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Circadian Variations in the Pharmacokinetics of Pentoxifylline in Man

P. SRINIVASU, B. RAMESH RAO, Y. MADHUSUDHAN RAO AND D. RAMBHAU

University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 009 (A.P.), India

Abstract

Optimization of therapy by chronopharmacology requires knowledge of rhythmic manifestations of disease activity and chronopharmacokinetic data of the drugs prescribed. Rhythmic functioning of the cardiovascular system in healthy and diseased subjects is manifested as circadian rhythms in blood pressure, cardiac output, heart rate, etc. The disposition of several cardiovascular drugs in man has been reported to be time-dependent. This study reports the effect of time of administration on the disposition of pentoxifylline.

Twelve healthy volunteers were treated with 400 mg pentoxifylline orally at 0100, 0700, 1300 and 1900 h in a randomized crossover Latin-square design with a wash-out period of one week. Serum samples were analysed for unchanged pentoxifylline by HPLC. Pharmacokinetic parameters were calculated using a model-independent method. The mean values of various pharmacokinetic parameters after drug treatment at these times were, respectively: maximum plasma concentration (C_{max}) 485 ± 174, 646 ± 175, 735 ± 271 and 781 ± 217 ng mL^{-1}; time to reach the maximum plasma concentration (T_{max}) $1{\cdot}90 \pm 0{\cdot}39$, $1{\cdot}66 \pm 0{\cdot}4$, $1{\cdot}31 \pm 0{\cdot}41$ and $1{\cdot}32 \pm 0{\cdot}44$ h, mean residence time (MRT) $3{\cdot}8 \pm 0{\cdot}8$, $2{\cdot}9 \pm 0{\cdot}5$, $2{\cdot}9 \pm 0{\cdot}4$ and $2{\cdot}7 \pm 0{\cdot}3$ h, elimination half-life (t½) $1{\cdot}93 \pm 0{\cdot}86$, $1{\cdot}23 \pm 0{\cdot}3$, $1{\cdot}39 \pm 0{\cdot}3$ and $1{\cdot}23 \pm 0{\cdot}18$ h and volume of distribution at steady state (Vd_{SS}/f) 11991 ± 4862, 8823 ± 3484, 8275 ± 2357 and 7063 ± 1950 mL kg^{-1}. The mean C_{max} value was significantly ($P < 0{\cdot}05$) lower after drug administration at 0100 h than after other time-points whereas mean T_{max}, MRT, Vd_{SS}/f and t½ values were significantly ($P < 0{\cdot}05$) higher.

These variations might be because of time-dependent changes in absorption and biliary excretion of pentoxifylline and should be borne in mind when designing sustained action dosage forms for the drug.

Pentoxifylline (oxpentifylline) is a haemorrheologic agent widely used in the therapeutic management of peripheral and cerebrovascular diseases (Ward & Clissold 1987) and of defective microcirculation (intermittent claudication) (Bollinger & Frei 1977). It improves peripheral circulation by increasing erythrocyte deformability (Aviado & Dettelbach 1984), inhibiting platelet aggregation (Sowemimo-Coker & Turmer 1985) and reducing fibrinogen concentration (Jarret et al 1977).

Circadian rhythm has been shown in the cardiovascular functions such asblood pressure, blood flow to various organs, cardiac output and heart rate (Euler et al 1955; Koneko et al 1968; Smolensky et al 1976), and time-dependent changes in the pharmacokinetics of several cardiovascular drugs have also been reported (Lemmer 1990; Rao & Rambhau 1993, 1995). Because of these circadian changes in the functioning of the cardiovascular system and the reported chronokinetics of drugs used in cardiovascular disorders the chronokinetics of pentoxifylline assume importance. Hence, we have investigated the chronopharmacokinetics of pentoxifylline in healthy volunteers.

Correspondence: D. Rambhau, College of Pharmacy, Kakatiya University, Warangal-506 009 (A.P.), India.

Materials and Methods

Volunteers

The study was conducted with 12 healthy adult male volunteers, 20–27 years, 50–80 kg, 160–175 cm. The study protocol was approved by the Institution's

Ethical committee and informed consent was obtained before enrolment of each volunteer.

Methods

The study was conducted during the months of March and April. Before selection each participant's health was checked by thorough medical examination that included routine blood tests, ECG and urine analysis. Neither alcoholic beverages nor additional medication were allowed for two weeks before the investigation or during it. The volunteers were divided into four treatment groups and the study was conducted in a cross-over manner with a wash-out period of seven days.

Drug administration

After approximately 10 h fast and a standard breakfast, pentoxifylline (400 mg; an immediate release capsule) was administered to the volunteers with 200 mL water at four different times (0100, 0700, 1300 and 1900 h) during a 24-h cycle. Food and drink were not permitted for 3 h after drug administration; regular meals before and after stipulated times were allowed. The subjects were maintained in a sitting position for the first 3 h after drug administration and were confined to the laboratory during the study days.

