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The influence of the time-of-day administration of the drug on the pharmacokinetics of sunitinib in rabbits

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Abstract. – OBJECTIVES: At present it is known that the adjustment of the anticancer therapy to the circadian rhythms in tissues reduces the toxicity of the treatment. Chronotherapy also increases the efficacy of the anticancer treatment, which has been proved for many drugs. Sunitinib is a tyrosine kinase inhibitor, which is broadly used for the treatment of numerous cancers. The aim of the study was a comparison of the concentrations and pharmacokinetics of sunitinib after a single administration to rabbits at 08:00 (control group) and 20:00. Additionally, the effect of sunitinib on glucose levels was investigated.

MATERIALS AND METHODS: The research was carried out on two groups of rabbits: $I_{08:00}$, a group with the drug administered at 08:00 (n=8) and $II_{20:00}$, a group with the drug administered at 20:00 (n=8). The rabbits were treated with sunitinib at an oral dose of 25 mg. Plasma concentrations of sunitinib and its metabolite (SU12662) were measured with a validated HPLC method with UV detection.

RESULTS: The comparison of the sunitinib C_{max} and AUC_{0-t} in the group with sunitinib administered at 20:00 with the control group gave the ratios of 2.20 (90% confidence interval (CI) (2.17; 2.22) and 1.64 (1.61; 1.68), respectively. Statistically significant differences between the groups under analysis were revealed for C_{max} ($p < 0.0001$), AUC_{0-t} ($p = 0.0079$), $AUC_{0-\infty}$ ($p = 0.0149$), and t_{max} ($p = 0.0085$). The mean glycemia drop was higher in group $I_{08:00}$. than in group $II_{20:00}$ (22.7% vs. 14.3%; $p = 0.0622$). The glycemia values returned to the initial values in 24 h after the administration of the drug in both groups.

CONCLUSIONS: The research proved a significant influence of the time-of-day administration on the pharmacokinetics of sunitinib.

Key Words:
Sunitinib, SU12662, Chronopharmacokinetics, Rabbits, Glycaemia.

Introduction

Daylight is the most significant stimulus regulating the activity of the supraoptic nucleus. Together with the pineal gland it affects the secretion of melatonin. Additional stimuli synchronizing the circadian rhythm include routine activities such as activity, sleep and meals. At present it is known that the adjustment of the anticancer therapy to the circadian rhythms in healthy tissues reduces the toxicity of the treatment and taking the circadian rhythms of neoplastic tissues into account enables treatment at the time of the day when the largest numbers of them are divided[1,2]. It is the most important aim of cancer chronotherapy. Numerous research findings indicate that if cytostatics are administered at the time of the day when the proliferative activity of the cells in a particular tissue reaches its peak, the damage to the tissue is the greatest[3]. Investigating circadian rhythms in patients suffering from cancer is a very complex problem, because this group of patients has been observed to exhibit changes in the regulations of circadian rhythms[4]. So far there has been no chronopharmacokinetic research on tyrosine kinase inhibitors (TKI) although they are gaining more and more indications. Sunitinib is a representative of this group.

Sunitinib belongs to the group of molecularly targeted drugs with indications for the treatment of advanced and/or metastatic renal cell cancer, (MRCC), pancreatic neuroendocrine tumours, (PNET), and imatinib-resistant gastrointestinal stromal tumours (GIST)[5]. Sunitinib disrupts cell signalling by inhibition of selected tyrosine kinases such as the vascular endothelial growth factor (VEGF), platelet-derived growth factor

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(PDGF), stem cell factor (SCF), fms-like tyrosine kinase 3 (FLT-3), colony-stimulating factor (CSF-1R). The drug was released under the commercial name Sutent®. Sunitinib and its main metabolite SU 12662 are responsible for the antineoplastic activity of the drug[6]. The drug exhibits the bioavailability of about 50% after oral administration[7] and it reaches its maximum concentration in 6-12 h following the administration[8]. A daily dose of 50 mg of sunitinib enables the concentration of 50-100 ng/mL at steady state, which determines the pharmacological effect of the drug[9]. *In vitro* investigations proved that both sunitinib and its active metabolite bind to plasma proteins to a large extent (95% and 90% respectively)[10]. The volume of distribution of sunitinib is 2030 - 2230 L, whereas the volume of distribution of its metabolite is about 3080 L[8,10]. Due to the fact that sunitinib and SU 12662 have long elimination half-life (40-60 h and 80-110 h respectively), the time necessary to reach the steady state is 7-14 days for sunitinib and about 14 days for its metabolite[11]. Sunitinib is chiefly eliminated with faeces (61%) and to a lesser extent with urine (16%)[8].

