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Research paper

Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs

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Abstract

Clinical studies have shown that circadian patterns influence the pharmacokinetics of certain drugs used in the treatment of different diseases. For such drugs, the bioavailability is influenced by the time of administration. The objective of this study was to investigate differences in the pharmacokinetic patterns between a pulsatile drug delivery system using a pulsatile capsule, an immediate release tablet and a controlled release tablet. Metoprolol was chosen as a model drug because of its high solubility and high permeability pattern throughout the GI tract. The dosage forms were administered to four dogs and the plasma levels were measured using LC-MS/MS. Pharmacokinetic parameters were determined for each dosage form. Fluctuations in the plasma time curves over the observation period indicated that physiological factors like motility have an influence on the drug absorption. The comparison of the plasma time curves of the dosage forms showed that each dosage form caused significant differences in the drug plasma levels. The pulsatile drug delivery capsule caused two defined C_{max} values for each dose between 1–1.75 and 2.5–3.5 h. Implications for the use of a pulsatile drug delivery device for chronopharmacotherapy are discussed. Pulsatile drug delivery offers a promising way for chronopharmacotherapy if the time of administration and pulse time are adjusted to the circadian pattern.

Keywords: Metoprolol; LC-MS/MS; Pulsatile drug delivery; Chronopharmacotherapy; Pharmacokinetics; Beta blocker; Dog study; In vivo study; Immediate release; Controlled release; Sustained release; Pulsatile release

1. Introduction

The oral route is the most common route of drug administration. Modern drug delivery strategies try to improve oral drug delivery. The most common way to prolong drug delivery is to use sustained or extended release dosage forms [1]. The aim of such strategies is to increase the availability of the drug at the site of drug action over a prolonged time period [2]. A controlled drug delivery may result in a lower but constant pharmacological availability which might reduce toxic side effects. In many cases, this overcomes compliance problems with patients by reducing the dosing frequency to one dose per day. Other controlled drug delivery strategies utilize the pH change within the GI passage to control the drug release [3]. This can be used for drugs which are easily decomposed in the acidic environment of the stomach e.g. peptides, or to protect the stomach from drug side effects e.g. aspirin. Such systems are also promising for a local therapy in the lower parts of the intestine e.g. colon targeting to treat diseases like ulcerative colitis [4].

However, constant drug release is not desirable for all drugs; some drugs require repeated drug administration during a day. This might be due to factors such as high metabolism, short half life or a limited absorption window as shown for levodopa [5]. If such drugs are delivered using a sustained release formulation, their bioavailability might decrease due to the mentioned factors [6,7]. Another reason

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for repeated dosing might be the development of receptor tolerances. A prolonged stimulus of nitrates, for example, decreases the drug efficacy [8]. For such drugs constant drug plasma concentrations can cause a failure of the therapeutic intervention.

Different biopharmaceutical and pharmacodynamic reasons point out that there are certain circumstances in which a repeated dosing is advantageous compared to sustained release dosage forms. However, a patient's compliance might be lower if a drug has to be taken more than once a day. If drug absorption throughout the gastrointestinal tract is not limited, then pulstile drug delivery might be a suitable alternative to repeated dosing. This might be especially useful if peak plasma levels are desirable in the night time or the early morning hours.

The pulsatile capsule used in this study was designed to release two drug doses at different time points [9]. The first dose was immediately released after administration, while the second dose was released after a predetermined time due to the composition of the osmotic system (Fig. 1). The osmotic system presses a plug out of the non-soluble capsule body and initiates the second drug release. The second dose can be released as an immediate or a controlled release dosage.

