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Morning versus evening dosing of ibuprofen using conventional and time-controlled release formulations

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Abstract

Many functions of the human body vary considerably during a day. These variations can lead to changes in drug plasma concentrations. In the study on healthy volunteers described here it was determined whether ibuprofen plasma levels following single oral doses of immediate-release and press-coated time-controlled release tablet formulations depend on time of drug administration (08:00 or 22:00 h). The difference between morning and evening dosing of the immediate-release formulation was minimal. The results with the press-coated formulation were unexpected having regard to results of previous studies on non-steroidal anti-inflammatory analgesics. Time to peak concentration was 6 h after morning administration, 4 h after evening administration. Both the rate and extent of bioavailability of ibuprofen were lower when dosing took place at 08:00 h than when dosing took place at 22:00 h. The influence of food on the pharmacokinetic profile of an evening dose of the press-coated formulation was also studied. When tablets were administered with a meal the ratio C_{max}/AUC and t_{max} and AUC values indicated that bioavailability was reduced. The main conclusion was that the chronopharmacokinetic behaviour of the press-coated ibuprofen tablet is related to the formulation, not the drug substance as such.

Keywords: Ibuprofen; Time-controlled release; Chronopharmacokinetics; Food effect; Press-coated tablet; Hydroxypropylmethylcellulose

1. Introduction

Many physiological functions of the body exhibit circadian rhythms. For example gastric acid secretion, gastrointestinal blood flow, metabolic activity of the liver and renal blood flow fluctuate over a 24-h cycle. All of these variations can have marked effects on the pharmacokinetic behaviour of drugs. Numerous studies on the chronopharmacokinetics of drugs in man have been carried out in recent years. Results of these studies show

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that many non-steroidal anti-inflammatory drugs (NSAIDs), e.g. indomethacin and ketoprofen, have greater rates and/or extents of bioavailability when administered in the morning than when administered in the evening (Clench et al., 1981; Ollangier et al., 1987). It has been suggested that daytime absorption of the drugs is better than night-time absorption. Circadian changes in renal function or hepatic blood flow may also explain temporal variation in drug plasma levels (Bruguolle and Lemmer, 1993). Circadian rhythm in relation to pharmacokinetics could therefore explain time-dependent changes in efficacy of drug therapy and should be taken into account in developing dosage forms for use in drug treatment at night.

Another important factor concerning timing of drug dosing is the effect of food on drug absorption. Food can have a considerable effect on the gastric emptying of solid dosage forms and can increase pH in the stomach. The normal fasting pH in the stomach is about 1.8. A meal can increase it to between 3 and 5 (McLaughlan et al., 1989). Food is a major factor controlling the onset of drug absorption, but it can also decrease or enhance drug bioavailability. If a non-disintegrating dosage form is administered with food, in particular with a high in fat meal, it can remain in the stomach for several hours, up to 12 h, and drug pharmacokinetics can markedly be affected (Khosla et al., 1989; Wilson et al., 1989).

In previous studies (Marvola and Sirkiä, 1995; Halsas et al., 1998a,b) press-coated time-controlled release tablets to be used as an evening dose in the treatment of diseases displaying the most intense symptoms during the early hours of the morning have been developed. Asthma, rheumatoid arthritis and many cardiovascular diseases are examples. The coat of the tablet contains hydrophilic polymer, e.g. hydroxypropylmethylcellulose (HPMC), which controls drug release. The core is a conventional tablet, acting as a drug reservoir. Some drug can also be situated in the coat. By varying the thickness of the coat and using combinations of different viscosity grades of HPMC it is possible to adjust the time to peak plasma concentration (t_{max}) from 4 to 12 h (Halsas et al., 1998a,b).