The current study was conducted to investigate the effect of the time of administration of sunitinib on its pharmacokinetics (PK) in rabbits, because there is no available data concerning the circadian clock of the pharmacokinetics of this tyrosine kinase inhibitor. Rabbits are not very often used in chronopharmacokinetic studies, because of their unimodal or bimodal pattern of activity, but feeding conditions can synchronize the circadian clock of laboratory rabbits[12-14].

Materials and Methods

Reagents

Sunitinib and SU12662 were purchased from LGC Standards (Łomianki, Poland), HPLC grade

Table I. Plasma pharmacokinetic parameters for sunitinib and metabolite (SU12662) following a single oral dose of sunitinib 25 mg.

Pharmacokinetics parameters[a]	$I_{8:00}$ (n=8)	$II_{20:00}$ (n=8)	Gmean ratio[b] (90% CI) $II_{20:00}$ vs. $I_{8:00}$
	Sunitinib		
AUC_{0-t} (ng×h/mL)	3301.7 ± 1383.9 (41.9)	5128.4 ± 932.9 (18.2)	1.64 (1.61; 1.68)
AUC_{∞} (ng×h/mL)	3523.1 ± 1443.7 (41.0)	5210.0 ± 935.9 (18.0)	1.56 (1.53; 1.59)
C_{max} (ng/mL)	110.7 ± 23.6 (21.3)	240.9 ± 35.3 (14.7)	2.20 (2.17; 2.22)
t_{max} (h)	8.1 ± 2.2 (26.7)	5.8 ± 1.2 (20.3)	-1.0 (-3.15; 1.15)
$AUMC_{0-t}$ (ng×h^2/mL)	87254.7 ± 52800.2 (60.5)	101208.6 ± 37519.9 (37.1)	1.25 (1.22; 1.29)
$t_{1/2kel}$ (h)	26.7 ± 9.1 (34.1)	15.6 ± 2.6 (16.4)	0.60 (0.59; 0.61)
Cl (L/h)	8.1 ± 2.8 (34.4)	4.9 ± 0.9 (18.2)	0.64 (0.63; 0.65)
	SU12662		
AUC_{0-t} (ng×h/mL)	344.6 ± 164.6 (47.8)	505.6 ± 178.2 (35.2)	1.53 (1.49; 1.58)
$AUC_{0-\infty}$ (ng×h/mL)	460.5 ± 160.5 (34.9)	534.0 ± 176.6 (33.1)	1.16 (1.14; 1.18)
C_{max} (ng/mL)	10.4 ± 4.9 (46.9)	25.8 ± 10.8 (41.7)	2.49 (2.42; 2.57)
t_{max} (h)	11.6 ± 5.2 (45.0)	7.6 ± 1.6 (21.0)	-3 (-5.05; -0.95)
	SU12662/sunitinib[c]		
AUC_{0-t} (ng×h/mL)	0.105 ± 0.033 (31.0)	0.101 ± 0.038 (37.5)	0.93 (0.91; 0.95)
$AUC_{0-\infty}$ (ng×h/mL)	0.138 ± 0.036 (25.9)	0.105 ± 0.039 (36.7)	0.74 (0.73; 0.76)
C_{max} (ng/mL)	0.091 ± 0.028 (30.7)	0.106 ± 0.037 (35.5)	1.13 (1.11; 1.16)

$I_{8:00}$, sunitinib at 8:00; $II_{20:00}$, sunitinib at 20:00; CI, confidence interval; AUC_{0-t} – area under the plasma concentration-time curve from zero to the time of last measurable concentration; $AUC_{0-\infty}$ – area under the plasma concentration-time curve from zero to infinity; C_{max} – maximum observed plasma concentration; t_{max} – time to reach maximum concentration; $AUMC_{0-t}$ – area under the first moment curve; $t_{1/2kel}$ – elimination half-life time; Cl – clearance.