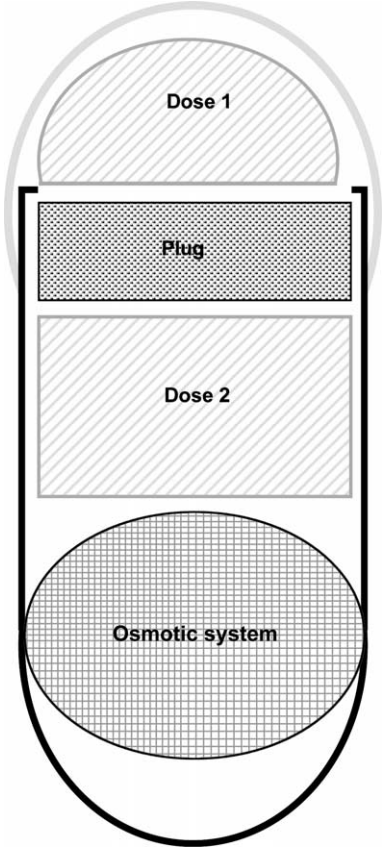

Fig. 1. The pulsatile capsule is designed for two drug doses. The first is placed into the capsule cap while the second dose is released from an insoluble capsule body. The pulse time is determined by an osmotic system which presses an insoluble plug out of the capsule body.

The objective of this study was to investigate differences in the pharmacokinetic pattern between a pulsatile drug delivery system delivering two times (50 mg) metoprolol, an immediate release tablet (50 mg) and a controlled release tablet (50 mg). Metoprolol was chosen as the model drug because of its high solubility and high permeability pattern throughout the GI tract. The dosage forms were administered to dogs and the plasma levels were measured. Pharmacokinetic parameters were calculated using non-compartmental. Implications for the use of a pulsatile drug delivery device for chronopharmacotherapy are discussed.

2. Material and methods

2.1. Preparation of the pulsatile capsule

Metoprolol tartrate (MT) was purchased from Sigma (St Louis), the pulsatile capsule (PC) was supplied by Port Systems (Ann Arbor), and contained two doses of metoprolol tartrate each 50 mg the pulse time was adjusted to 2 h. Metoprolol tartrate Tablets USP (Geneva Pharmaceuticals INC, Broomfield CO) and a controlled release dosage form (Beloc Duriles, Astra Promed, Germany) were used for the study. All other chemicals were of analytical grade.

2.2. Dissolution test

The in vitro dissolution of the PC was tested in a USP XXIII apparatus 2 at 75 rpm. The dissolution medium was 500 ml Simulated Gastric Fluid USP XXIII without enzyme (SGF) for the first hour. The SGF was changed to Simulated Intestinal Fluid USP XXIII (SIF) by adding 400 ml of a 37 °C heated phosphate buffer containing 2.72 g monobasic potassium phosphate and 1.25 g sodium hydroxide. The pH was adjusted to pH 6.8. The samples were analyzed by a HPLC assay using a LiChrospher 60 RP-select B column (E. Merck, Darmstadt, Germany), and a Thermo Quest HPLC system (San Jose, CA) equipped with an UV detector at a wavelength of 230 nm. An 80:20 mixture of a 25 mmol phosphate buffer, pH 6.5 and acetonitrile was used as a mobile phase at a flow rate of 1 ml per minute. A five point calibration curve was prepared with a regression coefficient >0.999, ranging from 5 to 150% of the maximum expected drug content per capsule.

2.3. Animal study

The University Committee on Use and Care of Animals (UCUCA) approved the animal protocol 6879A and the dogs were under the care of the Unit for Laboratory Animal Medicine (ULAM).

Two male and two female mongrel dogs were used for the study. Each dog was fasted over night before

the experiment, but the dogs had free access to water. The start of the studies was always between 7 and 8 am.

2.4. Intravenous administration

Five milligrams MT were dissolved in 5 ml of an isotonic saline. The solution was administered into the cephalic vein over a period of 5 s. Blood samples (2.0 ml) were obtained from an indwelling catheter comprised of an Angiocath catheter No: 3828161 1.3 mm×5.1 cm 18 GA X2 IN (Becton Dickinson Sandy, UT), Vacutainer blood collection set 19G3/4 No: 4919 (Becton Dickinson Sandy, UT), InterLink injection site No: 2N3379 (Baxter, Deerfield IL), Ultra 4-Way Stopcock, No: MX234-1L (Medex, Hilliard, OH). The blood collection set was placed in the cephalic vein of the leg opposite to the injected leg. Blood samples were collected using a Vacutainer blood container No: 16939 (Becton Dickinson, Franklin Lakes NJ). The blood samples were centrifuged for 10 min at 3000 rpm at 4 °C using an IEC Centra GP8R centrifuge (Needham Heights, MA). One milliliter of the plasma fraction was separated into culture tubes and stored at −20 °C prior to extraction. The sampling times were 1, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360 and 480 min. In order to control hemodynamic factors, blood loss was compensated by injection of an equivalent volume of saline.