Blood sampling

Blood samples (3 mL) were collected from the median cubital vein 0, 0·25, 0·5, 0·75, 1·0, 1·5, 2, 2·5, 3, 4, 5, 6 and 8 h after drug administration. The samples were left to clot and serum was separated and stored frozen until analysis.

Assay

Unchanged pentoxifylline in serum samples was analysed by a modification of the HPLC method of Lambert et al (1989); salicylamide was used as internal standard.

Chromatography was performed with a Shimadzu HPLC unit equipped with an SCL-6A module system controller, an LC-6A solvent-delivery module, a 15 cm × 4·6 mm i.d. octadecylsilane reversed-phase stainless steel column, a CTO-6A column oven, an SPD-6A UV-vis spectrophotometric detector and a C-R4A Chromatopac data processor.

The mobile phase was acetonitrile–water–acetic acid, 18:81·9:0·1. The flow rate was 1 mL min^{-1}, the pressure 60 kgf cm^{-2}, the column temperature 40°C, the detector wavelength 274 nm and the detector sensitivity 0·01 aufs.

The retention times of internal standard and pentoxifylline were 5·4 and 8 min, respectively. A calibration curve was prepared by adding 0, 62·5, 125, 250, 500, 750, 1000 and 1500 ng pentoxifylline in methanol to 1-mL samples of serum from untreated volunteers. These samples were treated in the same manner as the test samples. The peak height ratios (drug/internal standard) obtained for different concentrations of the drug were plotted against the drug concentration; the slope of the plot was determined by least squares regression analysis and used to calculate the unknown pentoxifylline concentrations in serum samples.

The reproducibility of the assay was checked by fivefold analysis of serum samples to which different concentrations of the drug had been added. The coefficient of variation was less than 5·8% at all concentrations.

The pharmacokinetic parameters of pentoxifylline were computed using a model-independent method. The time-dependent changes in the pharmacokinetic parameters were tested by analysis of variance and new multiple range tests at a probability level of 95%.

Results

Figure 1 shows the time-courses of the mean serum concentrations of pentoxifylline after administration of 400 mg pentoxifylline at 0100, 0700, 1300 and 1900 h. The mean values of the pharmacokinetic parameters of pentoxifylline after administration at these four different times are given in Table 1.

The mean peak serum pentoxifylline concentrations were $485·45 \pm 174·75$, $646·37 \pm 175·01$, $735·58 \pm 271·36$ and $781·80 \pm 217·57$ ng mL^{-1} after administration of the drug at 0100, 0700, 1300 and 1900 h, respectively. The mean C_{max} value after administration at 0100 h was significantly ($F = 4·52$, $P < 0·05$, $n = 12$) lower than that after

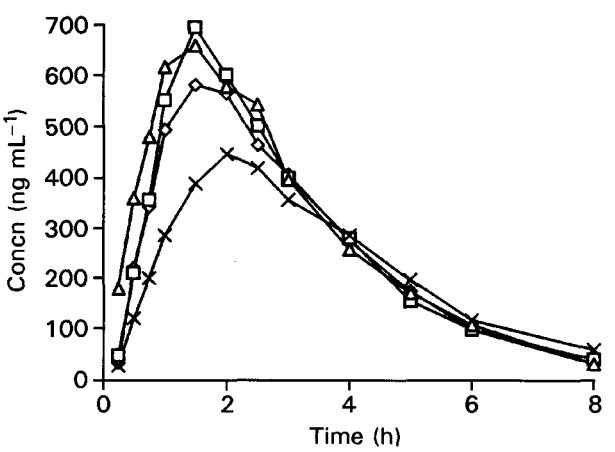

Figure 1. Mean (n = 12) serum pentoxifylline levels after oral administration of 400 mg at 0100 (×), 0700 (◇), 1300 (□) and 1900 (△) h.

Table 1. Mean (± s.d., n = 12) pharmacokinetic parameters of pentoxifylline after a single oral dose of 400 mg at different times.

	0700 h	1300 h	1900 h	0100 h
Maximum plasma concentration (ng mL^{-1})	646·3 ± 175·0	735·5 ± 271·3	781·8 ± 217·6	485·4 ± 174·7
Time to reach maximum plasma concentration (h)	1·66 ± 0·40	1·31 ± 0·41	1·32 ± 0·44	1·90 ± 0·39
Absorption rate constant (h^{-1})	2·96 ± 0·87	3·83 ± 1·18	3·73 ± 1·40	2·71 ± 0·74
Elimination half-life (h)	1·23 ± 0·30	1·39 ± 0·30	1·23 ± 0·18	1·93 ± 0·86
Clearance (mL kg^{-1})	3508 ± 1530	3334 ± 1163	2819 ± 803	3404 ± 1361
Volume of distribution (mL kg^{-1})	5396 ± 1673	6281 ± 2478	5736 ± 224	8996 ± 4621
Volume of distribution at steady state (mL kg^{-1})	8823 ± 3484	8275 ± 2357	7063 ± 1950	11991 ± 4862
Area under the plasma concentration–time curve (ng mL^{-1} h)	2143 ± 615	2081 ± 681	2365 ± 589	2028 ± 652
Area under the moment of the plasma concentration–time curve (ng mL^{-1} h^2)	6526 ± 2514	6310 ± 2486	6802 ± 2023	8265 ± 3622
Mean residence time (h)	2·9 ± 0·5	2·9 ± 0·4	2·7 ± 0·3	3·8 ± 0·8