[a]Arithmetic means ± standard deviations are presented with CV (%) in the brackets.

[b]Ratio of geometric means (Gmeans) between groups (%) with the lower and upper bounds of a 90% confidence interval in the brackets are presented.

[c]Ratio of SU12662/sunitinib exposure.

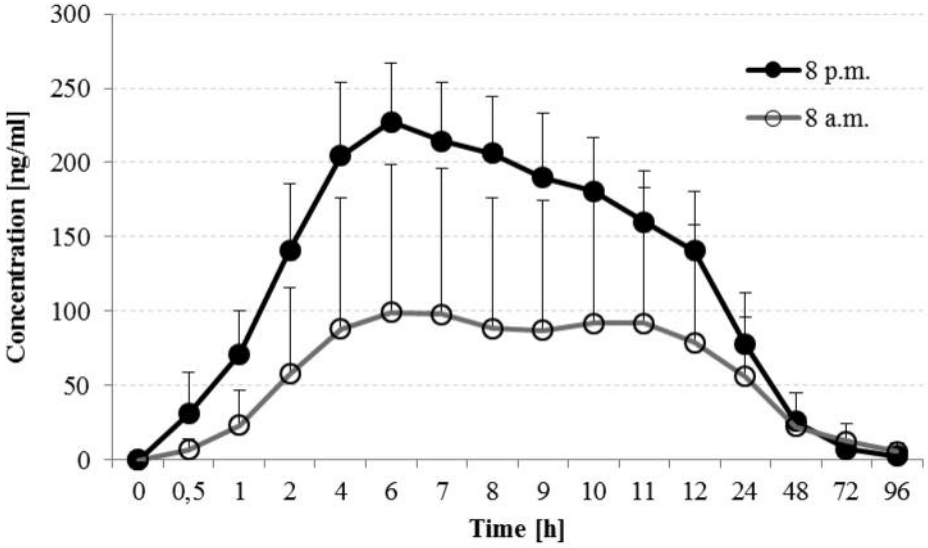

Figure 1. Sunitinib plasma concentration–time profiles following a single oral dose of sunitinib 25 mg in rabbits after drug administration in the morning (8:00), and in the evening (20:00) (arithmetic mean with standard deviation).

acetonitrile, ammonium acetate and acetic acid from Sigma-Aldrich (St Louis, MO, USA) and methanol from Merck (Darmstadt, Germany). Water used in the mobile phase was deionized, distilled and filtered through a Millipore system before use. Sutent® were purchased (batch number P177H) from Pfizer Trading Polska Sp. z o.o., Warsaw, Poland.

Animals

Adult New Zealand male rabbits, weighing 2.7-4.5 kg, were used for experiments. All the rabbits were kept in individual metal cages located in the animal laboratory of the University of Medical Sciences, Department and Unit of Clinical Pharmacy and Biopharmacy. They were acclimatized for four weeks prior to the experiments and were maintained under standard conditions of temperature (23±2°C) and humidity (56-60%) with an alternating 12 h light/dark cycles to habituate them to experimental conditions (light-on: 07:00-19:00 h). New Zealand rabbits were provided with 100 g of commercial pelleted diet (Labofeed KB®: Kcynia, Poland) 9.8 MJ/kg metabolic energy, 16.00% total protein, 0.65% vitamin P, 15,000 IU vitamin A, 1500 JU vitamin D_3, and 65 mg vitamin E), once daily between 08:00 and 12:00 h, and tap water *ad libitum*. The water intake was controlled five times a day (07:00, 11:00, 15:00, 19:00 and 23:00 h) in order to measure the activity of rabbits (the greater intake - the higher activity). The experiments were conducted in June. All experimental procedures related to this study were approved by the Local Ethical Committee for Animal Research.

