faulty, as revealed by very wide interpatient variability. In our hands this variability is in the region of 30%, similar to that of other cytotoxic agents. Moreover, other groups have shown a relationship between 5-FU plasma pharmacokinetics (but not dose) and response to treatment[2,3] or toxicity,[2] even though concentration was not measured at the site of action, suggesting that plasma pharmacokinetics is indicative of therapeutic activity.

We report that we did not find a difference in plasma 5-FU pharmacokinetics in the presence of oxaliplatin, suggesting that the interaction does indeed take place at the cellular level. This would support further studies, with the use of methods such as those suggested by Drs Wolf and Presant, to investigate the anabolism or catabolism of 5-FU within the tumor. Such intratumoral methods have their own inherent problems, however, such as variation in the ratio of tumor to stroma or viable tissue to necrotic tissue, and are also less relevant to drug toxicity. In addition, although important in probing this interaction further at the clinical level, such approaches ask different questions than those posed in our own study. For example, it was important to establish that the increased rate of diarrhea seen with oxaliplatin–5-FU compared with the rate for 5-FU alone is not simply a result of reduced 5-FU clearance.

In understanding the mechanism underlying clinically important drug interactions, we believe there is clearly a role for both types of study.

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Drug interaction of tizanidine and fluvoxamine

To the Editor:

Tizanidine is an α_2-adrenergic receptor agonist commonly used for muscle spasm[1] and spasticity associated with central nervous system disorders, such as multiple sclerosis. Granfors et al[2] recently reported a pharmacokinetic drug interaction between tizanidine and fluvoxamine in healthy subjects, where the area under the drug concentration–time curve (AUC) for tizanidine increased by 14- to 103-fold after coadministration of fluvoxamine (100 mg/d for 4 days). They hypothesized that fluvoxamine strongly inhibited tizanidine metabolism by cytochrome P450 (CYP) 1A2, resulting in the increased blood concentration of tizanidine. This report is a very important warning regarding the combined use of tizanidine with fluvoxamine. We report a case and a clinical survey regarding the interaction between tizanidine and fluvoxamine that supports the findings of Granfors et al. This study was approved by the Ethical Committee of University of Tsukuba (Tsukuba, Japan).

A 70-year-old woman (weighing 54.7 kg) with cerebral infarction was admitted to our hospital for pain and numbness of her leg. She had received fluvoxamine for depression. On the 15th day after starting fluvoxamine (150 mg/d), tizanidine (3 mg/d) was coadministered for her left leg pain. She had dry mouth and anuresis (85 mL/d), which required urinary catheterization on that day. A low heart rate (56-60 beats/min) and low body temperature (36.1°C-36.3°C) were also observed during tizanidine administration (Fig 1). After tizanidine treatment was stopped, the symptoms improved immediately. Although the patient received other medications including zopiclone, flunitrazepam, benidipine, candesartan, ticlopidine, famotidine, bezafibrate, and carbamazepine, the dosing schedule for these drugs remained unchanged during tizani-

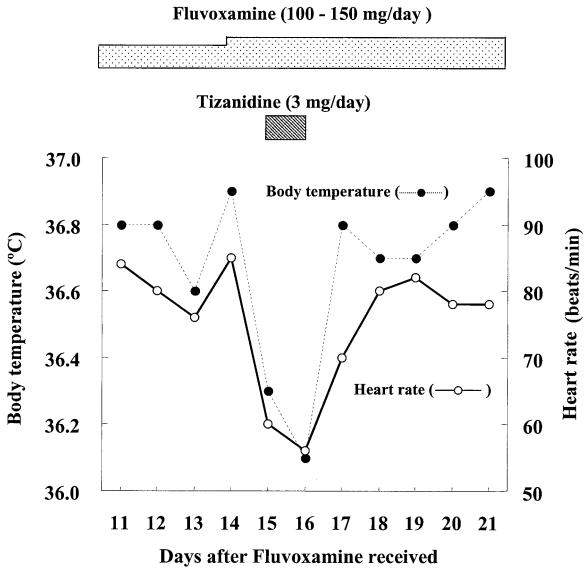

Fig 1. Clinical course of case described.

Table I. Patient characteristics

Variable	*Patients with adverse events (n = 6)*	*Patients without adverse events (n = 14)*
Sex (male/female)	3/3	7/7
Age (y)	66.2 ± 6.9*	46.3 ± 14.5
Body weight (kg)	50.6 ± 8.6	54.4 ± 9.2
Laboratory data		
AST (IU/L)	24.2 ± 4.8	19.2 ± 7.9
ALT (IU/L)	26.0 ± 13.7	20.4 ± 18.1
Blood urea nitrogen (mg/dL)	15.4 ± 6.6	15.6 ± 7.7
Serum creatinine (mg/dL)	0.7 ± 0.1	1.1 ± 1.3
Coadministered period (d)	3.5 (1–98)	33 (2–498)
Tizanidine dose ($mg \cdot kg^{-1} \cdot d^{-1}$)	0.08 ± 0.03*	0.04 ± 0.02
Fluvoxamine dose ($mg \cdot kg^{-1} \cdot d^{-1}$)	1.63 ± 0.61*	0.78 ± 0.40

Data are presented as mean ± SD or median and range.
*Significant difference was observed between 2 groups ($P < .01$).

dine administration. Liver function and kidney function were normal (AST, 18 IU/L; ALT, 8 IU/L; blood urea nitrogen, 22.6 mg/dL; and serum creatinine, 0.8 mg/dL), and no other laboratory data were changed throughout the coadministration. We assumed that her adverse symptoms (low heart rate, low body temperature, dry mouth, and anuresis) were caused by tizanidine enhanced by fluvoxamine coadministration.

We retrospectively surveyed the combined use of tizanidine and fluvoxamine in the medical records of 913 patients treated with tizanidine. Of these patients, 23 had received fluvoxamine together with tizanidine. Adverse events caused by tizanidine were observed in 6 patients (low heart rate in 6, dizziness in 3, and low body temperature, drowsiness, hypotension, and speech disorder in 2). No subjects received any drugs, except for fluvoxamine, that are known to inhibit CYP1A2. The occurrence of adverse events in the patients treated with both drugs in our hospital (6/23 [26.1%]) was significantly higher than that reported for tizanidine[3] (770/14,627 [5.3%]) ($P < .0001$). This occurrence rate also exceeded the incidence of poor metabolizers of CYP1A2 in a Japanese population (14.1%).[4] Thus it is evident that the combined use of tizanidine and fluvoxamine increases the risk of tizanidine-associated adverse reactions.

We compared patients with and without adverse events after receiving tizanidine with fluvoxamine (Table I). A significant difference was observed in age and daily dose of tizanidine and fluvoxamine between the groups. The patients with adverse events were older and received a higher daily dose of both drugs compared with those without adverse events ($P < .01$). These observations suggest that the drug interaction between tizanidine and fluvoxamine is affected by the patient's age and the dose received.

The simultaneous use of tizanidine and fluvoxamine should generally be avoided. We emphasize that medical staff including physicians and pharmacists should immediately pay attention to patients receiving the combination of tizanidine and fluvoxamine and consider stopping the simultaneous prescription of the 2 drugs.

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