In the studies ibuprofen has been used as a model drug in press-coated tablets (Halsas et al., 1998a,b). It has been selected for this purpose because it is an NSAID used to treat rheumatic diseases, and is absorbed throughout the gastrointestinal tract (Wilson and Washington, 1988). It is an organic acid, sparingly soluble in water with a short elimination half-life of only about 2 h (Ritschel, 1992).

The first objective of the study reported here was to investigate whether ibuprofen pharmacokinetics varied with time in healthy humans. Two formulations, a conventional hard gelatin capsule and a press-coated time-controlled release tablet, were administered under fasting conditions, in the morning and in the evening.

A second goal was to study the effect of time of food intake (concomitantly and two hours prior to drug administration) on the bioavailability of the time-controlled release ibuprofen tablet. The test was carried out with drug administration in the evening because the ultimate purpose of the study was to evaluate whether it is possible that maximal effect after an evening dose of the press-coated formulation could take place in the early morning hours (04:00–06:00 h).

2. Materials and methods

2.1. Formulations

The conventional capsule formulation contained only 150 mg of ibuprofen (Ph. Eur.) in a hard gelatin capsule (size 0, Elanco, USA). The controlled-release formulation was a press-coated tablet containing 100 mg of ibuprofen. The core of the tablet consisted of the drug (80 mg), 40 mg of directly compressible lactose (Pharmatose DCL 21, DMV, The Netherlands) and 20 mg of potassium carbonate (Merck, Germany). The coat contained 20 mg of ibuprofen and a combination of HPMC Methocel K100 (158 mg) and K4M (22 mg) (Colorcon, UK) to adjust drug release. Magnesium stearate (Ph. Eur) and talc (Ph. Eur.) were used as lubricant and glidant. Tabletting of cores and compression coating have been described in a previous paper (Halsas et al., 1998b).

2.2. Pharmacokinetic study

A group of five healthy volunteers participated in three cross-over single-dose investigations carried out in accordance with the recommendations of the Declaration of Helsinki (World Medical Assembly, 1964) as revised in Tokyo in 1975. The volunteers varied in age from 20 to 37 years. Their weights varied from 45 to 82 kg. All were examined physically, routine laboratory tests and an ECG were carried out. The volunteers were informed of the possible risks and side effects of the drug, and written consent was obtained. The study protocol had been approved by the Ethical Committee of the University of Tartu.

In the initial stage two ibuprofen capsules (300 mg of ibuprofen) were administered. In a subsequent stage the dose was three press-coated tablets (total dose 300 mg). Both formulations were administered at 08:00 and 22:00 h. Between morning and evening administration there was a washout period of at least 1 week. A 10 h fast was maintained before the daytime investigations. Lunch was provided 3 h after drug ingestion. In the night-time investigations dinner was served 5 h prior to drug administration and breakfast at 06:00 h on the following morning. In a third stage the press-coated tablets were administered 2 h after a light meal (1500 kJ, two slices of bread with cheese or ham, yoghurt and juice) or immediately after the meal at 22:00 h. The volunteers were told to avoid any physical activity and to lie down and sleep (if possible) during the night. There was a test free period of 3 months between each of the three stages of the study.

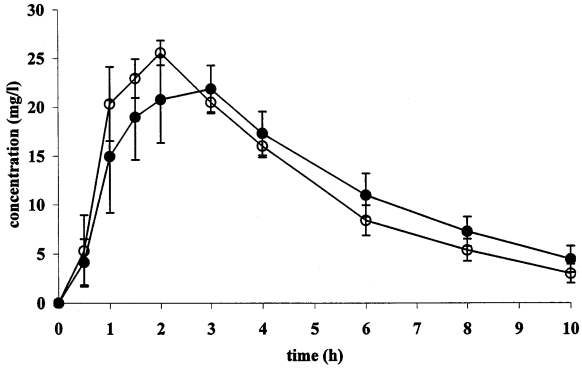

Fig. 1. Mean plasma concentrations of ibuprofen after administration of capsules under fasting conditions at 08:00 h (open symbol) and 22:00 h (closed symbol). The bars represent S.E.M., $n = 5$.

