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BRIEF COMMUNICATION

Interaction of a caffeine overdose with clinical doses of contraceptive ethinyl estradiol in a young woman

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Abstract

Aim: The overdose of caffeine, a cytochrome P450 1A2 probe, in young women has become a problem. The aim of this study was to evaluate possible drug interactions between intentionally overdosed caffeine (12 g) and oral contraceptive doses of ethinyl estradiol prescribed to a young woman in a suicide attempt.

Methods: The serum concentrations of caffeine in the patient and the time-dependent ethinyl estradiol inhibition of caffeine oxidation in vitro were evaluated.

Results: The serum concentration of caffeine 4 h after overdose was 136 μg/mL; from the data obtained between 4 and 28 h after overdose, the half-life was estimated to be 33 h, which is many times larger than the normal value. Prescribed ethinyl estradiol prolonged caffeine elimination in vivo and inhibited paraxanthine formation, as evidenced by the low serum concentrations. In human liver microsomes, ethinyl estradiol (50 nM) inhibited half of caffeine N_3-demethylation. Pre-incubation of human liver microsomes with ethinyl estradiol resulted in a powerful time-dependent inhibitory effect on caffeine N_3-demethylation in human liver microsomes.

Conclusion: These results suggest that a prescription history of contraceptives at clinical doses may have a strong effect on the pharmacokinetics of overdosed caffeine in young women, resulting in dangerous drug interactions.

KEYWORDS
caffeine, ethinyl estradiol, overdose, pharmacokinetics

INTRODUCTION

Caffeine is a readily available, over-the-counter drug. Caffeine overdose in young women has recently become a problem in Japan. Typical symptoms of caffeine intoxication include gastrointestinal problems, fatal arrhythmias, impaired consciousness, and electrolyte disturbances.[1] A lethal dose of caffeine is estimated to be 10 g, with a fatal blood concentration being 80–100 μg/mL.[2–4] Caffeine is mainly metabolized by cytochrome P450 1A2 to paraxanthine as the major metabolite and theobromine and theophylline as minor metabolites.[5–7] However, in patients with caffeine toxicity, there is little to no reported analysis of the total concentration of metabolites or individual metabolite concentration measurements to facilitate pharmacokinetic investigations.[8] Ethinyl estradiol, present in oral contraceptives, has been reported to significantly inhibit hepatic microsomal function,[9] and the mechanism may be the inhibition of P450 3A4 and/or 1A2.[10,11] The co-administration of ethinyl estradiol and tizanidine, a substrate of P450 1A2, reportedly resulted in increased blood concentrations of tizanidine.[11] In Caucasians, there have been reports of reduced caffeine clearance resulting from interactions with estrogens, including ethinyl

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estradiol.[12–14] However, no information is available on drug interactions with caffeine in cases of caffeine overdose. We report a 23-year-old woman (body weight, 67 kg) who intentionally took an overdose of 12 g caffeine (purchased from multiple pharmacies) as a suicide attempt was emergently admitted to the Kyoto Medical Center. The patient had a history of obsessive-compulsive disorder and was prescribed a combination of paroxetine, diazepam, magnesium oxide, and a tablet of drospirenone and ethinyl estradiol. We measured the serum concentrations of caffeine and its metabolites and analyzed the pharmacokinetics of the caffeine overdose. In addition, we performed in vitro experiments to investigate the inhibitory effects of ethinyl estradiol on caffeine oxidation.

MATERIALS AND METHODS

Detailed case presentation, measurement of serum drug concentrations, and analysis of caffeine N_3-demethylation activities are shown in the Supporting Information. The clinical laboratory results relevant to this case are presented in Table S1.

RESULT AND DISCUSSION

Figure 1 shows the concentrations of caffeine, paraxanthine, theophylline, and diazepam measured 4, 10, 14, and 28 h after an overdose of 12 g caffeine and 140 mg diazepam. The dotted line shows the predicted serum concentrations of a hypothetical single oral dose of 12 g caffeine according to a physiologically based pharmacokinetic model taken from a previous report.[15] The serum concentrations of these drugs at 4, 10, 14, and 24 h post-dosing were as follows: 136, 132, 115, and 80.3 μg/mL for caffeine; 3.35, 4.43, 5.17, and 4.17 μg/mL for paraxanthine; 2.32, 3.25, 3.34, and 4.64 μg/mL for theophylline; and 1.96, 2.06, 1.78, and 2.24 μg/mL for diazepam. When caffeine intake exceeds 500 mg (approximately 7 mg/kg), metabolic enzyme activity reportedly becomes saturated.[16] When comparing the simulation results (assuming no drug absorption or metabolic saturation) with the actual caffeine concentration profile, it is evident that the disappearance of caffeine was delayed in the current patient (Figure 1). After the 12 g overdose, the observed elimination half-life of caffeine of 33 h (calculated from the four data points from 4 to 28 h) was several times longer than the reported normal value of 2–12 h.[17] In a case report of caffeine ingestion (9 g), the blood concentrations of caffeine and paraxanthine 3.5 h after caffeine overdose were 124 and 3.64 μg/mL, respectively.[8] After dialysis (approximately 16 h after ingestion), the blood concentrations were 35.6 and 13.7 μg/mL, respectively.[8] In contrast, in the current case, the peak blood concentration of paraxanthine up to 28 h after overdose was 5.17 μg/mL, despite dialysis not being carried out, which was lower than the previously reported values.[8]

