Influence of menstrual cycle on antipyrine pharmacokinetics in healthy Indian female volunteers

V. K. NAYAK, N. A. KSHIRSAGAR, N. K. DESAI & R. S. SATOSKAR

Clinical Pharmacology Unit (CDRI) and the Department of Pharmacology, Seth G. S. Medical College and K. E. M. Hospital, Parel, Bombay 400 012, India.

The effect of the menstrual cycle on antipyrine pharmacokinetics was studied in 11 normal, healthy Indian female volunteers. Antipyrine half-life, apparent volume of distribution, clearance and AUC were calculated by standard methods. Results indicated that in females, antipyrine half-life was significantly longer on day 5 as compared with that on days 15 and 21 of the menstrual cycle. It appears that hormonal changes during the menstrual cycle affect the pharmacokinetics of drugs in normal healthy females.

Keywords antipyrine pharmacokinetics menstrual cycle Indian females

Introduction

An influence of sex differences on the disposition of drugs has been reported (Kato *et al.*, 1962; Roberts *et al.*, 1979; Trnavská & Trnavský, 1983). The nature and degree of this influence is dependent on both the species and the drug under study. Kato and coworkers (1962) demonstrated that androgens increased the activity of microsomal mixed function oxidases resulting in more rapid elimination of drugs in male rats than in females. However, such sex differences were not observed in other species including guinea pig, dog and rabbit. Sex differences in humans have been observed to influence the disposition of drugs including chlordiazepoxide (Roberts *et al.*, 1979), paracetamol (Miners *et al.*, 1983), and salicylic acid (Trnavská & Trnavský, 1983). However, controversy exists regarding antipyrine metabolism in humans with reference to sex differences and the menstrual cycle. Thus, O'Malley *et al.* (1971) observed a difference in the rate of metabolism in males and females, whereas Fraser *et al.* (1977) did not. Kellerman *et al.* (1976) observed a decreased antipyrine half-life on day 13 of the menstrual cycle. However, Riester *et al.* (1980) reported that the menstrual cycle had very little or no effect on antipyrine kinetics.

The present study describes antipyrine pharmacokinetics in healthy Indian volunteers in relation to sex and menstrual cycle.

Methods

Ten normal, healthy male and 11 normal, healthy female volunteers, 19–35 years, participated in this study. They were confirmed to be healthy by physical examination and routine laboratory investigations of haematology, renal function and liver function tests. The range of body weights for the male volunteers was 41 to 56 kg and for the females it was 39 to 51 kg. The female volunteers had regular menstrual cycles of approximately 28–35 days, with bleeding lasting for 4–5 days. None of the females was on anti-fertility drugs. The volunteers did not take any drugs for at least 1 month prior to and during the study. They were non-smokers and did not take alcohol. This was an out-patient study. Daily physical activity was not restricted and diet and beverage intake was not standardized. Written, informed consent was obtained from each of the volunteers prior to the study. Local ethics committee approval was obtained.

Antipyrine was administered orally in a dose of 18 mg kg⁻¹ body weight after overnight fasting, and the volunteers continued fasting for a further 3 h. Five ml of unstimulated saliva were collected prior to and at 3, 5, 7, 9, 11, 13 and 24 h after administration of antipyrine. The subjects were asked to wash their mouths 3–4 times before each collection of saliva. In the female volunteers, the above procedure was carried out on the 5th, 15th and 21st day of the menstrual cycle and on

the 5th day of the subsequent two cycles. In males, the antipyrine disposition test was carried out thrice with a gap of 10 days in between.

Antipyrine was measured in saliva by the spectrophotometric method of Desai *et al.* (1982) modified from Brodie *et al.* (1949). Half-life ($t_{1/2}$), apparent volume of distribution (V), clearance (CL) and the area under the drug concentration-time curve (AUC) were calculated using standard equations (Shargel & Yu, 1980).

Results

The results are summarised in Tables 1 and 2. In the male volunteers, no significant differences were observed in any of the pharmacokinetic parameters. In females, the AUC values measured on the 5th day of the first, second and third menstrual cycle showed no significant differences. However, the mean AUC on day 15 of the menstrual cycle was significantly smaller than that observed on day 5. Similarly, the antipyrine half-life on day 5 of the first, second and third menstrual cycle, revealed no significant differences. However, the antipyrine half-life and clearance measured on days 15 and 21 of the menstrual cycle did show significant changes. Thus, the mean antipyrine half-life was shorter ($P < 0.01$) and the mean clearance was greater ($P < 0.05$) on days 15 and 21 of the menstrual cycle compared with day 5. This was in contrast to

the values observed on days 11 and 21 in male volunteers which showed no significant difference from corresponding values observed on day 1.