Venous blood samples were collected 0, 1, 1.5, 2, 3, 4, 6, 8 and 10 h after capsule administration and 0, 2, 4, 6, 8, 10 and 12 h after tablet administration. Plasma was separated and stored at −20°C until analysed. Drug plasma concentrations were determined by means of high performance liquid chromatography (HPLC) using the method described by Avgerinos and Hutt (1986), with slight modifications. The HPLC system and its validation has been described by Halsas et al. (1998b). The accuracy and precision of the method were investigated as recommended by Shah et al. (1992) by analysing six parallel plasma samples spiked with ibuprofen over the concentration range 0.5–40 mg/l.

2.3. Pharmacokinetic and statistical analysis

Pharmacokinetic parameters assessed, using the Siphar™ program (Simed, France), were mean residence time (MRT), apparent elimination half-life ($t_{1/2}$) and area under the curve ($AUC_{0-10/12h}$). Maximum concentration (C_{max}) and time to peak concentration (t_{max}) were determined directly from the individual time versus plasma concentration curves. AUC values were calculated using the trapezoidal method, without logarithmic transformation. The rate of the absorption phase was evaluated by means of the ratio C_{max}/AUC. Statistical analyses were carried out using Student's paired t-test and Wilcoxon's matched-pairs rank test.

3. Results and discussion

3.1. Chronopharmacokinetic behaviour of different ibuprofen formulations

Mean plasma concentration of ibuprofen after administration of the capsule formulation and the press-coated tablet formulation are shown in Figs. 1 and 2. The corresponding individual curves are shown in the upper and middle panels of Fig. 4.

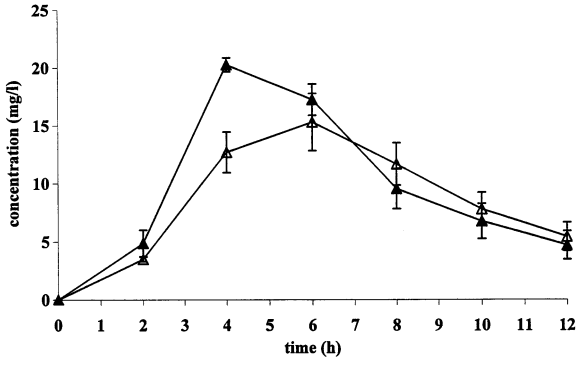

Fig. 2. Mean plasma concentrations of ibuprofen after administration of press-coated tablets under fasting conditions at 08:00 h (open symbol) or at 22:00 h (closed symbol). The bars represent S.E.M., $n = 5$.

The pharmacokinetic parameters are given in Table 1.

There were no statistically significant differences in the pharmacokinetic parameters between evening and morning dosing of ibuprofen capsules (Table 1). However, a tendency towards a slower absorption after the evening dose is evident from Fig. 1. In four subjects, time to peak concentration was shorter after dosing at 08:00 h than after dosing at 22:00 h (Fig. 4, upper panel). Circadian rhythms in relation to the bioavailability of other lipophilic NSAIDs have previously been studied. For example C_{max} value of ketoprofen has been shown to be twice as high after administration at 07:00 h than after other administration times (Ollangier et al., 1987). The rate of absorption of ketoprofen was also found to be higher when it was administered in the morning. Clench et al. (1981) have studied the effect of dosing time on the bioavailability of indomethacin. Markedly higher and earlier peak concentrations were obtained when the drug was given at 07:00 or 11:00 h than at 15:00, 19:00 or 23:00 h. The same phenomenon can also be seen in the mean curves for our study on the capsule formulation (Fig. 1). The formulation (active ingredient in a hard gelatin capsule) was simple, to allow definition of the chronopharmacokinetic properties of the drug substance used in the controlled-release formulation.

