

Increased theophylline metabolism in the menstrual phase of healthy women

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Background: We previously reported on a Japanese woman with premenstrual asthma whose serum theophylline concentration was lower before the onset of her menstrual period. We evaluated the clearance of theophylline in each phase of her menstrual cycle and found an increase in clearance in the premenstrual and menstrual phases.

Objective: This study was designed to investigate whether changes in theophylline clearance may occur with the menstrual cycle in nonasthmatic women.

Methods: Aminophylline, 250 mg, was infused intravenously for 45 minutes, and the clearance of theophylline was calculated in seven healthy, ovulatory women on days 1 or 2, 10, and 20 or 25 of the menstrual cycle. The serum concentration of theophylline was determined with an enzyme immunoassay (homogeneous).

Results: Theophylline clearance was significantly higher and its half-life was significantly shorter in the menstrual phase than in the follicular phase.

Conclusion: The metabolism of theophylline, and consequently, its clearance were increased in healthy women around the onset of menses. Clinicians must therefore consider the menstrual variation in theophylline metabolism when prescribing this drug to female patients. (*J Allergy Clin Immunol* 1997;100:39-43.)

Key words: Theophylline, menstrual cycle, estrogen, premenstrual asthma

We previously reported in a Japanese journal (English abstract¹) on a patient with premenstrual attacks of asthma. Her serum levels of theophylline were decreased whenever she came to our hospital with an asthma attack before the onset of her menstrual period. Although her usual theophylline levels were about 13 µg/ml, they had fallen almost out of the therapeutic range. We evaluated theophylline clearance in each phase of this patient's menstrual cycle. She had been receiving a sustained-release theophylline preparation orally at home, and after she was admitted to the hospital, an intravenous drip infusion was added. The use of other drugs was kept consistent throughout the study. We found that theophylline clearance was higher during the menstrual phase than during any other phase

Abbreviation used

ANOVA: Analysis of variance

of this patient's cycle. We thought that an increase in theophylline metabolism was responsible for the lowered level of serum theophylline during the menstrual phase.

If an increase in theophylline metabolism generally occurs in normal women during menstruation, clinicians must give attention to the menstrual cycle when prescribing this agent for female patients with asthma. This study therefore investigated changes in theophylline clearance as related to the menstrual cycle in normal women.

METHODS

Subjects

Seven healthy, ovulatory Japanese women aged 30 to 44 years (mean age, 34.9 years) were investigated. No subject had asthma, and none of them had received theophylline previously. They recorded their basal body temperature during the 1-month study. All subjects gave their informed consent to participate in this study.

Sampling

Blood samples were collected after 30 minutes of bed rest and before breakfast on the day of onset or day 2 of menses, day 10, and day 20 or 25. These sampling times corresponded to the menstrual phase, follicular phase, and luteal phase of the menstrual cycle.

On each day of sampling, 250 mg of aminophylline with 250 ml of isotonic saline solution was drip-infused intravenously over 45 minutes. Aminophylline is a mixture of theophylline and ethylenediamine. We used intravenous infusion as the route of administration, because we could consider the end of the infusion as the time of 100% absorption; if the drug had been given orally, there may have been problems of bioavailability.

On the study days, subjects came to our hospital in the morning before breakfast. They went home after the infusion and returned to the hospital during the sampling times. The subjects were asked not to consume tea, coffee, chocolate, charcoal-broiled beef, or any medicines. They were also asked not to adhere to a diet extremely low in protein or high in carbohydrates. They were asked not to change their daily work.

The 2 ml blood samples were drawn before the infusion and 45 minutes, 2 hours, 4 hours, 6 hours, and 8 hours after the beginning of the infusion. The serum was separated and stored at -40° C until assayed.

