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Chronopharmacokinetics of Sumatriptan in Healthy Human Subjects

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Abstract

Rhythms in the onset and symptoms of several diseases are well established. Migraine is a disorder that exhibits periodicity in its symptoms and so chronotherapy may be beneficial in treating the problem. Designing a chronotherapeutic schedule requires chronopharmacokinetic and chronopharmacodynamic data of the drugs prescribed. We have studied the chronopharmacokinetics of sumatriptan, a drug of choice in migraine treatment.

Twelve healthy male volunteers were treated with 100 mg sumatriptan orally at 07 00, 13 00, 19 00 and 01 00 h in a randomized 4 × 4 Latin square crossover design, with a washout period of one week. Serum samples were analysed by high performance liquid chromatography with an electrochemical detector. Pharmacokinetic parameters were calculated using noncompartmental methods. The pharmacokinetic parameters were analysed using analysis of variance and a two-tailed paired *t*-test at the probability of 95%.

The mean peak serum concentration following the 07 00 h administration (C_{max}; $59{\cdot}09 \pm 10{\cdot}53$ ng mL^{-1}) was significantly ($P < 0{\cdot}05$; n = 12) higher than after the 19 00 h administration (C_{max} $41{\cdot}88 \pm 12{\cdot}21$ ng mL^{-1}). The mean area under the serum concentration–time curve from time zero to the last time-point (AUC_{o-t}), the area under the serum concentration-time curve from zero to infinity ($AUC_{0-\infty}$), and the area under the first moment curve (AUMC) were significantly ($P < 0{\cdot}05$; n = 12) higher following the 07 00 and 01 00 h administrations than after the 19 00 h administration. Following administration at 07 00 h, the mean oral clearance (CL_s/f; 781 ± 186 mL h^{-1} kg^{-1}) and the apparent volume of distribution (Vd/f; 2379 ± 684) were significantly lower ($P < 0{\cdot}05$; n = 12) than after the 19 00 h administration (CL_s/f 1208 ± 458 mL h^{-1} kg^{-1}, Vd/f 4655 ± 2096 mL kg^{-1}). The mean Vd/f value was again lower after the 1300 h administration than after the 19 00 h administration (2763 ± 1417 vs 4655 ± 2096 mL kg^{-1}; $P < 0{\cdot}05$; n = 12).

The variations may be due to the time dependent changes in the extent of absorption and/or circadian variations in hepatic blood flow.

The establishment of definite rhythms in the onset and symptoms of disease, and the availability of chronopharmacokinetic data for prescribed drugs, has led to chronotherapy being tried, successfully, in the treatment of asthma (Goldenheim & Schein 1991; Pincus et al 1995), rheumatoid arthritis (Reinberg et al 1991), cardiovascular disorders (Cooke & Lynch 1994; Conte et al 1998; Smolensky & Portaluppi 1999) and cancer (Levi 1995, 1996). Migraine is a highly prevalent disorder, affecting approximately 6% of men and 15–18% of women. Its prevalence is highest between the ages of 25 and 55 years, which accounts for its enormous impact in the work place leading to a substantial burden on society, as measured by direct and indirect costs. Migraine is a heterogeneous disorder; attacks vary in pain intensity, duration, and pattern of associated features and frequency of occurrence (Solomon 1992; Ninan 1997). Its manifestations also vary within individuals over time (Solomon 1992; Ninan 1997). The onset of migraine shows circadian variations, with a marked increase in attacks between 06 00 and 08 00 h, peak frequency of migraine onset between 08 00 and 10 00 h and a dramatic decrease in frequency between 20 00 and 04 00 h. Optimization of therapy

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as a function of time of administration may be beneficial. In view of the absence of chronopharmacokinetic data of drugs used in migraine treatment, we have investigated the chronopharmacokinetics of sumatriptan, a drug of choice in the treatment of migraine.

Materials and Methods

Protocol

The study was carried out in 12 diurnally active, healthy male volunteers (weight 49–70 kg, height 165–175 cm and age 19–30 years) with the approval of the Institutional Ethical Committee. The subjects were in good health documented by a complete medical examination by a physician, medical history and standard laboratory tests. Volunteers were not allowed alcoholic beverages nor any medication from two weeks before the study and throughout its duration. The study was conducted in a randomized 4×4 Latin square crossover design during the months of December and January with a seven-day wash-out period between treatments.