As can be seen from Fig. 2, the chronopharmacokinetic behaviour of the press-coated ibuprofen tablet administered under fasting conditions was the opposite to that with the capsule formulation. After the evening dose, peak plasma level was obtained significantly ($P < 0.05$) earlier than after the morning dose, meaning that the absorption had been faster. The extent of bioavailability (AUC_{0-12h}) was significantly ($P < 0.01$) higher when drug was administered in the evening (Table 1). The concentration/time curve after the morning dose is very similar (e.g. t_{max} at 6 h) to that in a previous study of the same formulation (Halsas et al., 1998b). Interindividual variation in plasma curves was minimal after evening dosing of tablets

Table 1
Pharmacokinetic parameters of ibuprofen in capsules and press-coated tablets (single dose of 300 mg) administered after fasting, 2 h after a meal and with a meal, mean ± S.D., $n = 5$

Dosing time	Capsule		Press-coated tablet			
	08:00	22:00	08:00	22:00	22:00 2 h after a meal	22:00 With a meal
C_{max} (mg/l)	27.2 ± 3.6	26.3 ± 4.3	17.0 ± 5.0	20.3 ± 1.3	21.6 ± 2.2	21.1 ± 1.2
t_{max} (h)	1.8 ± 0.5	2.6 ± 1.1	6.0 ± 1.4	4.0 ± 0.0[a,c]	5.2 ± 0.5	6.0 ± 0.6
$t_{1/2}$ (h)	2.6 ± 0.8	3.0 ± 1.0	4.0 ± 1.2	3.2 ± 1.0	3.8 ± 1.4	2.9 ± 0.7
MRT (h)	3.6 ± 1.2	4.1 ± 1.4	5.7 ± 1.8	5.0 ± 1.7	5.4 ± 1.8	5.7 ± 1.1
AUC_{0-12h} (mg/l · h)	119 ± 25	127 ± 24	107 ± 27	122 ± 29[b,c]	117 ± 29	101 ± 21[a]
C_{max}/AUC (l/h)	0.23 ± 0.03	0.22 ± 0.05	0.16 ± 0.02	0.17 ± 0.01[c]	0.19 ± 0.05	0.22 ± 0.04

[a] $P < 0$ 05;
[b] $P < 0.01$ differences are with previous column;
[c] $P < 0.05$ differences are with tablet administered with a meal at 22.00 h.

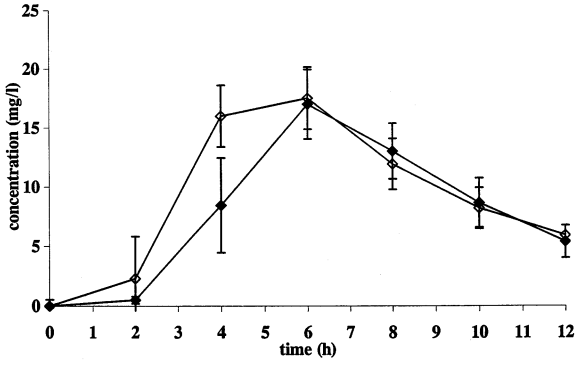

Fig. 3. Mean plasma concentrations of ibuprofen after administration of press-coated tablets at 22:00 h, 2 h after meal (open) or at 22:00 h with meal (closed). The bars represent S.E.M., $n = 5$.

(markedly lower than with the ibuprofen capsules) (Fig. 4). There were no significant differences between the AUC values for the capsule and the press-coated tablet formulation (Table 1).