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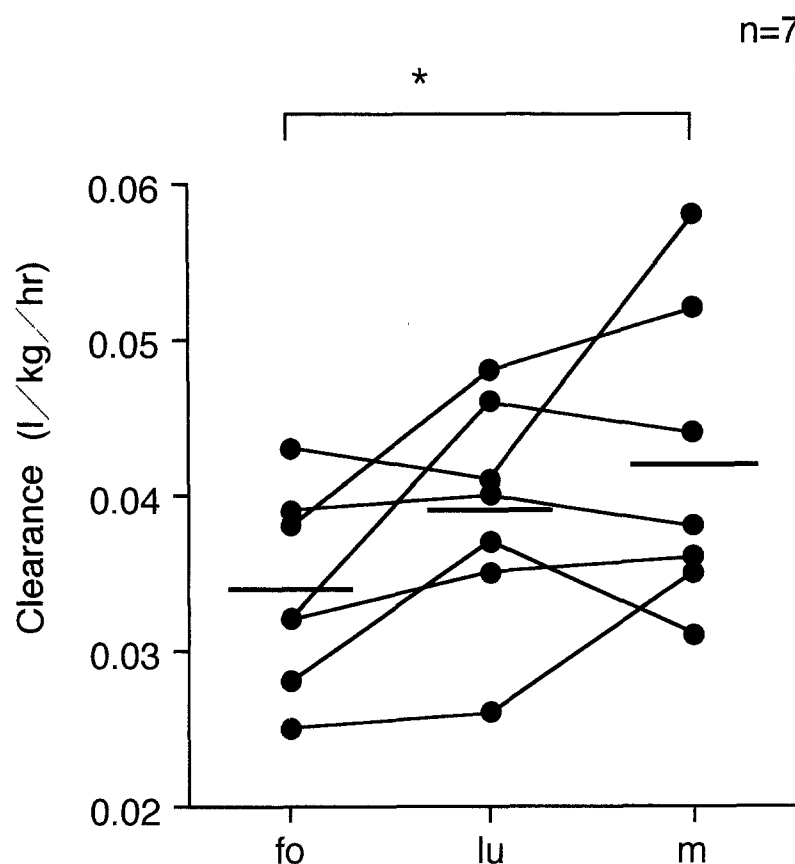


FIG. 1. Changes in theophylline clearance in healthy women *fo*, follicular phase; *lu*, luteal phase; *m*, menstrual phase. Horizontal bars represent means. *Significant difference between follicular phase and menstrual phase ($p < 0.05$).

TABLE I. Serum levels of estradiol and progesterone in seven subjects

Phase	Estradiol (pg/ml)	Progesterone (ng/ml)
Follicular	80.7 ± 44.2	0.26 ± 0.14
Luteal	154.4 ± 123.1	13.17 ± 5.23
Menstrual	22.8 ± 12.6	0.46 ± 0.24

Values are expressed as means ± SD.

Theophylline assay

Serum theophylline was assayed with a commercial enzyme immunoassay (homogeneous) kit (Behring Diagnostics Inc., San Jose, Calif.) and an Emit Clinical Processor (model CP-5000, Behring Diagnostics Inc.). The limit of detection was 2.5 µg/ml, and the coefficient of variation was less than 10%. Theophylline maximum concentration was estimated by inspection; and theophylline clearance, volume of distribution, and half-life were calculated.

Hormone assay

Serum concentrations of estradiol and progesterone were determined in the sample obtained before the aminophylline infusion. A commercial radioimmunoassay kit (Diagnostic

Products Co., Los Angeles, Calif.) was used. The reference limit for estradiol was 10 pg/ml (coefficient of variation < 8.1%), and the reference limit for progesterone was 0.05 ng/ml (coefficient of variation < 10%). The menstrual phase on the day of the experiment was confirmed with these data.

Statistical analysis

Data were analyzed by two-way analysis of variance (ANOVA). For multiple comparisons, the Tukey test, Newman-Keuls test, and Scheffe's test were used. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Menstrual cycle

All subjects showed a biphasic pattern of basal body temperature and an increase in progesterone level in the luteal phase, indicating that they were in the ovulatory cycle. A normal pattern of change was seen in the estrogen and progesterone levels for all subjects (Table I). These estrogen and progesterone values were used to determine the menstrual phase in each subject.

