 10–20 μg/ml) was confirmed on October 5, 2005. Phenytoin and clonazepam were discontinued. His symptoms, including lightheadedness, improved. Since he requested continuation of phenytoin treatment to prevent myoclonic seizures, he was prescribed phenytoin 50 mg (Aleviatin 10% powder) three times daily after meals on October 6, 2005. Serum phenytoin concentration decreased to 16.7 and 7.4 μg/ml on October 13 and 20, 2005, respectively. The dose of phenytoin was then increased to 100 mg three times daily after meals. On November 4, 2005, serum phenytoin concentration was 6.9 μg/ml. Figure 1 shows the time profile of serum phenytoin concentration.

Discussion

The patient reported here appeared to have experienced phenytoin toxicity due to inhibition of phenytoin metabolism by components of TS-1 or their active metabolites. Prior to the case described here, adverse events associated with the concomitant use of TS-1 and phenytoin had been reported in only one case [19]. Both the present patient and the previous one received phenytoin at standard

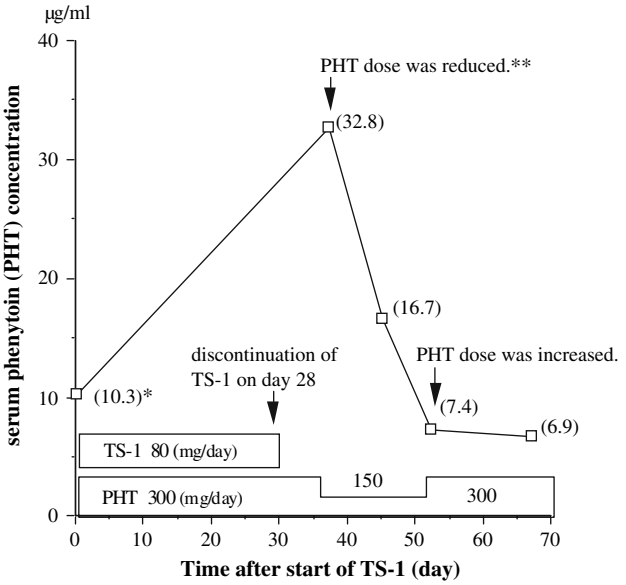

Fig. 1 Clinical course of the present case, values in *parentheses* show the serum phenytoin (PHT) concentration. * Mean serum phenytoin concentration a year before the case; ** phenytoin (PHT) was discontinued in just 1 day

doses; the dose of TS-1 was lower for the present than in the previous patient. Although the recommended dose for the present patient was 60 mg (as tegafur) twice daily, with the dose of TS-1 calculated according to body surface area, the patient received a lower dose, 40 mg twice daily, because of his age. Although in the previous patient as well the dose received was smaller than the calculated recommended dose (40 mg twice daily rather than the calculated recommended dose of 50 mg twice daily), the decrement was larger in the present case. TS-1 is a combination preparation used for increasing the bioavailability of 5-FU, according to its pharmacokinetics. The concentration of 5-FU when administered along with a low dose of TS-1 is not lower [18] than that when administered along with tegafur [3]. Therefore, comparing between the doses of TS-1 and other fluoropyrimidines is not reasonable.

Phenytoin toxicity developed 14 days after the conclusion of the first course in the previous case, whereas immediately after the first course in the present case. Renal function findings were not reported in the previous case, whereas this was normal in the present case (mean creatinine clearance 97 ml/min). These findings suggest that phenytoin toxicity may develop regardless of the dose of TS-1 and presence or absence of renal dysfunction.

There have been many cases of phenytoin toxication in patients receiving phenytoin concomitantly with tegafur or its active form 5-FU, including the previous case of adverse events associated with TS-1 noted above (Table 1) [2, 5–7, 9, 12, 15, 19–22]. In the previously reported case [19], an increase in the serum phenytoin concentration was noticed, and the patient presented with severe vomiting and a loss of appetite (side effects involving the central nervous system did not occur) within 14 days after the termination of the first course of therapy. However, the medical condition of this patient was critical. (She died sometime after the presentation of this case.) Moreover, the case report did not explicitly indicate that these side effects correlated with phenytoin intoxication induced by the concomitant use of TS-1. Hence, our case is considered as the first case of symptomatic phenytoin toxicity associated with a combined treatment with phenytoin and TS-1.

In many of the cases listed in the table, phenytoin toxicity was associated with a significant increase in serum phenytoin concentration that developed more than 1 month after the start of combined treatment with TF/5-FU and phenytoin; and the serum phenytoin concentration at onset was several times higher than the therapeutic range. In two patients who experienced serious adverse events [2, 7], serum phenytoin concentration was above 30–40 μg/ml, the range believed to induce ataxia and psychiatric symptoms.