Drug administration

After approximately 10 h fasting, sumatriptan succinate (100 mg) (an immediate release capsule) was administered to the volunteers with 200 mL water at four different times (07 00, 13 00, 19 00 and 01 00 h) during a 24-h cycle. Food and drinks were not permitted for 3 h after drug administration, however, regular meals before and after stipulated times were allowed. The subjects maintained 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 at intervals of 0, 0·5, 1, 1·5, 2, 2·5, 3, 4, 5, 6, 8, 10 and 12 h after drug administration. The samples were allowed to clot, serum was separated and stored under frozen conditions until analysis was performed.

Assay

Serum samples were analysed for unchanged sumatriptan using the modified HPLC method of Andrew et al (1993) with ofloxacin as internal standard.

Serum (1 mL) was basified with 4 M sodium hydroxide solution (0·1 mL), and 0·1 mL internal standard (1 μg ofloxacin in methanol) and 4 mL dichloromethane were added. The mixture was agitated on a rotational shaker for 15 min and then centrifuged at 2000 *g* for 5 min. The organic layer was transferred to a clean test tube and dried under vacuum. The residue was reconstituted in 100 μL methanol and a 20-μL sample was injected onto the column.

Instrumentation

An HPLC system (Shimadzu Corporation, Japan) equipped with a SCL-6A system controller, a LC-6A solvent delivery unit, a CTO-6A column oven, an ECD-6A electrochemical detector, and a C-R4A chromatopac data processor was used for the analysis. An octadecyl silane reverse-phase stainless steel column ($150 \times 4{\cdot}6$ mm, 5 μm particle size) was used.

Chromatographic conditions

The mobile phase was aqueous pH 7·0 phosphate buffer (5·25 g disodium hydrogen orthophosphate and 2·79 g potassium dihydrogen orthophosphate dissolved in 1 L water) and methanol (60 : 40). The flow rate was 1 mL min^{-1}, pressure 90 kg f cm^{-2}, column temperature 40°C, the electrochemical analytical cell was set at $+0{\cdot}8$ V and the detector sensitivity at 4 nA. The retention times were 5·1 and 7·3 min for sumatriptan and internal standard, respectively.

Preparation of standard graph

A calibration curve was prepared by adding 0, 1·56, 3·13, 6·25, 12·5, 25, and 50 ng sumatriptan succinate to 1-mL samples of serum from untreated volunteers. These samples were treated in the same manner as described in the assay procedure. The peak height ratios (drug/internal standard) obtained at different concentrations of the drug were plotted against the drug concentrations. The slope of the plot determined by the method of least-square regression analysis was used to calculate the sumatriptan concentration in the unknown serum samples. The reproducibility of the assay was checked by analysing the spiked serum samples with different concentrations of the drug five times during the course of analysis. The co-efficient of variation was less than 7·4% at all concentrations. The limit of quantification was 1 ng mL^{-1}.

Pharmacokinetic analysis

The peak serum concentration (C_{max}) and time to reach peak concentration (t_{max}) were obtained from the experimental data. The other pharmacokinetic parameters were calculated using model independent methods (Ritschel 1986; Gibaldi & Perrier 1992).

The absorption rate constant (K_a), assuming first-order kinetics, was obtained using the equation:

$$K_a = 4{\cdot}61/ta$$

where ta is the absorption time obtained from a semilogarithmic plot of serum concentration vs time data. The area under the serum concentration–time curve from time zero to the last time-point (AUC_{o-t}) at which a measurable drug concentration exists was calculated by the trapezoidal rule.

The elimination rate constant (K_e) was obtained from the slope of the regression line in the terminal portion of the log concentration–time profile.

The half-life ($t_{½}$) was calculated by the following equation assuming the elimination to be a first-order process:

$$t\tfrac{1}{2} = 0{\cdot}693/K_e$$

The area under the serum concentration–time curve from zero to infinity ($AUC_{o-\infty}$) was calculated by using the equation:

$$AUC_{0-\infty} = AUC_{0-t} + C/K_e$$

Where C is the serum sumatriptan concentration at the last sampling time point, t.

The area under the first moment curve ($AUMC_{0-\infty}$) was also computed by the trapezoidal rule, and represented the area under the curve resulting from plotting the product of serum concentration and time vs time.

$$AUMC_{0-\infty} = AUMC_{0-t} + [Ct/K_e + C/K_e^2]$$

Mean residence time (MRT) represents the time for 63·2% of the administered dose to be eliminated, and is the statistical moment analogue of $t_{½}$:

$$MRT = AUMC_{0-\infty}/AUC_{0-\infty}$$

Oral clearance (CL_s/f) was obtained using the equation:

$$CL_s/f = \text{dose}/(AUC_{0-\infty} \times \text{body weight})$$

The apparent volume of distribution (Vd/f) was calculated by:

$$Vd/f = \text{dose}/(AUC_{0-\infty} \times K_e \times (\text{body weight}))$$

The apparent volume of distribution at steady state (Vd_{ss}/f) was calculated by:

$$Vd_{ss}/f = \text{dose}\,(AUMC_{o-\infty}/AUC_{0-\infty})^2$$

The pharmacokinetic data were analysed using analysis of variance and a two-tailed paired *t*-test at 95% probability level to test the dosing time related changes.