An important finding is that circadian variation in bioavailability of a drug can be explained by the behaviour of the dosage form in the biological environment. Other explanations could be related to drug substance characteristics or circadian changes in physiological activity (blood flow in the gastrointestinal tract, metabolic activity, renal excretion etc.). The effect of formulation evident with the press-coated tablet could be explained on the basis that the gel forming properties of HPMC depend on environmental pH. The gel layer around the press-coated tablet forms a physical barrier controlling drug release (Halsas et al., 1998a,b). In aqueous solutions, a stable HPMC gel is formed over the pH range 3–11 (Alderman, 1984). In this case, a lower pH leads to a less stable gel around the tablet and the formulation losses its integrity. Gastric acid secretion in man is highest and, consequently, the pH of the gastric contents lowest (pH 1–3), between 18:00 and 24:00 h (Moore and Englert, 1970). The HPMC gel formed after the morning dose will therefore obviously be more stable than that formed after the evening dose. This can be seen in the profile of the concentration–time curve for ibuprofen (Fig. 2).

3.2. Effect of food intake on bioavailability of ibuprofen from the press-coated ibuprofen tablets

In the first stage of the study the bioavailability of ibuprofen from the press-coated tablets after an evening dose was studied under fasting conditions. In drug therapy, it is evident that a drug dose is unlikely to be taken 5 h after the last meal of the day. A meal was therefore served 2 h before and just before drug administration. The effects of times of the meal on the absorption curves of ibuprofen from press-coated tablets are shown in Figs. 3 and 4 (lowest panels). The mean curves show that when the drug was taken with food, the rate and extent of bioavailability decreased. There were statistically significant differences between the C_{max}/AUC, t_{max} and AUC_{0-12h} (Table 1). Concomitant intake of food increased variation between concentration/time curves (Fig. 4, lowest panels). Two hours was not long enough to eliminate the effect of food on bioavailability (Fig. 4, left middle panel vs left lower panel). Although the number of subjects was limited the consistency of effect shown in five volunteers suggest that the data is valid.

The results conflict with those from earlier studies on sustained release ibuprofen formulations. In these studies it was found that food ingestion even raise maximum concentration, although it delays gastric emptying (Borin et al., 1990; Pargal et al., 1996). Food ingestion did not influence AUC values in either of the latter two studies. In the study of Borin et al. (1990) the tablet was a pH-independent erodible matrix. In the study reported here drug release from a core was controlled by a hydrophilic gel layer. The effect of food seems likely to be highly dependent on the nature of a formulation. Meal content also appears to influence the pharmacokinetic profile of ibuprofen (Wilson et al., 1989). Differing caloric and protein contents of meals might explain the differences in results between the studies.

The most marked effect of food intake on bioavailability of ibuprofen from press-coated tablets was a decrease in the rate of absorption. This may have reflected the general retarding effect of food on drug absorption but could also be a result of the gel forming properties of HPMC

mentioned above. Gastric pH is readily elevated by meals up to pH 4–6 (McLaughlan et al., 1989). A high pH may facilitate formation of HPMC gel, resulting as slower release of ibuprofen. However, the situation is more complex. Food affects the viscosity of the stomach contents, markedly delaying gel formation of the tablet coat. Ingestion of food with the press-coated formulation gives peak plasma concentration approximately 6 h after the evening dose, with maximum therapeutic effect appearing at 04:00 to 06:00 h. A better way of achieving this goal is to increase the thickness of the HPMC coat, or increase the relative amount of high viscosity grade HPMC in the tablet coat (Halsas et al., 1998a,b).