Clearance of theophylline

The mean theophylline clearance was 0.034 L/kg/hr in the follicular phase, 0.039 L/kg/hr in the luteal phase,

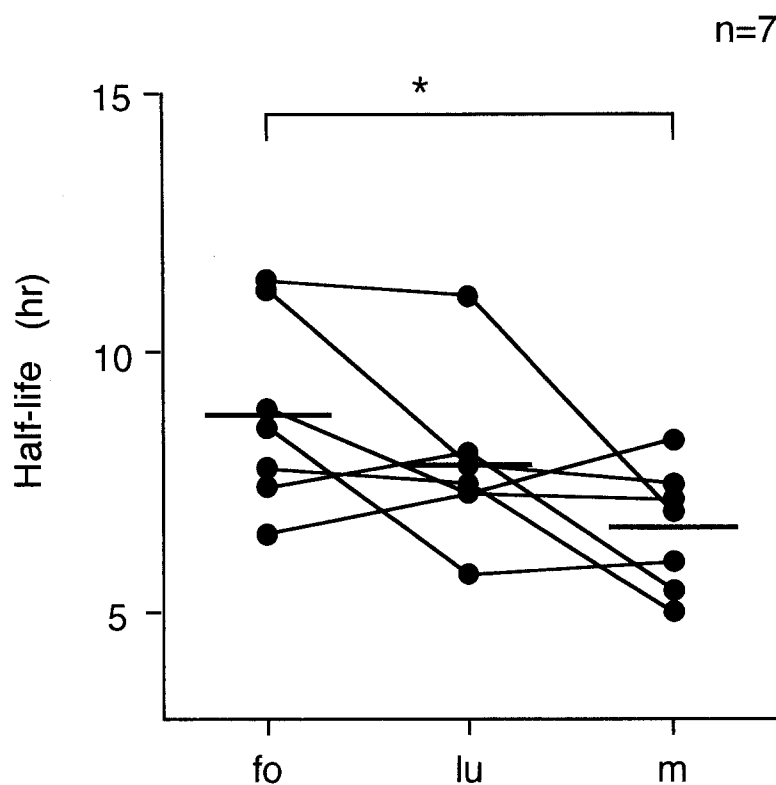


FIG. 2. Changes in theophylline half-life in healthy women *fo*, Follicular phase; *lu*, luteal phase; *m*, menstrual phase. Horizontal bars represent means. *Significant difference between follicular phase and menstrual phase ($p < 0.05$).

TABLE II. Pharmacokinetic parameters in seven subjects

	Clearance (L/kg/hr)	Half-life (hr)	Volume of distribution (L/kg)	Maximum concentration (μ g/ml)
Follicular phase	0.034 ± 0.0064	8.8 ± 1.9	0.42 ± 0.036	8.8 ± 1.2
Luteal phase	0.039 ± 0.0073	7.8 ± 1.6	0.43 ± 0.059	8.8 ± 1.8
Menstrual phase	$0.042 \pm 0.0098^*$	$6.6 \pm 1.2^*$	0.40 ± 0.025	9.2 ± 0.9
F value of ANOVA	$5.331 (p = 0.022)$	$5.503 (p = 0.020)$	$0.761 (p = 0.489)$	$0.626 (p = 0.551)$

Values for phases are expressed as means $\pm$ SD.

* $p < 0.05$.

and 0.042 L/kg/hr in the menstrual phase (Table II, Fig. 1). The change in the menstrual cycle was significant with the two-way ANOVA. The differences between the follicular and menstrual phases were significant.

Half-life of theophylline

The mean half-life of theophylline was 8.8 hours in the follicular phase, 7.8 hours in the luteal phase, and 6.6 hours in the menstrual phase (Table II, Fig. 2). This menstrual change was statistically significant with the 2-way ANOVA. The difference between the follicular and the menstrual phases was statistically significant.

Volume of theophylline distribution

The mean volume of distribution of theophylline was 0.42 L/kg in the follicular phase, 0.43 L/kg in the luteal phase, and 0.40 L/kg in the menstrual phase (Table II). This change was not significant.