2.5. Oral administration

A immediate release tablet (IR) containing 50 mg MT, a pulsatile capsule (PC) containing two doses of 50 mg MT, and a controlled release dosage form containing 50 mg MT were administered orally into the stomach of the dogs using 50 ml of water. Blood samples were taken at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 180, 210, 240, 300, 360 and 480 min and handled as previously described.

2.6. Sample preparation and extraction

An internal standard stock solution containing 100 ng propranolol/ml was prepared. 0.5 ml of dog plasma was transferred to a 2 ml micro-centrifuge tube. 50 μL of the internal standard was added to each sample. 1.0 ml ethyl acetate was added and then mixed for 1 min using a Fisher Vortex-Genie 2 mixer (Fisher Scientific, Chicago, IL). After mixing, the samples were centrifuged at 14,000 rpm using an Eppendorf micro centrifuge (Brinkmann Instruments, Inc., Westbury, NY) for 10 min. Five hundred microliter of the organic layer was transferred to a sample vial. The organic phase was evaporated at room temperature to complete dryness in a vortex evaporator (Labconco Corporation, Kansas City, MS) and the sample was reconstituted with 0.5 ml of mobile phase.

2.7. LC-MS/MS assay

A Hewlett Packard HPLC system 1100 series (Hewlett–Packard Co, Wilmington, DE) was used with a Zorbax C-18 Column (Hewlett–Packard, Co Wilmington, DE). The mobile phase consisted of a 1:1 mixture of water containing 0.5% formic acid and acetonitrile at a flow rate of 200 μL/min. A five point calibration curve was prepared with a regression coefficient >0.99, ranging from 25 to 500 ng/ml. The recovery of metoprolol was 88%. Ten microliter of the solution was directly injected into a Quattro II MS/MS detector (Micromass Inc., Beverly, MA), using an Electrospray source (ES) at a temperature of 135 °C. The mass spectrometer was operated in Multiple Reaction Monitoring mode (MRM) with collision energy of 20 V and a cone voltage of 38 V. Metoprolol and the internal standard were monitored at transitions m/z 268.3→116.3 and 260.4→183.1, respectively, with a dwell time of 150 ms each. The collision gas pressure was 2.0×10^{-3} mBar, the drying gas was at a flow of 550 L/h, and the ES nebulizing gas was at 20 L/h.

2.8. Pharmacokinetic data analysis and statistics

The maximum plasma concentration (C_{max}) and the time of the maximum plasma concentration (T_{max}) are reported in Table 1 as observed data. The Area Under the Plasma Curve (AUC) was calculated between $t=0$ and $t=8$ h using

Table 1
Pharmacokinetic data of four dogs (B, D, J, K) measured after administration of a immediate release (IR), a controlled release CR, and pulsatile capsule (PC)

Dosage form	Dog	B	D	J	K	Mean	±SD
IR	T_{max}, (h)	3.00	0.50	0.75	2.25	1.63	1.20
IR	C_{max}, (ng/ml)	41	84	94	46	66	26
IR	AUC	170	235	301	173	220	62
CR	T_{max}, (h)	2.50	2.00	2.50	5.00	3.00	1.35
CR	C_{max}, (ng/ml)	35	82	54	50	55	20
CR	AUC	140	370	233	304	262	99
PC dose 1	T_{max}, (h)	1.25	1.00	1.00	1.75	1.25	0.35
PC dose 1	C_{max}, (ng/ml)	55	55	66	29	51	16
PC dose 2	T_{max}, (h)	2.50	3.00	2.50	3.50	2.88	0.48
PC dose 2	C_{max}, (ng/ml)	96	125	117	74	103	23
PC dose 1+2	AUC	339	432	410	233	353	90

AUC, area under the curve; C_{max}, maximum measured plasma concentration; T_{max}, time of maximum plasma concentration; SD, standard deviation.