The serum albumin or other carrier protein levels may affect the serum phenytoin concentration. However, because we did not measure these levels, this effect could not be investigated. Disopyramide and diltiazem are metabolized by CYP3A4. Therefore, tegafur-induced decrease in the expression of CYP enzymes may affect the pharmacokinetics of these concomitant drugs. However, because we have not measured the levels of these drugs, we could not investigate how these drugs can induce the side effect, but no report has described the interaction of disopyramide, diltiazem with TS-1. And, tamsulosin is not metabolized by CYP enzymes; therefore the tegafur-induced decrease in the expression of CYP enzymes such as CYP2C9 would not affect the pharmacokinetics of tamsulosin. In addition, no report has described the interaction of trimebutine, medicinal charcoal, alumi wiess, and sodium bicarbonate with TS-1. Hence, the effect of these medications on TS-1 is considered negligible. Thus, we believe that the side effect observed in our patient was not a side effect derived from disopyramide, diltiazem, or tamsulosin.

Given the reported drug interactions between 5-FU and phenytoin, it appears that drug interaction between TS-1 and phenytoin is induced by 5-FU, the active form of FT included in TS-1.

Many of the patients listed in the table began exhibiting symptoms suspected to be those of phenytoin toxicity at least 1 month after initiation of treatment with TF/5-FU. The presence of a time lag between exposure and onset of

Table 1 Cases of phenytoin intoxication associated with the concomitant use of phenytoin and nucleoside analogues (5-FU, UFT, TS-1, TGF, 5′-DFUR)

	Patient (age/ F , M)	Nucleoside analogue	Dose of nucleoside analogue (mg:mg/m^2)	Dose of phenytoin (PHT) (mg/day)	Phenytoin (PHT) concentration		Adverse effects (→ d/w/mo/y shows period taken to experience the adverse effect)	Concomitant medications (mg/day)	References
					Before chemotherapy (μg/ml)	After start of chemotherapy (d/w/mo:μg/ml)			
1	22/M	(1) UFT (2) 5-FU (3) UFT (4) UFT (5) UFT (6) UFT	(1) 400* (2) 150 (3) 400* (4) tapered to 200* (5) tapered to 300* (6) 300*	(1) 150–200 (2) 150–200 (3) 200 (4) tapered to about 140 (5) about 140 (6) 100	(0) low	(1) 6.6 (2) NS (3) 1mo: 48.2 (4) 6.2 (5) 22 (6) 10	(1) none (2) none (3) dizziness, unsteadiness, nausea, nystagmus, dysarthria, gingival hypertrophy (→ 1 mo)	PB (49.8–66.4)	20
2	60/F	(1) UFT (2) UFT (3) UFT	(1) 400* (2) withdrawal (3) 300*	(1) 268 (2) 134 (3) 134	(0) 4.3	(1) 2 w: 14.6, 30.9 (2) 1.5 (3) NS	(1) nausea, drowsiness	PB (132)	20
3	60/M	(1) UFT (2) UFT (3) UFT	(1) 400* (2) withdrawal (3) 400*	(1) 150 (3) 100	(0) NS	(1) 1 mo: 24.2 (2) therapeutic range (3) therapeutic range	(1) nausea, loss of appetite, fatigue, ataxic gait (2) subside symptoms of PHT intoxication after withdrawal	PB (49.8)	20
4	54/M	(1) UFT	(1) 400*	(1) 250 (3) tapered to 150 (4) withdrawal	(0) 7.7	(1) 5 mo: 28.8 (2) about 6 mo: 36.6 (3) 8 d after reduction of PHT dose: 45.5 10 d after reduction of PHT dose: 48.2 (4) 7 d after withdrawal of PHT: 10.3 14 d after withdrawal of PHT: below measurable limits	(1) stagger, hypersensitive	ZNS (400) CBZ (600)	22
5	51/M	(1) UFT	(1) 300*	(0) 240 (3) tapered to 80 (4) incresed to 120		(1) about 2 mo: NS (2) about 4 mo: 44.96 (3) 10 d after reduction of PHT dose: 20.81 21 d after reduction of PHT dose: 8.36	(1) apraxia of gait, alalia (2) stagger, horizontal nystagmus, ambiopia (3) disappearance of adverse effects	PB (80), CZP (1), methylphenidate, maprotiline (3) withdrawal of methylphenidate and maprotiline	12
6	51/F	(1) UFT	(1) 150*	(1) 210 (2) 105 (3) 80–100	(0) <10	(1) about 1 mo: 30.91 (2) 13.1 (3) 10–20	(1) stagger, dizziness, dysarthria	PRM (600)	21
7	49/M	(1)TGF (2) TGF after 7 mo (3) TGF restart after 3 mo (4) TGF	(1) 600 (2) 600 (3) withdrawal (4) 600	(1) 300 (2) 120 (3) 100 (4) 100	(0) 2.9–9.6 (3) before withdrawal: 6.0–8.5 (4) below 2.0	(1) 2 mo: 35.0 (2) 4w after reduction of PHT dose: 2.5 (3) 4w after withdrawal of TGF: 2.0 (4) 3w: 2.4 4w: 3.9 3.5 mo: 5.7	(1) stagger, apraxia of gait, jerk nystagmus (2) disappearance of adverse effect	PRM (750) VPA (400) therapeutic range	6
8	52/F	5-FU	(1) 200 (2) withdrawal	(1) 200 (2) shift to VPA1200	(0) NS (It's probably therapeutic range**)	(1) 5 mo: 65.6	(1) stagger, dysarthria, apraxia of gait, confusion (→ 5 mo) (2) (→ 2w) disappearance of adverse effects	PB (67)	7
9	66/M	(1) 5-FU + LV	(1) 750: 425 (LV; 35: 20) (2) withdrawal	(1) 300 (2) 200	(0) 10.6	(1) 11 w: 36 (2) after reduction of PHT dose: 16	(1) unsteady on his feet, fallen (→ 11 w)	doxepin hydrochloride (50) haloperidol (7.5) fluphenazine Decanoate IM (25 mg/mo) etc	5
10	50/F	5-FU	500–450 mg/m^2 (during 5w of radiotherapy dose was 225 mg/m^2)	(1) 300	(0) NS (It's probably therapeutic range**)	(1) 188	(1) blurring of vision, apraxia of gait	conjugated estrogens (1.25)	15

