Propranolol pharmacokinetics during the menstrual cycle

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Summary: The pharmacokinetics of propranolol during menstruation and in the mid menstrual cycle have been studied in nine young women taking a single 80 mg tablet on each occasion. There were wide between-individual differences in the serum concentration at any given time (4–5 fold at peak concentrations) but the serum concentration time curves within individuals showed only mild variations. The differences between the average pharmacokinetic parameter estimates for the group did not differ significantly between the two periods of study.

Introduction

Propranolol has an established role in the prophylaxis of migraine, but its mechanism of action in this condition remains uncertain (Weerasuriya *et al.*, 1982). The varying dosages required for effective control of attack in different patients indicates that there is unlikely to be a simple relationship between serum propranolol concentration and its effectiveness. Cortelli *et al.* (1985) have indeed shown that there is no relationship between plasma levels and relief of headaches. However, Gengo *et al.* (1984) found that regular premenstrual failure of migraine prophylaxis with this agent in an otherwise well controlled patient was associated with lowered steady-state serum level. Further studies in the same patient revealed that following the same oral dose, serum propranolol concentrations were markedly lower on her first menstrual day compared to those on the sixteenth day.

In order to confirm that the serum propranolol concentrations may be influenced by the menstrual cycle we undertook a study in a group of healthy young volunteers. We also studied the influence of the menstrual cycle on the average pharmacokinetic parameter estimates of the drug.

Patients and methods

We studied nine volunteers (average age 24 years, range 18–43 years). Local ethical committee approval was obtained and each volunteer gave informed consent. There was no evidence of respiratory or cardiovascular disease in any of the volunteers and none was taking oral contraceptive pills. Each volunteer attended for study twice, first within 24 hours of

beginning menstruation and secondly 16 days later.

After an overnight fast, an 80 mg propranolol tablet was given by mouth and 10 ml blood samples were taken from an antecubital vein through an indwelling catheter at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8 and 10 hours for estimation of serum propranolol levels. The blood was allowed to clot and centrifuged to separate the serum. Samples were stored at -20°C until analysed. During the study, volunteers were allowed only a low protein breakfast 2 hours, and low protein lunch 5 hours, after taking the tablet.

Measurement of propranolol concentrations was carried out by a modified spectrofluorimetric method as described by Heagerty *et al.* (1981) using a Perkin-Elmer LS-5 luminescence spectrometer. Three ml rather than 1.5 ml of 0.01 N acid was used because of the larger sized cuvette available. Quality controls using 10, 30 and 80 ng/ml of propranolol in blank serum were measured after every ten volunteer samples.

The serum concentrations of propranolol obtained for each volunteer on the two separate occasions were individually submitted to pharmacokinetic analysis by a computer program, STRIPE, as described by Johnston & Woollard (1983).

The means of the data obtained for a particular parameter obtained in all the volunteers were computed and compared by means of Student's *t* test for paired data on a Hewlett Packard HP-85 computer.

Results

The means of the quality control samples were 10.9, 29.4 and 79.8 ng/ml and their coefficients of variation were 8, 6.5 and 8% respectively. Figure 1 shows the mean serum propranolol concentration time curves

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Figure 1 Serum propranolol levels (mean $\pm$ s.e.m.) in 9 healthy women following 80 mg propranolol orally on day 1 (○---○) and day 16 (●—●) of the menstrual cycle.

over the 10 hours of measurement for the two days of study. On a semi-log plot the data fit a one compartment model. The estimates varied from day 1 to day 16 but there was no consistent pattern. Table I shows the average of the estimated pharmacokinetic parameters and the results of statistical analysis. As can be seen from the *P* values, the differences between the means do not reach a level of statistical significance on any of the parameters.

Discussion

The influence of the menstrual cycle on drug metabolism has not been the subject of much study. However, Reister *et al.* (1980) showed that the menstrual cycle had little or no effect on the mean antipyrine salivary half life, mean metabolic clearance rate or apparent volume of distribution. They found individual variation in kinetic parameters from day to day but noted that there was no consistent pattern in this variation.

Propranolol pharmacokinetics are influenced by several factors. Shand *et al.* (1970) showed that the half life was shorter following an intravenous dose when compared to an oral dose. The same result was found if the oral dose was taken on an empty stomach. Castleden *et al.* (1975) found that given the same oral dose, substantially greater plasma levels were attained in elderly subjects compared with younger ones. Heagerty *et al.* (1981) showed that concurrent cimetidine therapy led to both a higher blood propranolol concentration and relative bioavailability. Patel *et al.* (1983) demonstrated that the area under the curve for propranolol administered per vaginam was significantly greater than that after oral administration. In addition, Walle *et al.* (1985) have shown that higher serum levels occurred for a given dose in women than in men, in Caucasians than in Blacks and in non-smokers than smokers.

The serum propranolol levels obtained in this group of volunteers are similar to those described by Salem and McDevitt (1984) and notwithstanding the problems associated with this type of study (Martin *et al.*, 1984), we believe that these results do not indicate that the pharmacokinetics of propranolol are significantly different between these two days in our volunteers.

Table I Mean ($\pm$ s.e.m.) estimated pharmacokinetic parameters of oral propranolol in 9 healthy volunteers on the 1st and 16th day of the menstrual cycle.

Pharmacokinetic parameter	Day 1	Day 16	<i>P</i>
Mean resident time (MRT) (hours)	5.5 (0.5)	6.3 (0.7)	NS
Absorption half life ($t_{1/2\alpha}$) (hours)	0.5 (0.06)	0.6 (0.08)	NS
Elimination half life ($t_{1/2\lambda}$) (hours)	3.2 (0.4)	3.7 (0.5)	NS
Lag time (hours)	0.1 (0.06)	0.1 (0.03)	NS
Area under the curve [(ng/ml). h]			
0–10 h	422.4 (77.1)	391.0 (58.2)	NS
0–infinity	486.9 (81.3)	486.8 (83.9)	NS
Time to peak (hours)	1.7 (0.24)	2.1 (0.34)	NS
Peak concentration (ng/ml)	93.2 (20.4)	82.8 (11.7)	NS
Clearance (litres/h)	3264.6 (435.5)	3294.6 (615.7)	NS
Volume of distribution (Vd) (litres)	975.5 (147.3)	1026.8 (168.9)	NS

NS indicates that the difference between the means do not reach a level of statistical significance ($P > 0.05$).

It is possible that there might be a relationship between migraine and the phenomenon reported by Gengo *et al.* (1984) and we suggest that the study should be repeated in a suitable group of migrainous women whose attacks are related to the menstrual flow.

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