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PHARMACOKINETICS AND DISPOSITION

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Effect of diet on the single- and multiple-dose pharmacokinetics of sustained-release ketoprofen

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Abstract The indirect effect of diet on the single-and multiple-dose pharmacokinetics of sustained-release ketoprofen was studied in 16 healthy male volunteers. In an open, cross-over design, 200 mg ketoprofen was administered as a gastric-juice-resistant, sustained-release tablet once daily during two periods of 5 days. A low-calorie/low-fat diet (LCFD) was given in the first period and a high-calorie/high-fat diet (HCFD) in the second period. The first meal on each day was given 4 h after drug intake. Ketoprofen plasma concentrations were measured over 24 h after the first dose on day 1 and over 36 h after the final dose on day 5 of each period.

On average, plasma concentrations of ketoprofen were higher with the LCFD than with the HCFD. With the HCFD there was a tendency to longer absorption-lag times on day 5. The maximum concentration and the area under the curve over one 24-h dosage period (AUC_{0-24}) were significantly higher with the LCFD, both on day 1 and on day 5. For AUC_{0-24} the differences were on average 15 % (day 1) and 24 % (day 5). The same tendency was observed for the amount excreted in urine over 24 h (A_e), but the difference was only significant on day 1 (14 %). The elimination rate constant (K_β) and the mean residence time were similar for the two diets, both on day 1 and on day 5.

From these results, we conclude that there was an acute indirect effect of diet when a meal was had 4 h after intake of the medication. This resulted in a greater extent of ketoprofen absorption with the LCFD than with the HCFD. The absorption rate was apparently not influenced by this acute effect. The longer gastric residence time of ketoprofen with the HCFD may be the result of a long-term indirect effect on gastric emptying rate. If the extreme difference between the diets in this study is taken into account, it seems unlikely that the observed indirect effects have implications for clinical practice.

Key words Ketoprofen; diet, bioavailability, pharmacokinetics, sustained release

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Ketoprofen, ± 2-(3-benzoylphenyl) propionic acid, is a nonsteroidal anti-inflammatory drug (NSAID) [1, 2]. The efficacy of oral ketoprofen is comparable with that of other NSAIDs in the treatment of rheumatic diseases [3, 4].

In the last two decades studies have been performed to investigate the effect of food on the metabolism [5] and the pharmacokinetics of drugs, in particular on their bioavailability [6–8]. Food may affect the extent and rate of absorption, especially of drugs given as sustained-release formulations.The change in drug absorption may result from an effect of food on the rate of dissolution or release, gastric emptying rate, intestinal transit time, splanchnic blood flow and from preferential binding of the drug to food components [6]. Food may also alter the metabolic clearance of drugs through an influence on first-pass oxidative metabolism [6]. In principle, the extent and rate of absorption of any type of drug may be changed by food. However, only drugs undergoing extensive first-pass oxidative metabolism are susceptible to effects of food on their hepatic metabolism.

Absorption of the anti-inflammatory analgesics fenoprofen [9], ibuprofen [10] and indoprofen [11] is influenced by the concurrent intake of food. Since ketoprofen is chemically related to these drugs, an effect of food on bioavailability and, therefore, on steady-state plasma levels during chronic treatment cannot

be excluded, especially with sustained-release ketoprofen.

In practice, analgesic drugs such as ketoprofen are taken with food to avoid gastrointestinal irritation. For this reason, it is of interest to study the effect of concomitant food intake on the absorption of sustained-release ketoprofen.

This paper describes a study on the influence of a low-calorie/low-fat and a high-calorie/high-fat diet on the steady-state pharmacokinetics of sustained-release ketoprofen. Its primary objective was to assess the influence of any diet-induced physiological changes on ketoprofen pharmacokinetics.

Materials and methods

Protocol

The study protocol and written informed consent form were approved by the regional medical ethics committee prior to the start of the study. Written informed consent was obtained from all participants.

Subjects

Subjects were 16 male volunteers between 18 and 35 years of age (mean 23 years), weighing between 62 and 96 kg (mean 77 kg), and physically healthy as seen in a pre-study examination, including ECGs, haematology and chemistry tests. In addition, urine was screened for drugs or abuse during the pre-study examination. No other medication was used for 2 weeks prior to and during the study. No food or drinks containing alcohol or methylxanthines were used during either study period.