Table 1 continued

	Patient (age/F, M)	Nucleoside analogue	Dose of nucleoside analogue (mg:mg/m^2)	Dose of phenytoin (PHT) (mg/day)	Phenytoin (PHT) concentration		Adverse effects (→ d/w/mo/y shows period taken to experience the adverse effect)	Concomitant medications (mg/day)	References
					Before chemotherapy (μg/ml)	After start of chemotherapy (d/w/mo:μg/ml)			
11	65/M	(1) 5-FU + FA (4) withdrawal	(1) 370/w (FA: 20/w)	(1) 300 (2) withdrawal (3) 230	(0) NS (It's probably therapeutic range**)	(1) 7 w:42.4 (2) 5 d after withdrawal of PHT: 22.4 (3) 18.9 (4) 5 w after withdrawal of chemotherapy: 5.5	(1) confusion, apraxia of gait dysarthria, fatigue (2) disappearance of adverse effects	PB (90)	2
12	60/M	(1) 5-FU + FA	(1) 370/w (FA: 20/w)	(1) 430 (2) withdrawal (3) 300 (4) 100 (5) 200	(0) 18.9	(1) 4 w: 53.7 (2) 7 d after withdrawal of PHT: 10.6 (3)29.7 (4) 6.0 (having convulsions)	(1) feeling of floating, apraxia of gait (2) disappearance of adverse effects		2
13	73/F	TS-1	80	200	(0) 4.6	4d: 4.2 8d: 5.1 14d: 7.1 29d: 17.6 (1 d after withdrawal of TS-1) 49d: 22.4 (20 d after withdrawal of TS-1)			19
14	51/F	5'-DFUR	(1) 800	(0) 200 (1) 200 (2) withdrawal	(0) 11.2	(1) 1 mo: 41.6–45.2 (2) not measured	(1) stagger, apraxia of gait (2) disappearance of adverse events	CPM (100) MPA (800) aspirin (81) Dicyclomine (15) etc	9
15	54/M	5'-DFUR	(1) NS (2) withdrawal	(0) 250 (1) 250		(1) 1 mo: 43.93 (2) after withdrawal of 5'-DFUR 12 d: 33.79 18 d: 6.45 24 d: 0.5	(1) stagger, cognitive dysfunction	CBZ (400) PB (120)	12

Abbreviations: *F* female, *M* male, *5-FU* 5-fluorouracil, *LV* levofolinate calcium, *UFT*: combination drug containing uracil and tegafur, *TS-1* combination drug containing tegafur, gimeracil, and oteracil potassium, *TGF*: tegafur, *FA*: folic acid, *5′-DFUR* doxifluridine, *CPM* cyclophosphamide, *MPA* medroxyprogesterone acetate, *VPA* sodium valproate, *PB* phenobarbital, *PRM* primidone, *ZNS* zonisamide, *CBZ* carbamazepine, *CZP* clonazepam, *CLB* clobazam, *IM* intramuscular administration, *NS* not stated, *d/w/mo/y* day/week/month/year, *dose as tegafur **based on the fact that no adverse effects nor convulsions occurred, it was probably therapeutic range, (0) shows the state before concomitant with phenytoin and antimetabolite agent

symptoms suggests that inhibition of phenytoin metabolism by 5-FU is not the result of direct competitive inhibition of CYP enzymes but of indirect effects on enzymes, as described in several studies [2, 5, 6, 9, 15, 22].

In an in vitro experiment, 5-FU did not inhibit the activity of CYP2C9, the main enzyme metabolizing phenytoin, at a concentration of 200 μM, about 28 times the maximum clinical serum phenytoin concentration [13]. In rats, single high-dose administration of 5-FU decreased expression of CYP enzymes in the liver [1], and long-term administration of 5-FU decreased the amounts of hepatic microsomal enzymes [17]. These findings indicate that 5-FU decreases the rate of phenytoin metabolism indirectly by decreasing the amounts of hepatic microsomal enzymes. When patients receive drugs containing 5-FU or its prodrugs together with phenytoin, serum phenytoin concentration should be monitored closely during treatment and for about 1 month after discontinuation of treatment in order to prevent adverse reactions to phenytoin.

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