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The authors report no conflicts of interest.

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## Drug interaction of tizanidine and ciprofloxacin: Case report

*To the Editor:*

Tizanidine is used as an antispastic agent for central nervous system disorders, such as multiple sclerosis.[1] Because tizanidine is metabolized by cytochrome P450 (CYP) 1A2,[2] drug interaction may occur when coadministered with CYP1A2 inducers and inhibitors. Granfors et al[3-5] revealed that the pharmacokinetics of tizanidine was altered dramatically by coadministration of CYP1A2 inhibitors (fluvoxamine, ciprofloxacin, and oral contraceptives) in healthy subjects, where elevation of the blood tizanidine concentration and a decrease in psychomotor activities, blood pressure (BP), and heart rate (HR) were observed simultaneously. In this letter we describe a case and clinical survey of the drug interaction between tizani-

**Table I.** Comparison between ciprofloxacin and fluvoxamine coadministration in patients treated with tizanidine

| *Variable* | *Ciprofloxacin* | *Fluvoxamine* |
|---|---|---|
| No. (M/F) | 7 (2/5) | 11 (4/7) |
| Age (y) | 57.6 ± 9.9 | 59.2 ± 16.2 |
| Body weight (kg) | 55.0 ± 6.2 | 51.8 ± 9.8 |
| Tizanidine dose ($mg \cdot kg^{-1} \cdot d^{-1}$) | 0.06 ± 0.007 | 0.07 ± 0.02 |
| Ciprofloxacin dose ($mg \cdot kg^{-1} \cdot d^{-1}$) | 8.5 ± 1.7 | — |
| Fluvoxamine dose ($mg \cdot kg^{-1} \cdot d^{-1}$) | — | 1.2 ± 0.4 |
| Coadministration period (d) [median (range)] | 7 (4–32) | 15 (1–498) |
| Systolic blood pressure (mm Hg) | | |
| Before | 112.6 ± 12.5 * | 117.7 ± 21.9 |
| After | 91.3 ± 8.8 * | 104.7 ± 14.9 |
| Change | −21.3 ± 16.0 | −13.0 ± 14.5 |
| Diastolic blood pressure (mm Hg) | | |
| Before | 71.4 ± 12.1 * | 71.5 ± 14.9 |
| After | 56.0 ± 4.5 * | 63.7 ± 10.5 |
| Change | −15.4 ± 13.0 | −7.8 ± 9.4 |
| Heart rate (beats/min) | | |
| Before | 82.6 ± 15.9 | 74.7 ± 15.9 * |
| After | 67.7 ± 10.0 | 59.3 ± 13.7 * |
| Change | −14.9 ± 17.5 | −15.5 ± 9.6 |
| Body temperature (°C) | | |
| Before | 36.5 ± 0.3 * | 36.1 ± 0.6 * |
| After | 35.9 ± 0.5 * | 35.6 ± 0.5 * |
| Change | −0.6 ± 0.5 | −0.6 ± 0.4 |

Data are presented as mean ± SD unless otherwise indicated.
*A significant difference was observed between the two groups ($P < .05$).

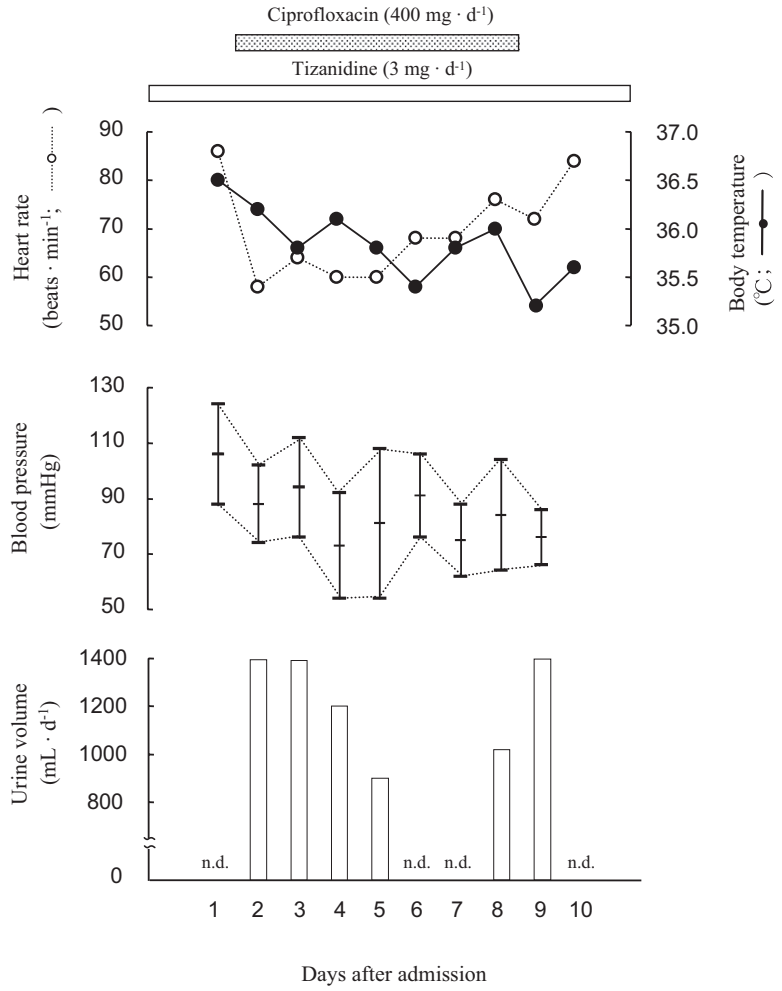


**Fig 1.** Clinical course of patient receiving ciprofloxacin and tizanidine. n.d., No data.

dine and ciprofloxacin to assess the potential clinical impact of this combination therapy. This study was approved by the Ethical Committee of Tsukuba University Hospital (Tsukuba, Japan).