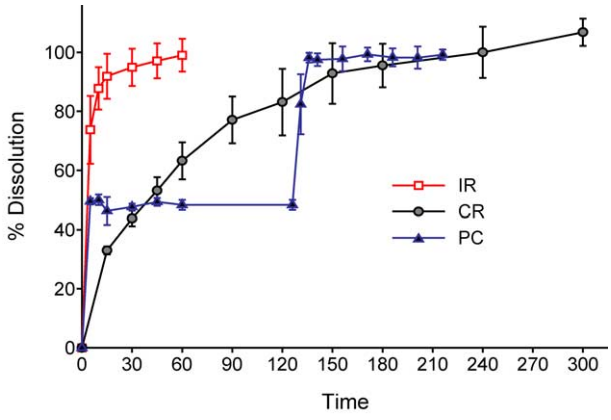

Fig. 2. Dissolution test ($n=6$) of an IR, CR dosage form containing 100 mg metoprolol and a PC dosage form containing 2 times 50 mg metoprolol. The dissolution was performed in USP 24 apparatus 2 using SGF, USP 24 for the first 60 min and in SIF, USP 24 after 60 min (time in minutes).

a linear trapezoidal method. The absorption rate was computed using the Loo-Riegelmann two-compartment model (Kinetica™ software package, InnaPhase, Philadelphia). The statistical analysis of the drug plasma levels were done by ANOVA at a $P<0.05$.

3. Results and discussion

The dissolution profiles of the different dosage forms are summarized in Fig. 2. More then 85% of the content of the immediate release (IR) dosage form was released within 10 min. Hundred percent drug release was observed within 60 min. The dissolution profile of the Pulsatile Capsule (PC) showed that the first dose was released within 5 min in simulated gastric fluid. The second dose was dissolved within 10 min, after pulsing in Simulated Intestinal Fluid. The pulse time was 126 ± 5.4 min (mean $\pm$ s.d.). The controlled release (CR) dosage form released the drug content over an extended time period of 5 h.

The semi-logarithmic plot of the MT plasma levels versus time after intravenous administration showed that the MT pharmacokinetics are best described by a two compartment model (graph not shown).

The mean plasma curve of four dogs after administration of an IR dosage form are given in Fig. 3. Two dogs, B and K showed a slower drug absorption resulting in a lower C_{max}, a later T_{max} and a lower AUC compared to the other two dogs, see Table 1. No statistical differences were observed between dogs B and K and between dogs D and J. However, if all four curves were compared then statistical differences were observed. The differences between the dogs might be due to their sex and age [10,11]. Dog B and K were 5 and 6-year-old female dogs while the other dogs (D and J) were 3 year old male dogs.

Fig. 4 shows the mean plasma curve after administration of the CR dosage form. The pharmacokinetic parameters are summarized in Table 1. The lowest C_{max} was observed in dog B. However, the shape of the drug plasma curves was similar for dogs B, D and J, but statistical analysis pointed out differences between the curves. The observed T_{max} was 2.5, 2.0 and 2.5 h, respectively (Table 1). Dog K had also a rapid drug absorption in the first 1.25 h and the plasma concentration reached 45.6 ng/ml at this time point. In the following hours and until the end of the observation period, the plasma levels fluctuated between 50.3 ng/ml at 5 h as