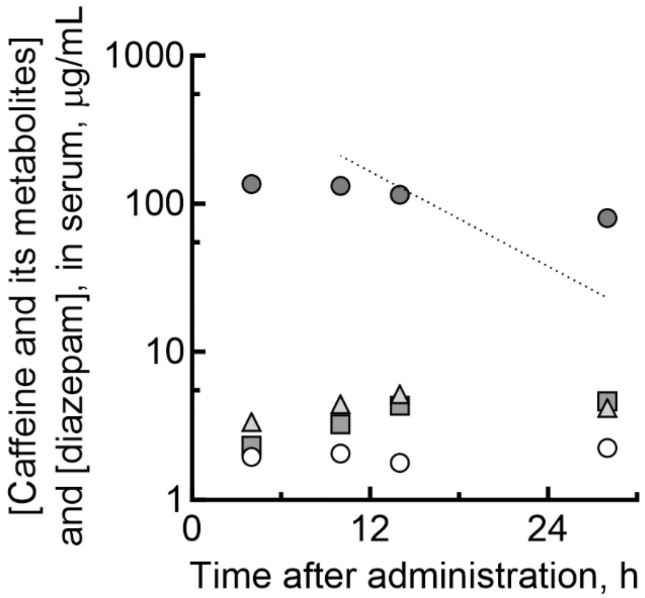

FIGURE 1 Measured concentrations (plots) of caffeine, its metabolites, and diazepam in a female patient who took an oral overdose of 12 g caffeine. Measured serum concentrations of caffeine (solid circles), paraxanthine (triangles), and theophylline (squares), and the estimated decreasing caffeine concentrations (dotted line) for 10–28 h following a virtual administration of 12 g caffeine generated by a previously reported simplified physiologically based pharmacokinetic model.[15] The observed serum diazepam concentrations (open circles) are also shown after the co-administration of 140 mg diazepam.

In human caffeine metabolism, paraxanthine reportedly accounts for 67.3% of the total dimethylxanthines in plasma, while theobromine and theophylline account for 24.4% and 8.3%, respectively.[6] In the current case, the concentration ratio of paraxanthine to theophylline was nearly 1:1, which was significantly different from typical human caffeine metabolism, looked like that of monkeys.[6,18,19] Consequently, it was speculated that factors other than liver metabolic saturation resulting from overdose may have affected caffeine metabolism. Considering these results, we investigated the impact on the caffeine metabolism of P450 1A2 inhibition by ethinyl estradiol. The paraxanthine production rates obtained using human liver microsomes with inactivated P450 1A2 and the control microsomes are presented in Figure 2. It was confirmed that the paraxanthine production rate decreased by 75% in the P450 1A2 inactivation group, with a rate of 11.7 pmol/min/mg protein, compared with the control group rate of 77.9 pmol/min/mg protein (Figure 2A). This confirmed that the majority of caffeine metabolism was carried out by P450 1A2. When ethinyl estradiol was added in the concentration range 0.20–1.2 μM, the apparent half-maximal inhibitory concentration value was 50 nM, indicating that ethinyl estradiol competitively inhibits P450 1A2-dependent caffeine N_3-demethylation (Figure 2B). Similarly, when ethinyl estradiol was added to liver microsomes and caffeine metabolism was initiated after a 10-min pre-incubation period, the half-maximal inhibitory concentration value was 38 nM, which was 25% lower than the value