Evaluation of Sunitinib and SU12662 Pharmacokinetics and Glucose Levels

The animals were fasted on the day of drug administration. The rabbits were divided into two groups (8 animals in each): I - receiving sunitinib in the morning (08:00), and II - receiving sunitinib in the evening (20:00). Sunitinib (Sutent® 25 mg) was administered *p.o.* at the single dose of 25 mg[15]. Blood samples (3 mL) for sunitinib, SU12662 and glucose assays were collected before and 0.5, 1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 24, 48, 72, 96 hours following drug administration. The blood samples were transferred into heparinized tubes and they were centrifuged at 4000 rpm for 10 min at 4ºC. Next the plasma was transferred to propylene tubes and stored at –20°C until analysis. The measurement of sunitinib concentration in the blood plasma was made by means of the HPLC (high-performance liquid chromatography) method with UV detection, which was a modification of the method developed by Faivre et al[5]. Separation was achieved by isocratic elution of the mobile phase, ammonium acetate 20 mM pH 3.4 (adjusted with acetic acid) - acetonitrile (60:40, v/v), at a flow rate of 1.0 mL/min through a

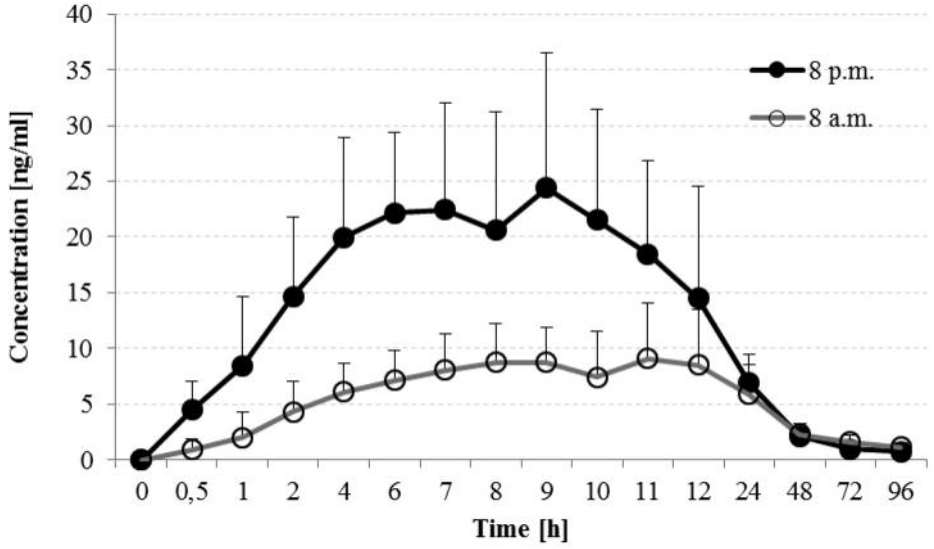

Figure 2. Metabolite (SU12662) plasma concentration–time profiles following a single oral dose of sunitinib 25 mg in rabbits after drug administration in the morning (08:00), and in the evening (20:00) (arithmetic mean with standard deviation).

Symmetry® RP-C8 column (250 mm × 4.6 mm, 5.0 mm particle size) (Waters®, Millford, MA, USA). The column temperature was maintained at 40°C, the UV detection wavelength was set at 431 nm. The total analysis time for each run was 6 min. The lower limit of quantification (LLOQ) and limit of detection (LOD) for sunitinib and SU12662 were 1.0 ng/mL and 0.5 ng/mL, respectively. Intra- and inter-day precision and accuracy of the LLOQ, low quality control (2.5 ng/mL), medium quality control (25.0, 125.0 ng/mL), and high quality control (45.0, 200.0 ng/mL) were well within the acceptable limit of 10% coefficient of variation (CV%) for SU12662 and sunitinib, respectively. The calibration for sunitinib was linear in the range 1.0-250.0 ng/mL (r = 0.999), for SU12662 in the range 1.0-50.0 ng/mL (r = 0.998).

The blood sugar levels of each of the rabbits were checked after administration of sunitinib with an autoanalyzer (AccuCheck Active®) glucose kit. The percentage reduction of the glucose levels of the rabbits was calculated using the formula:

$$\text{reduction}_{\text{glucose}} = \frac{(V_0 - V_1)\cdot 100}{V_0}$$

Where V_0 - glucose concentration at zero hour and V_t - glucose concentration at hour with maximum reduction.