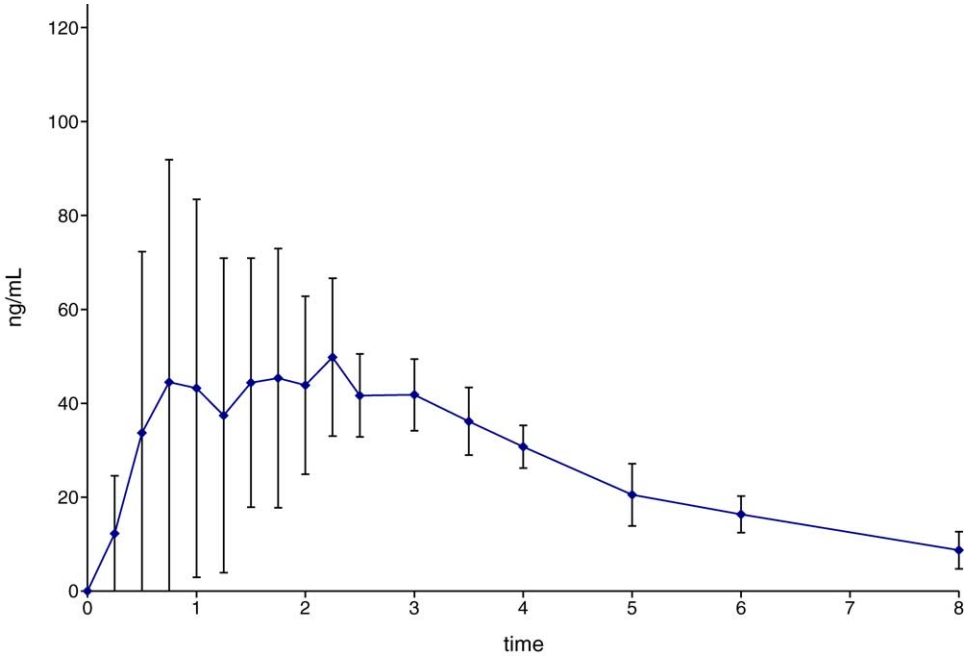

Fig. 3. Mean metoprolol plasma concentrations of four dogs after administration of an immediate release dosage form (time in hours).

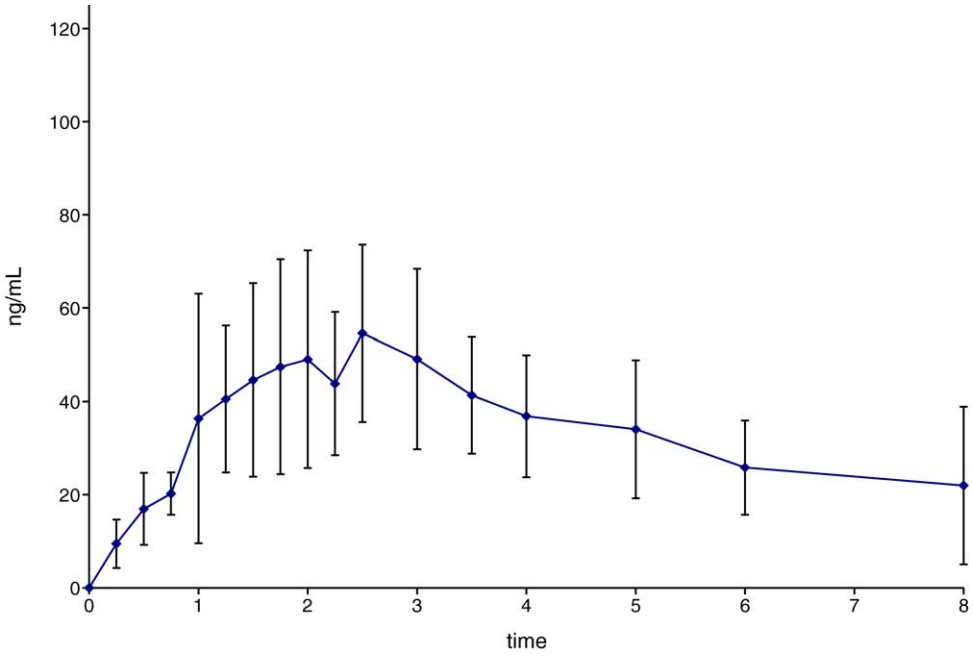

Fig. 4. Mean metoprolol plasma concentrations in four dogs after administration of a controlled release dosage form (time in hours).

the highest and 33.2 ng/ml at 6 h as the lowest observed plasma concentration. The in vitro dissolution test of the CR dosage form had shown that 100% drug release can be expected within 5 h. Dog K showed relatively constant plasma levels between 1.25 and 8 h. Metoprolol is a highly soluble and highly permeable drug [12] and, therefore, it is normally not expected that its drug release or its permeability are limited. However, if the intestinal motility does not sufficiently agitate the dosage form then a decrease in the dissolution rate might be possible [13]. Additionally, a lack of intestinal movements might also prevent the distribution of the dissolved drug throughout a sufficient absorption area and the total absorption rate might be limited due to a small surface area [14].