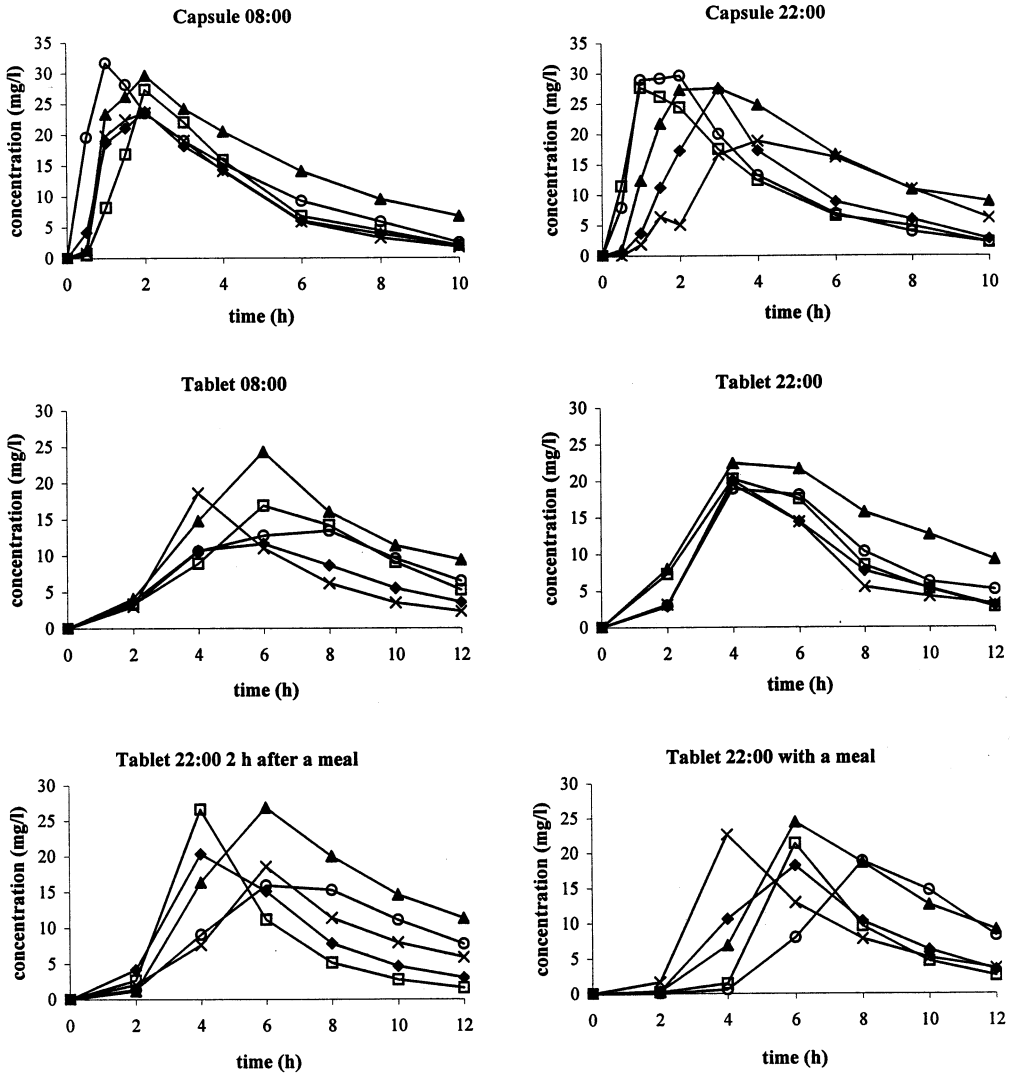

Fig. 4. Individual plasma concentration curves of ibuprofen after administration of the capsule formulation and press-coated tablets under different conditions. Each subject is represented by the same symbol throughout.

4. Conclusions

One conclusion is that the bioavailability of ibuprofen undergoes only minimal circadian variation, markedly less than that of ketoprofen or indomethacin. The main conclusion is, however, that the chronopharmacokinetic behaviour of the press-coated time-controlled release ibuprofen tablet is primarily related to the formulation, not the drug substance. Before development modified-release drug formulations aimed at achievement of highest drug levels in the body during the early hours of the morning, it is important to study bioavailability following administration of the drug concerned in the evening. With the kind of press-coated tablets studied, at least, probably also with other extended-release dosage forms, especially if they contain HPMC, the effects of meals on bioavailability need to be studied after both morning dose evening doses. It would seem appropriate to recommend that evening doses be taken at least 2 h after a meal, to assure that the effects of food on drug absorption are not pronounced.

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