Maximum theophylline concentration

The mean maximum concentration was 8.8 μ g/ml in the follicular phase, 8.8 μ g/ml in the luteal phase, and 9.2 μ g/ml in the menstrual phase (Table II). This change was not significant.

DISCUSSION

In our previous study of a woman with asthma, theophylline clearance was higher, and the half-life was shorter in the premenstrual and menstrual phases.¹ In this study of healthy nonasthmatic women, theophylline clearance was significantly higher in the menstrual phase than in the follicular phase, and the half-life was shorter in the menstrual phase than in the follicular phase. These results are compatible with those in our previous report.

Diet and activity are significant factors for measuring theophylline metabolism. Subjects were either office staff at our university (daytime only) or housewives who lived nearby; none of them changed their daily office work or housekeeping chores. They were asked not to consume tea, coffee, chocolate, or any medicines. They were also asked not to adhere to a diet extremely high in protein or carbohydrates. These points were checked during the sampling times every 2 hours.

The volume of distribution of theophylline remains relatively constant at approximately 0.5 L/kg body weight.² Therefore theophylline clearance is dependent on its half-life, which represents its hepatic metabolism.^{2,3} In our study both the clearance and half-life of theophylline showed significant changes, but the volume of distribution did not change significantly. Therefore the increase in theophylline clearance in the menstrual phase was caused by an increase in its metabolism.

Bruguerolle et al.⁴ reported that theophylline clearance was significantly lower on day 20 (luteal phase) in women with asthma. Their patients had experienced bronchial asthma for a long time, and some had received corticosteroid therapy, but it is not clear whether all of them had normal ovulatory cycles. In their report clearance was significantly higher on day 0 (menstrual phase), as we observed in our study, but the half-life was not shorter then. Therefore Bruguerolle et al.⁴ did not conclude that the increased theophylline clearance depended on an increase in theophylline metabolism.

Because theophylline clearance changed during the menstrual cycle, we thought that it depended on hormonal changes, specifically in estradiol and progesterone. The estrogen level was high in both the follicular and luteal phases, but a high level of progesterone was seen only in the luteal phase. However, there was no significant difference in clearance between the follicular and luteal phases in this study. The patient with asthma in our previous report had a regular anovulatory cycle as a result of long-term oral steroid therapy. Because she had no increase in progesterone, estradiol was thought to be the main factor. In women using oral contraceptives (high-estrogen state), the half-life of theophylline is prolonged, and its clearance is decreased because of the inhibitory effect of estrogen on the hepatic microsomal enzyme system and the hepatotoxicity of estrogen.^{2,5-10} Liver dysfunction is sometimes observed in pregnant women, and several forms of liver disease occur only in pregnancy, another high-estrogen state.¹¹ In some pregnant women, because of the increased volume of distri-

bution, the clearance of theophylline is unchanged, but its half-life is increased.^{2,12} In other pregnant women, the clearance is decreased.¹³ Thus in pregnancy the high level of estrogen may reduce theophylline metabolism. However, in the menstrual phase the serum concentration of estrogen is lowered, so that clearance should be increased.

On the other hand, despite the large differences in estrogen and progesterone levels between the luteal and menstrual phases, there were no significant differences in clearance between the luteal and menstrual phases, so the changes of estrogen and progesterone levels could not explain everything. Koren et al.¹⁴ reported that low-dose oral contraceptives did not affect theophylline elimination. The low-dose oral contraceptives they used consisted of ethyl estradiol and norethindrone, and this suggests the existence of factors other than estrogen or progesterone.

In conclusion, our findings suggest that theophylline clearance is increased in the menstrual phase, mainly because of an increase in theophylline metabolism. The pathogenic mechanisms of the premenstrual exacerbation of asthmatic symptoms are still unknown, and the increased theophylline clearance may not be the main factor. However, there are still many patients using theophylline, so there may be more patients whose lowered serum theophylline concentrations are out of the therapeutic range in their premenstrual phase, such as our patient with premenstrual asthma.

Thus it is important that one consider the menstrual cycle when prescribing theophylline to women with asthma, and it is necessary to check the serum concentration of theophylline when a woman complains of premenstrual worsening of asthma.

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