Fig. 5 shows the mean plasma curve after administration of the PC. The shape of all four curves exhibit a C_{max} between 1 and 1.75 h for the first dose and a second C_{max} between 2.5 and 3.5 h for the second dose (Table 1).

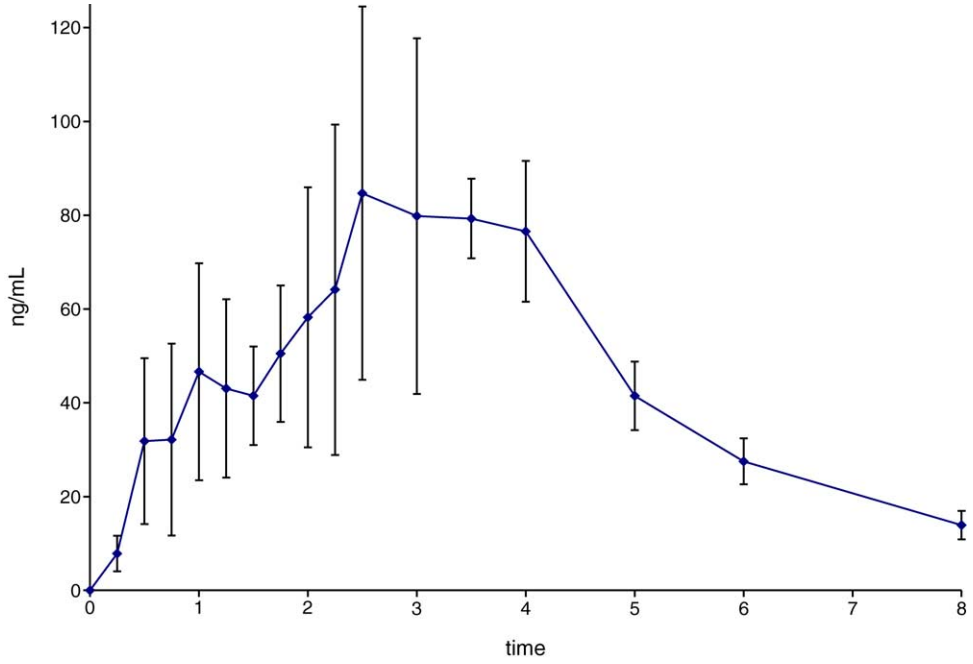

Fig. 5. Mean metoprolol plasma concentrations in four dogs after administration of a pulsatile capsule (time in hours).

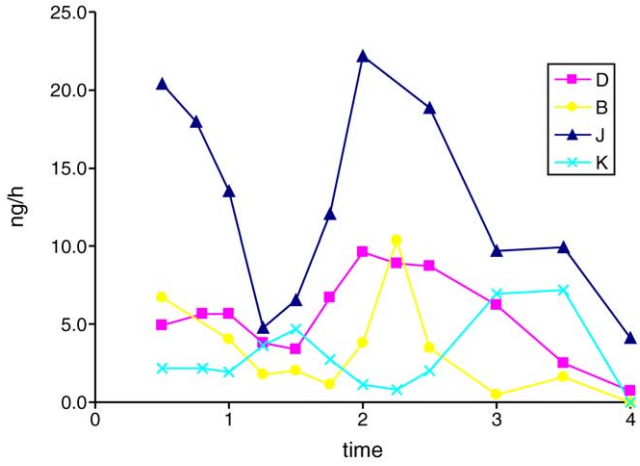

Fig. 6. Absorption rate of metoprolol in four dogs (B, D, J and K) between 0.5 and 4 h after administration of a pulsatile capsule.