Discussion

Sex differences in antipyrine metabolism have been investigated in the past. Fraser *et al.* (1977) observed that there was no significant difference in antipyrine half-life between men and women. O'Malley *et al.* (1971) reported that antipyrine half-life was shorter by 30% in females than that in males. In our study, antipyrine half-life was 28% shorter on days 15 and 21 of the menstrual cycle than that observed on day 5 in females, and assessed at different intervals in males. Similar observations were made by Kellerman *et al.* (1976) in a single subject with a normal menstrual cycle. They observed that the plasma half-life was high on day 5 of the menstrual cycle and declined to a minimum on day 13. Riester *et al.* (1980), on the other hand, found that the menstrual cycle had little or no effect on antipyrine metabolism and attributed the observed decline in antipyrine half-life to enzyme induction by antipyrine. However, the results of our study clearly demonstrate a decrease in antipyrine half-life serially during the menstrual cycle. This is not due to enzyme induction by antipyrine because antipyrine half-life estimated at similar intervals and with the same dose in males, showed no such change. Moreover, antipyrine half-life

Table 1 Pharmacokinetic data of antipyrine in normal healthy male volunteers ($n = 10$) (mean $\pm$ s.e. mean)

Parameters	Basal	On day 11	On day 21
$t_{1/2}$ (h)	11.07 $\pm$ 0.39	11.07 $\pm$ 0.39	11.12 $\pm$ 0.41
V (l)	39.8 $\pm$ 2.1	40.3 $\pm$ 2.5	37.6 $\pm$ 1.3
CL (l h ⁻¹)	2.48 $\pm$ 0.17	2.41 $\pm$ 0.12	2.49 $\pm$ 0.13
AUC (μ g ml ⁻¹ h)	488 $\pm$ 29	465 $\pm$ 28	459 $\pm$ 29

Table 2 Effect of the menstrual cycle on the pharmacokinetics of antipyrine in normal healthy female volunteers ($n = 11$) (mean $\pm$ s.e. mean)

	Day 5	First cycle Day 15	Day 21	Second cycle Day 5	Third cycle Day 5
$t_{1/2}$ (h)	10.96 $\pm$ 0.50	8.20 $\pm$ 0.38***	8.22 $\pm$ 0.35***	10.68 $\pm$ 0.61	10.70 $\pm$ 0.42
V (l)	34.04 $\pm$ 3.07	38.24 $\pm$ 2.96	35.40 $\pm$ 1.73	37.45 $\pm$ 2.14	35.26 $\pm$ 3.58
CL (l h ⁻¹)	2.27 $\pm$ 0.26	3.24 $\pm$ 0.12*	2.98 $\pm$ 0.19*	2.73 $\pm$ 0.22	2.34 $\pm$ 0.23
AUC (μ g ml ⁻¹ h)	448 $\pm$ 36	328 $\pm$ 23**	354 $\pm$ 28	424 $\pm$ 35	449 $\pm$ 42

*** $P < 0.01$, ** $P < 0.02$, * $P < 0.05$

values on the 5th day of the second and third cycles were also similar to those on the 5th day of the first cycle.

Our results indicate that antipyrine half-life, clearance and AUC as measured on days 15 and 21 of the menstrual cycle, are significantly different compared with the corresponding results obtained on day 5 of the menstrual cycle. Furthermore, the values in females for the various parameters studied on day 5 were similar to those in male volunteers. In a female subject with a normal regular menstrual cycle of 28 days, oestrogens and progesterones are lower at the beginning of the cycle. The oestrogens reach a peak just before ovulation and once again in the mid-luteal phase (Schwartz & McCormack, 1980). The shortening of half-life and increase of clearance of antipyrine in this study could be due to oestrogen-progesterone surges in mid-cycle. Similar observations in the metabolism of methaqualone were reported by Wilson *et al.* (1982): a higher serum clearance, shorter half-life and a smaller AUC on day 15 compared with day 1.

Oestrogens and progesterones have been shown to affect drug metabolism. Ethinyl oestradiol given for 5 days decreased the cytochrome P450 content of male rat livers and this was associated with decreased turnover of the P450 pool (Mackinnon *et al.*, 1977). Stilboestrol, administered to normal men, impaired the metabolism of pethidine (Crawford & Rudofsky, 1966). Blackham & Spencer (1969) have reported that oestrogens prolonged while progestagens reduced drug metabolism but this effect was dose related. Oram *et al.* (1982) observed that oral contraceptive administration abolished the increase in the rate of methaqualone metabolism during the mid-cycle. They attributed this increased metabolism during the mid-cycle to the involvement of the direct action of one or more hormones on hepatic enzymic activity. The circulating levels of a number of hormones including oestradiol, luteinizing hormone, follicle stimulating hormone and prolactin, all change dramatically around the time of ovulation, and this could affect the hepatic metabolism of drugs in women (Wilson *et al.*, 1982).

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