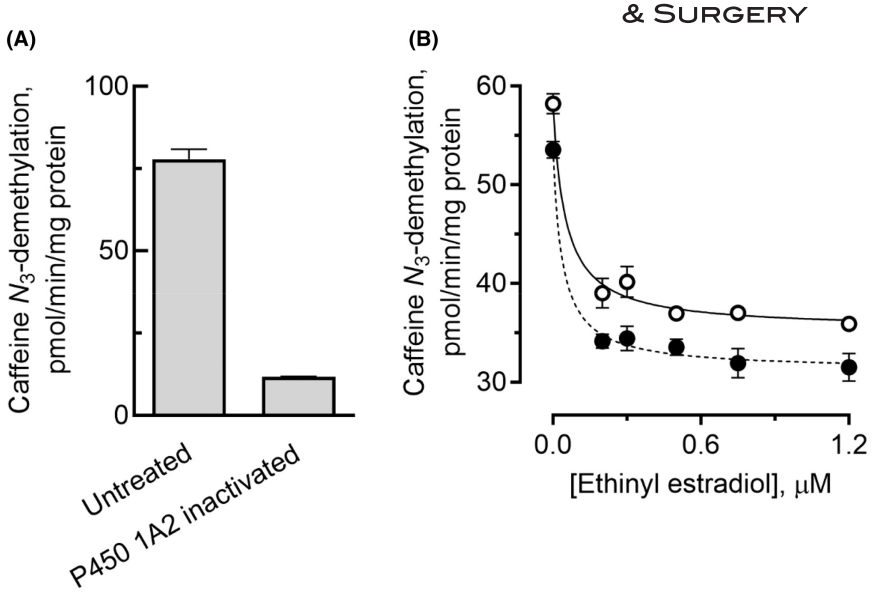

FIGURE 2 Inhibitory effects of ethinyl estradiol on caffeine N_3-demethylation activity. Caffeine (500 μM) was incubated for 30 min with human liver microsomes that were either untreated or P450 1A2 inactivated (A). Time-dependent inhibition of caffeine N_3-demethylation activity by ethinyl estradiol in human liver microsomes (B). Liver microsomes were pre-incubated for 10 min (solid circles) and co-incubated (open circles) in the presence of ethinyl estradiol (0.20–1.2 μM) and subjected to caffeine N_3-demethylation assays.

when pre-incubation was not performed (Figure 2B). This suggests that ethinyl estradiol is not only a competitive inhibitor of P450 1A2 substrates, but also a time-dependent or mechanism-based inhibitor.

This was a single-case report and did not examine whether the patient harbored any genetic polymorphism of P450 1A2. Furthermore, it is difficult to extrapolate the in vitro metabolic inhibition experiments to in vivo conditions. However, considering the results of the in vitro experiments in this study and the previously reported three-fold increase in peak blood concentrations of tizanidine with the concomitant use of oral contraceptives[11] and an approximately two-fold increase in the area under the caffeine concentration curve,[12–14] it was suggested that a significant delay in caffeine clearance in this case may have been caused by an interaction with ethinyl estradiol. If, as suggested by in vitro experiments, ethinyl estradiol affects caffeine metabolism as a mechanism-based inhibitor, the long-term use of oral contraceptives could significantly amplify the impact of reduced caffeine clearance. Indeed, previous reports in healthy adults have suggested that the long-term use of ethinyl estradiol reduces caffeine clearance, which is consistent with the results of our in vitro experiments. In general, many patients hospitalized due to drug overdoses are young women, and this demographic corresponds to the group of patients prescribed oral contraceptives.

Among other co-administered drugs that might be possible P450 modifiers for the reduced caffeine clearance in this case, paroxetine might be another candidate, which has been listed as a P450 1A2 inhibitor in an online database.[20] However, paroxetine is a well-known time-dependent inhibitor of P450 2D6 in vitro.[21] Moreover, paroxetine had a dose-dependently (20–80 mg per subject) affecting the P450 2D6-mediated sparteine metabolic ratios (up to 10-fold) in six young healthy male subjects, while the same doses of paroxetine administration did not have any significant effects on P450 1A2-dependent caffeine oxidation in the other five subjects in vivo.[22] Taken together, it could not be completely ruled out that the possibility of another co-administration of paroxetine, in addition to ethinyl estradiol, might contribute to the reduced metabolic clearance of caffeine in this case; paroxetine should have a minor role in the current drug interactions between intentionally overdosed caffeine (12 g) and clinically normal doses.

CONCLUSION

Prescribed ethinyl estradiol prolonged the overdosed caffeine elimination in vivo and inhibited paraxanthine formation, as evidenced by the low serum concentrations. If caffeine overdose is suspected in young women, it is advisable to check for a prescription history of low-dose contraceptives that may influence the pharmacokinetics of caffeine and to plan treatment in view of the reduced caffeine clearance.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Kyoto Medical Center (18–103). Informed consent was obtained from the patient.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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