Statistical differences between the plasma time curves were found between dog K and the other three dogs, while no differences were found between dogs B, D, and J. The absorption pattern of dog K was lower compared to the other dogs. The absorption rates of dog B, D, J, and K increased drastically at 1.75, 1.5, 1.25 and 2.25 h, due to the release of the second dose (Fig. 6). The in vitro results showed a pulse time of about 2 h, while the observed in vivo pulse times were earlier in three out of four dogs. This can be attributed to stronger motility movements in dogs, which does not correlate with the in vitro conditions used in the dissolution test [14]. The observation of a prolonged pulse time in dog K confirms the earlier assumed low motility pattern of this dog. The pulse time of the PC seems to be influenced by small intestine motility pattern of the dogs.

A comparison of the first 1.5 h of the plasma curves after administration of the IR and the PC showed statistical significant differences between both formulations. The C_{max} values of the IR formulation and the first dose of the PC formulation in dogs D and J showed that the drug absorption from the IR formulation was faster (earlier T_{max}) and caused higher drug plasma levels (C_{max}). This might be due to formulation effects caused by other ingredients of the formulations as described in other studies [15,16].

A comparison of the AUC (0 to 8 h) between the IR formulation containing 50 mg MT and the PC containing 2×50 mg MT showed an increase of the AUC by a factor of 2, 1.8, 1.3 and 1.3 for dog B, D, J and K, respectively (Table 1). This is in consensus with reports by Lucker et al. who reported a similar increase in AUC values for increasing MT doses in humans [17]. The same was observed for the peak plasma concentration caused by the two PC doses. C_{max} of the second dose shows an increase by factor 1.7, 2.25, 1.7, and 2.6 compared to the peak plasma concentration of the first dose for dogs B, D, J, and K, respectively.

The present study investigated the influence of the dosage form on the plasma time curves of metoprolol in vivo. Comparing the individual plasma time curves and dosage forms for each dog showed that drug absorption was significantly different in dog K. Factors like age and sex may be responsible for this observation. This is supported by the observation that the second female dog exhibited similar time plasma levels after the administration of the IR formulation compared to the two male dogs. However, statistically significant differences between the dogs for all tested dosage forms were only found in dog D.

Chronopharmcological studies have shown that different processes in the human body are influenced by a circadian pattern [18]. Clinical studies have shown that such patterns influence the pharmacokinetics of certain drugs used in the treatment of cardiovascular diseases [19], hypertension [20], asthma [21], and inflammation [22]. For drugs affected by circadian pattern the bioavailability is influenced by the time of administration. For the present study, it is not known if such factors have influenced the observed plasma time curves. However, circadian patterns have been observed for a variety of cardiovascular disorders, including cardiac arrhythmias, sudden cardiac death, cerebrovascular events, episodes of stable angina, unstable angina and acute myocardial infarction [23]. The early morning predominance of these events has been well documented in a number of large population studies [23]. Beta-receptor blocking agents reduce ischaemic events during daytime hours and are also of therapeutic value in the morning hours, which are the hours of high cardiovascular risk [24]. The present study shows that pulsatile drug delivery offers a promising way for repeated dosing to achieve defined peak plasma levels. If a pulsatile system with a later pulse time is taken shortly before bedtime, then the drug plasma levels might be sufficient for both the treatment and prevention of cardiovascular disorders, including myocardial infarction in the early morning [19].

The present study shows that pharmacokinetic patterns and factors influencing them, have to be carefully monitored for modified release dosage forms. The present set of experiments might not be statistically significant; however, fluctuations in the plasma time curves over the observation period indicate that physiological factors like motility and presumably metabolism additionally influence the pharmacokinetic pattern [25–27]. This is particularly important for drug delivery systems which might be considered for pulsatile drug delivery. Differences in the pulse time in the individual dogs indicate that motility pattern might impact the release of the second dose [28]. Pulsatile drug delivery offers a promising way to meet chronopharmacotherapy needs if the time of administration and pulse time are within the circadian pattern [29]. This has to be carefully monitored, and the pulse time has to be adjusted to meet the chronopharmacological necessities [30,31].

Acknowledgements

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