administration at 0700, 1300 or 1900 h. The mean values of T_{max} ($F = 5{\cdot}47$, $P < 0{\cdot}05$, n = 12), $t_{\frac{1}{2}}$ ($F = 5{\cdot}41$, $P < 0{\cdot}05$, n = 12), Vd_{SS}/f ($F = 4{\cdot}69$, $P < 0{\cdot}05$, n = 12) and MRT ($F = 8{\cdot}09$, $P < 0{\cdot}05$, n = 12) were significantly higher after administration at 0100 h than after administration at 0700, 1300 or 1900 h. No significant time-dependent changes were observed in other pharmacokinetic parameters such as area under the plasma concentration–time curve, area under the moment of the plasma concentration–time curve, elimination rate constant and clearance.

Discussion

Circadian variations in the blood flow to various organs and tissues in man have been reported (Koneko et al 1968). Fluctuation of approximately 40% has been observed in the resting and post-exercise forearm blood flow with peak values in the late afternoon and early evening. Circadian variations in calf blood flow with early evening peak and a late nocturnal trough have also been observed in patients with intermittent claudication (Bartoli et al 1970). Although minimum effective concentrations and the importance of steady-state plasma levels of pentoxifylline have not been established, the significant reduction in C_{max} after administration at 0100 h observed in this study might have clinical relevance because of the late nocturnal trough in the calf blood flow.

Circadian variations in blood coagulation times have been established. In rats blood coagulation was more rapid during resting periods than during activity, the clotting time being shortest at 1300 and 1700 h and longest between 0100 and 0900 h (Soulban & Labrecque 1988). The greatest anticoagulant effect of heparin is in the early evening (Decousus et al 1985). Pentoxifylline inhibits platelet aggregation by inhibiting phosphodiesterase, thereby increasing cyclic AMP levels in the platelet membrane (Ward & Clissold 1987). Circadian variations in cyclic AMP levels have been observed in plasma (Mikuni et al 1978), heart cells (Lang et al 1985) and brain (Lemmer et al 1985); peak levels occur during daytime and, consequently, troughs during the night. Thus if higher levels of cyclic AMP, via inhibition of phosphodiesterase, are needed to inhibit platelet aggregation, pentoxifylline levels should be maintained higher at night. However, the reduced plasma levels observed in this study after 0100 h dosing suggest that the evening dose of the drug should be increased.

Time-dependent changes in the bile output, bile acid concentration and cholecystokinin levels have been reported in rats, levels being 25% higher during the night than at noon (Henegouwen & Hofman 1978; Burthol et al 1980; Botham et al 1981). Occurrence of a second peak in plasma levels of digoxin, (β-methyldigoxin (Carosella et al 1978) and rifampicin (Avachat et al 1992) after nocturnal administration of the drugs has been attributed to biliary rhythms.

Pentoxifylline undergoes extensive enterohepatic cycling (Ward & Clissold 1987). The reduced C_{max} for pentoxifylline observed in this study might be explained by reported biliary rhythms (Henegouwen & Hofman 1978; Burthol et al 1980; Botham et al 1981). Because the gall bladder is not emptied during the night, the drug extracted into the bile could be concentrated in the gall bladder during the dark period and emptied into the gastrointestinal tract the next morning, thus providing the drug for absorption in the elimination phase. This might be the reason for the significantly higher $t_{\frac{1}{2}}$ and MRT of pentoxifylline after administration at 0100 h.

As well as biliary rhythms, the circadian changes in gastrointestinal motility and gastrointestinal blood flow (both lower during the night) might have contributed to the reduced C_{max} and pro-

longed T_{max} of pentoxifylline. Such rhythms in absorption have been observed for several drugs which do not undergo enterohepatic cycling (Vener & Moore 1988).

Pentoxifylline increases the peripheral blood flow by increasing the deformity of the erythrocytes, which is one of its main mechanisms of action. If susceptibility of the erythrocyte membrane to the action of drugs (pentoxifylline) is subject to circadian variation, as indicated by time-dependent changes in erythrocyte permeability to local anaesthetics (which is maximum at 0400 h and minimum at 1600 h; Bruguerolle & Prat (1988)), pentoxifylline levels might have to be suitably adjusted.

In conclusion, the importance of steady-state plasma levels or the minimum effective concentration and the therapeutic range (window) for pentoxifylline, or both, must be determined. When such data are available the clinical implications of the chronokinetics of pentoxifylline reported in this study can be clearly stated and chronotherapy with pentoxifylline recommended.

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