Results

Figure 1 shows the mean serum level vs time plots following 100 mg sumatriptan oral administration at 07 00, 13 00, 19 00 or 01 00 h. The mean pharmacokinetic parameters are given in Table 1. The mean C_{max} was significantly ($P < 0{\cdot}05$, $n = 12$) higher following the 07 00 h administration than after the 19 00 h administration. The mean AUC_{0-t}, $AUC_{0-\infty}$ and AUMC were significantly ($P < 0{\cdot}05$, $n = 12$) higher following the 07 00 and 01 00 h administrations than after the 19 00 h administration. The mean CL_s/f, Vd_{ss}/f and Vd/f values were significantly lower ($P < 0{\cdot}05$, $n = 12$) following the 07 00 h administration than after the 19 00 h administration. Also, the value of the mean Vd/f after the 13 00 h administration was lower ($P < 0{\cdot}05$, $n = 12$) than after the 19 00 h administration. The other pharmacokinetic parameters did not show significant circadian variations.

Discussion

Bruguerolle (1998) documented the circadian changes in the pharmacokinetics of several analgesics and anti-inflammatory drugs. For many of those, time-dependent changes in absorption were reported. Ollagnier et al (1987) reported that the peak plasma concentration of ketoprofen was twice as high after drug administration at 07 00 h compared with administration at any other time, and t_{max} was much longer after drug administration at 01 00 h compared with 13 00 h. Mustofa et al (1991) and Nagamahender et al (1995) found that the peak serum diclofenac concentration and the AUC value were significantly lower during the night compared with the day. Rao et al (1993)

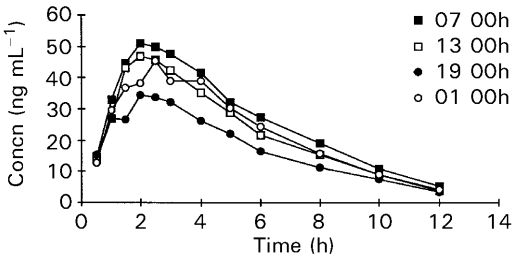

Figure 1. Mean (n = 12) serum concentrations of sumatriptan after oral administration of 100 mg at four different time points.

Table 1. Pharmacokinetic parameters of sumatriptan following 100 mg oral administration at 07 00, 13 00, 19 00 and 01 00 h.

Pharmacokinetic parameter	Time of administration			
	07 00 h	13 00 h	19 00 h	01 00 h
C_{max} (ng mL^{-1})	59·09 ± 10·5*	52·50 ± 13·8	41·88 ± 12·2*	51·59 ± 10·76
t_{max} (h)	1·96 ± 0·62	1·96 ± 0·50	1·67 ± 0·65	2·0 ± 0·60
K_a (h^{-1})	2·59 ± 0·86	2·48 ± 0·57	3·45 ± 2·11	2·53 ± 0·88
t½ (h)	2·13 ± 0·45	1·99 ± 0·42	2·65 ± 0·40	2·19 ± 0·50
CL_s/f (mL h^{-1} kg^{-1})	781 ± 186*	936 ± 272	1208 ± 458*	884 ± 144
Vd/f (mL kg^{-1})	2379 ± 684*	2763 ± 1417	4655 ± 2096*	2755 ± 562
Vd_{ss}/f (mL kg^{-1})	3604 ± 854*	4113 ± 1300	5804 ± 2333*	4090 ± 491
AUC_{o-t} (ng mL^{-1} h)	312 ± 62*	269 ± 77	207 ± 52*	271 ± 47*
$AUC_{0-\infty}$ (ng mL^{-1} h)	329 ± 69*	285 ± 55	220 ± 56*	284 ± 53*
$AUMC_{0-\infty}$ (ng mL^{-1} h^2)	1687 ± 479*	1370 ± 502	1134 ± 326*	1461 ± 345*
MRT (h)	5·08 ± 0·59	4·83 ± 0·53	5·15 ± 0·54	5·10 ± 0·34

Values are mean ± s.d., n = 12. *Values which are significantly different ($P < 0·05$). C_{max}, peak serum concentration; t_{max}, time to reach C_{max}; K_a, absorption rate constant; t½, elimination half-life; CL_s/f, systemic clearance; Vd/f, apparent volume of distribution; Vd_{ss}/f, apparent volume of distribution at steady state; AUC, area under the curve; AUMC, area under the first moment curve; MRT, mean residence time.