A 45-year-old Japanese woman (57.0 kg) who had severe multiple sclerosis for 11 years complained of left leg pain with difficulty in walking. She was admitted to our hospital to receive high-dose corticosteroids. She had been taking tizanidine (3 mg/d) before being admitted to the hospital. Reductions in HR (from 86 to 58 beats/min) and BP (from 124/88 to 102/74 mm Hg) were observed immediately after administration of ciprofloxacin (400 mg/d for 7 days) was started for pyuria on day 2 (Fig 1). On day 4, she complained of drowsiness and had low BP (92/54 mm Hg). Her urine volume and body temperature (BT) also decreased (from 1396 to 900 mL/d and from 36.5°C to 35.4°C, respectively) on days 5 and 6. These symptoms improved immediately after ciprofloxacin administration was stopped. The dosing schedule of her other medications remained unchanged during this period. Liver function and kidney function were normal, and no other laboratory data changed. We assumed that her symptoms (lowered HR, BP, and BT) were associated with adverse effects of tizanidine enhanced by ciprofloxacin coadministration, although tizanidine concentrations were not measured.

We retrospectively surveyed the combined use of tizanidine and ciprofloxacin in the medical records obtained from 1165 patients treated with tizanidine. Eight cases were found for the assessment of the drug interaction of tizanidine and ciprofloxacin. No patient received medications that were known to inhibit CYP1A2, except for ciprofloxacin. Adverse effects attributed to tizanidine were seen in 3 patients (low HR in 2, low BT in 1, low BP in 2, drowsiness in 2, and confusion in 1). In 1 patient ciprofloxacin was discontinued from the combination therapy because of confusion.

BP, HR, and BT before and after ciprofloxacin coadministration in 7 cases were compared with those in 11 cases coadministered with fluvoxamine, another CYP1A2 inhibitor[6] (Table I). The systolic and diastolic BP and the BT after

ciprofloxacin coadministration were significantly lower than those before ciprofloxacin use ($P < .05$). The mean reductions from baseline values in systolic BP, diastolic BP, HR, and BT were −21.3 mm Hg, −15.4 mm Hg, −14.9 beats/min, and −0.6°C, respectively, which were almost the same as those with fluvoxamine (−13.0 mm Hg, −7.8 mm Hg, −15.5 beats/min, and −0.6°C, respectively) (Table I).

The combined use of tizanidine and ciprofloxacin induced adverse effects of tizanidine, lowering BP, HR, and BT. The magnitude of this drug interaction is comparable to that with the coadministration of fluvoxamine,[6] whose inhibitory activity on CYP1A2 is stronger than that with ciprofloxacin. These data support the theory that both CYP1A2 inhibitors should be contraindicated for coadministration with tizanidine in Japan. It is also suggested that further clinical studies should be done to assess the clinical impact of drug interaction between tizanidine and other CYP1A2 inhibitors, even if the inhibitory activity is smaller than that of fluvoxamine and ciprofloxacin.

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## *CYP3A5* polymorphism and alprazolam pharmacokinetics/pharmacodynamics

*To the Editor:*

Park et al[1] recently demonstrated a modest effect of *CYP3A5* genotype on alprazolam pharmacokinetics, with oral clearance in individuals with 2 copies of the *CYP3A5*-expressing allele (**1/*1*) being approximately 40% higher than that in *CYP3A5* nonexpressors (**3/*3*). These pharmacokinetic differences may be expected to result in a modest effect on pharmacodynamic response based on a simple direct effect relationship.

The authors performed an analysis of the concentration-effect relationship for effects on the Digit Symbol Substitution Test by use of mean data in the 3 genotyped groups (Fig 5 in their article) by use of a sigmoid maximal effect ($E_{max}$) model.[1] However, visual inspection of the observed concentration-effect data did not reveal a plateau in effect over the concentration range achieved after the oral 1-mg dose. Furthermore, the authors conclude that subjects with the **1/*1* genotype have a lower $E_{max}$ (by 35%) relative to **1/*3* or **3/*3* genotype carriers as a result of lower alprazolam exposure, although visual inspection of the data suggests essentially superimposable concentration-effect relationships.

The results and interpretation of pharmacokinetic/pharmacodynamic relationships in this study are inconsistent with pharmacologic principles and may be explained by a lack of sufficient data to clearly define $E_{max}$ (especially in the **1/*1* group) resulting in biased parameter estimates. There is no reason to expect the fundamental pharmacodynamic parameters ($E_{max}$ and $EC_{50}$ [concentration producing half-maximal effect]) of a drug to be altered by a genetic polymorphism in a drug-metabolizing enzyme that results solely in a pharmacokinetic alteration. Conversely, genetic polymorphisms altering receptor function, such as those affecting the $\beta_2$-adrenergic receptor, have been shown to affect pharmacodynamic sensitivity.[2]

A more powerful and appropriate method is to use all available individual data rather than mean data in the context of a population pharmacokinetic/pharmacodynamic approach, permitting estimation of the effect of genotype as a