Pharmacokinetics Analysis

Pharmacokinetic parameters were estimated by non-compartmental methods using validated software (Phoenix™ WinNonlin® 6.3; Certara L.P., Saint Louis, MO, USA). The following pharmacokinetic parameters were calculated for sunitinib: area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), area under the plasma concentration-time curve from zero to the time of last measurable concentration (AUC_{0-t}), area under the first moment curve ($AUMC_{0-t}$), half-life in elimination phase ($t_{1/2kel}$), clearance (Cl).

Statistical Analysis

The differences in the values of pharmacokinetic parameters were analysed by means of Student t-test using PROC TTEST in SAS (SAS Institute Inc. 2002-2010). The SAS System for Windows version 9.3. Cary, NC 27513-2414 USA). The differences that generated $p < 0.05$ were considered statistically significant. The 90% confidence intervals for the ratio of geometric means were constructed, except for t_{max} for which the confidence intervals were based on the difference of medians.

Results

All the data was expressed as the mean ± standard deviation (SD). The two analyzed groups

under study did not differ significantly in body mass. There was a wide intersubject variability in the pharmacokinetic parameters, as evidenced by the coefficients of variation (CV%) (Table I).

Measurable sunitinib and SU12662 concentrations were achieved within 0.5 and 1 h, respectively, after dosing in all animals and remained quantifiable at almost all following time points. Peak sunitinib and SU12662 concentrations were achieved approximately 6-12 h after dosing. The arithmetic mean concentrations of sunitinib and SU12662 in the blood plasma in the different animal groups during 96-h period after administration of sunitinib are shown in Figures 1 and 2, respectively.

In the rabbits with administration at 20:00 elevated levels of sunitinib were noted. The mean C_{max} was higher in group $II_{20:00}$ than in the control group (240.9 ± 35.3 and 110.7 ± 23.6 ng/mL, respectively; Table I). The comparison of the C_{max} for group $II_{20:00}$ and the same parameter for group $I_{08:00}$ gave a ratio of 2.20 (90% CI 2.17; 2.22). The mean AUC_{0-t} of sunitinib was not similar for both groups (5128.4 ± 932.9 and 3301.7 ± 1383.9 ng×h/mL, respectively; Table I). The comparison of the AUC_{0-t} for group $II_{20:00.}$ and the same parameter for the control group gave a ratio of 1.64 (90% CI 1.61; 1.68). There were significant differences between the groups under analysis for C_{max} and AUC_{0-t} ($p < 0.0001$ and $p = 0.0079$, respectively).

The mean t_{max} of sunitinib was not similar for the two groups. The comparison of the difference for group $II_{20:00}$ and the same parameter for the control group gave an estimated decrease in t_{max} of 1.0 h (90% CI -3.15; 1.15). There were significant differences between the groups under analysis ($p = 0.0163$).

Statistically significant differences were revealed for elimination half-life ($p = 0.0106$), and clearance ($p = 0.0151$).

There were no significant differences between the two groups under analysis for the following pharmacokinetic parameters of SU12662: AUC_{0-t} ($p = 0.0814$), $AUC_{0-\infty}$ ($p = 0.3979$), but there were significant differences observed for C_{max} ($p = 0.0025$) and t_{max} ($p = 0.0144$).

Also, there were no statistically significant differences proved for the SU12662/sunitinib ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} ($p = 0.8023$, $p = 0.1029$, $p = 0.3992$, respectively).

In all the animals under analysis, a drop in glucose concentration in the blood was observed. The reduction in glycemia concentration was higher in the morning group and it ranged from 5.5 to 39.0 % for group $I_{08:00}$ and 7.2 to 20.3% for group $II_{20:00}$. The highest drop in glucose concentration was observed about sunitinib t_{max} (6-12 h).