observed significant delay in the occurrence of peak naproxen concentrations following administration at 22 00 h compared with 10 00 h. Srinivasu et al (1995) have reported significantly higher AUC_{o-t} and lower clearance values for ketorolac after administration at 19 00 and 01 00 h compared with 07 00 and 13 00 h administration. In this study the mean C_{max} value of sumatriptan was significantly higher after 07 00 h than after administration at 19 00 h, but t_{max} was unaltered. The mean AUC_{o-t} and $AUC_{o-\infty}$ values were also significantly higher following the 07 00 and 01 00 h administrations than the 19 00 h administration, indicating that the extent of absorption might have been affected as a function of dosing time.

Sumatriptan is a drug of low intrinsic clearance and is extensively metabolized. The AUC for total (bound plus unbound) drug will be a function of the extent of oral absorption, the unbound fraction in serum, and the intrinsic hepatic clearance of unbound drug. This study did not include intravenous administration and because of this, circadian variations in the extent of oral absorption cannot be ruled out. The significantly higher C_{max} value for the 07 00 h treatment compared with the 19 00 h treatment, and the higher AUC_{o-t} and $AUC_{o-\infty}$ values for the 01 00 h and 07 00 h treatments compared with the 19 00 h treatment could be due to circadian changes in the hepatic blood flow. Lemmer & Nold (1991) reported a circadian rhythm estimated peak at 04 00 h in plasma clearance of indocyanine green and estimated hepatic blood flow in healthy volunteers. Higher plasma concentrations for propranolol (Langner & Lemmer 1988) and nifedipine (Lemmer et al 1990) following morning dosing were also explained based on such circadian changes in hepatic blood flow.

Sumatriptan is bound to plasma proteins to an extent of 14–21% only and hence circadian changes in the plasma protein levels (reported to be approximately 10%) (Touitou et al 1986) should not have influenced the pharmacokinetics of sumatriptan as a function of dosing time via altered protein binding. However, the apparent volume of distribution of sumatriptan in this study was significantly higher for the 1900 h treatment, indicating that some factor other than protein binding has influenced the distribution of sumatriptan.

Circadian variations in the cardiac output, stroke volume and blood supply to different organs have been reported, with lower values of these parameters in the resting period (Kaneko et al 1968; Lemmer & Bathe 1982). Such time dependent changes in the blood supply to various tissues and organs might have contributed to the observed changes in the apparent volume of distribution in this study.

Sumatriptan undergoes extensive first-pass metabolism resulting in only 14% bioavailability upon oral administration. Much larger concentrations of the metabolite (indole acetic acid analogue) were found in plasma after oral administration compared with parenteral administration indicating the involvement of oxidation during first-pass metabolism (Plosker & McTarish 1994). The oxidation reactions are mediated by a multi-component electron transport system, which is present mainly in the smooth endoplasmic reticulum, and known as microsomal monooxygenase or mixed function oxidase system. It is well established that

the activity of many microsomal oxidases like aminopyrine-*N*-demethylase, hexobarbitol oxidase, paranitroanisole-*O*-demethylase in rat or mouse liver are higher during the dark phase, i.e. during the activity period of the animal, and minimal during the light phase, the resting period (Belanger 1988). The circadian variations in the activity of monoamine oxidase responsible for oxidative deamination of sumatriptan have yet to be investigated, but we presume that this factor may have effected the first-pass metabolism of sumatriptan. This would have contributed to the observed changes in the C_{max} and the AUC of the drug in the study. Estimation of metabolites of sumatriptan along with the drug may have resolved this.

According to Visser et al (1996), approximately 15% of patients with migraine did not experience headache relief after sumatriptan treatment. Solomon (1992) observed that in 17% of the subjects studied, the migraine attacks began between 14 00 and 20 00 h, unlike the majority of the subjects whose migraine attacks occurred between 06 00 h and 12 00 h. If the results of these two studies and our results are inter-linked, grossly it appears that in patients for whom sumatriptan was ineffective, the drug may have been administered in the evening. Such evening administration could result in an approximate 30% reduction in C_{max} and AUC as observed in this study and hence it might not be effective.

This study indicates the existence of dosing time related changes in the pharmacokinetics of sumatriptan. Such a study should be extended to migraine patients where time-dependent pharmacokinetics and pharmacodynamics can be worked out. Once such data is available, along with the data pertaining to rhythms in the 5-hydroxytryptamine$_{1D}$ receptor number and binding capacity, an effective chronotherapeutic schedule for the treatment of migraine can be designed.

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