Discussion

There have been numerous studies evaluating the influence of biological rhythms on the efficacy of drugs and reduction of their adverse reactions[16-19]. Clinicians are particularly interested in reduction of the toxicity of anticancer drugs, which are burdened with numerous serious adverse reactions, and in increasing the efficacy of therapy with the drugs depending on the time of the day[20-22]. Levi et al[22] sum up that over 30 anticancer agents vary by more than 50% as a function of time-of-day dosing in experimental models. So far there has been no research on the influence of biological rhythms on the pharmacokinetics of TKI. Due to their wider and wider range of indications it is important to investigate the most optimal possibilities of their dosage. If the patient sleeps during the highest concentrations of the drug at night, they might not suffer from adverse reactions resulting from C_{max}. On the other hand, if we achieve high concentrations of TKI in the blood, the therapy may be improved. This is also a chance to reduce the dose of the drug.

In our research in the animals which received the drug in the evening the C_{max} and AUC_{0-t} values of sunitinib were 117.6% and 55.3% higher, respectively, in comparison with the animals with the morning administration of the drug. The higher values of sunitinib AUC in the animals from group $II_{20:00.}$ prove higher exposure to the drug. Too high TK concentrations may involve a higher risk of adverse effects (AEs). The most frequent AEs of sunitinib are: fatigue, diarrhoea, hand-foot syndrome and hypertension[23]. This fact of higher exposure does not seem to be caused by slower metabolism. The metabolism of the drug, including CYP3A4 activity, is controlled by the circadian timing system[22,24,25], but the absence of statistically significant differences for SU12662/sunitinib ratios for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} (Table I) points to the fact that the degree of metabolism of the drug remained unchanged. The increase in the concentration of the metabolite is the consequence of the increased concentration of sunitinib.

It is too difficult to give a simple explanation to significant differences in the drug elimination pa-

rameters between the groups under analysis because of the long drug elimination process, which takes several days. The shorter $t_{1/2kel}$ and faster clearance of sunitinib in the group receiving the drug in the evening may result from the fact that the beginning of the elimination process (in about 12 h after administration of the drug) takes place as early as the daytime, which means that the drug is eliminated more effectively (higher motor activity, increased flow of blood in the tissues). This is reflected by the $k_{el(12-24h)}$ value, which is lower in the control group (0.040 *vs.* 0.049 h^{-1}), where the drug is eliminated at nighttime (lower motor activity, lower flow of blood in the tissues).

The results obtained in many studies[26-29] suggest the need to monitor glycaemia frequently both in diabetic patients and in those with normoglycaemia due to the risk of serious hypoglycaemia during a sunitinib therapy. In our animals the mean glycaemia drop was higher in group $I_{08:00}$ than in group $II_{20:00}$ (22.7% vs. 14.3%; p = 0.0622), which may have resulted from the rabbits' increased activity during the day. In our animals the maximum drop in the concentration of glucose in the blood was observed about the sunitinib t_{max} (6-12 hours). The glycemia values returned to the initial values in 24 h after the administration of sunitinib. It is also known that the concentration of glucose in the blood is chiefly regulated by insulin, the secretion of which is controlled by circadian rhythm. In healthy subjects the peak secretion of insulin in the circadian rhythm takes place in the afternoon hours. This is also the time when the concentrations of sunitinib were the highest. Therefore, we can suppose that the hypoglycaemic effect was stronger in the group of animals receiving sunitinib in the morning than in those receiving the drug in the evening. At night the concentration of insulin is physiologically the lowest. This may account for the least noticeable changes in the glycaemia value in the animals from group $II_{20.00}$. Thus, if the drug is administered in the evening, the risk of sunitinib-induced hypoglycemia may be lower (the t_{max} of the drug coincides with the physiological hyperglycaemia in the morning).

The authors wanted to note that a single check of glycaemia immediately before administration of next dose of sunitinib (usually 24 hours after administration of the drug) may be insufficient. It suggests the need to check the patient's glycaemia, e.g. at lunchtime (when sunitinib is administered in the morning). Moreover, due to higher concentrations of sunitinib at night after the evening administration it is necessary to pay attention to the risk of adverse effects of sunitinib.

Conclusions

The research proved a statistically significant influence of the time-of-day administration of the drug on the pharmacokinetics of sunitinib.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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