Study design

The study had an open, one-way, cross-over design (not randomised) and consisted of two periods of 5 days with administration once daily of 200 mg ketoprofen at 0700 hours. During these two periods, the subjects were hospitalised in the Clinical Research Centre of Pharma Bio-Research. Between the study periods there was a washout period of 14 days. The study design allowed us to define the pharmacokinetic profile and bioavailability of sustained-release ketoprofen in direct relation to two specific, strictly monitored diets (Tables 1, 2).

During the first period the subjects received the low-calorie/low-fat diet (LCFD) containing about 1200 calories per day and during the second period the high-calorie/high-fat diet (HCFD) containing approximately 3000 calories per day.With both diets, meals were served at 1100 hours (breakfast), 1400 hours (lunch) and 1900 hours (dinner). During the washout period, each volunteer followed his usual dietary pattern.

Venous blood samples of 8 ml were collected just before drug intake and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 17, 20 and 24 h after administration on days 1 and 5, and, in addition, blood samples were taken 30 and 36 h after drug administration on day 5. On days 2, 3 and 4 only pre-dose blood samples were collected.

Urine portions were collected for the periods 0–2, 2–4, 4–6, 6–8, 8–12 and 12–24 h after drug administration of the drug on days 1, 2, 3, 4 and 5, and, in addition, the 24–48 h portion was collected on day 5. Two aliquots of 30 ml were taken from the collected portions and stored at –20 °C until analysis.

Table 1 The low-calorie/low-fat diet (about 1,200 calories)

Days 1, 3 and 5	Days 2 and 4
Breakfast	Breakfast
Coffee or tea without sugar	Coffee or tea without sugar
Skimmed milk (200 ml)	Skimmed milk (200 ml)
1 Boiled egg	Cottage cheese 100 g: 0 % fat
1 Slice toast	1 Slice toast
Butter (5 g)	Butter (5 g)
Lunch	Lunch
Tomato salad	Green beans salad
Roast chicken without skin	Cold roast beef with gherkin
Green beans with parsley	Grilled tomatoes
Yoghurt 0 % fat without sugar	Gouda cheese (30 g)
Fruit	Apple
1 Slice of toast	1 Slice of toast
Dinner	Dinner
Green salad	Green salad
Grilled steak	2 Slices of ham
Mixed vegetables	Steamed spinach
Cottage cheese 100 g: 0 % fat	Yoghurt 0 % fat without sugar
Peach	Orange
1 Slice of toast	1 Slice of toast

Table 2 The high-calorie/high-fat diet (about 3,000 calories)

Days 1, 3 and 5	Days 2 and 4
Breakfast	Breakfast
Coffee or tea with 2 lumps of sugar	Coffee or tea with 2 lumps of sugar of sugar
Full cream milk (200 ml)	Leerdammer cheese (50 g)
4 Slices of toast + butter (25 g) + jam	4 Slices of toast + butter (25 g) + jam
2 Fried eggs	2 Fried eggs
Glass of fruit juice	Glass of fruit juice
Lunch	Lunch
Sausage (80 g)	Oil sardines
Roast chicken	Roast beef
French fries	Green peas
Gouda cheese (50 g)	Apple pie
Fruit	Fruit
3 Slices of toast	3 Slices of toast
Dinner	Dinner
White bean	Half salad grapefruit
Ham	Pork roast
Mixed vegetables	Mashed potatoes
Gouda cheese	Leerdammer cheese
Ice cream with 4 biscuits	Fruit with 4 biscuits
3 Slices of toast	3 Slices of toast

Study medication

Each dose was administered as a sustained-release, gastric-juice resistant tablet with a hydrophilic matrix coating (ketoprofen SR 200, Profenid LP 200 mg, Rhône-Poulenc Rorer, Antony, France) at 0700 hours following an overnight fast. Dissolution tests revealed that at pH 7.4 about 80 % of the dose is released during the first 21 h. At pH 1 the release of ketoprofen was less than 1 % after 2 h.

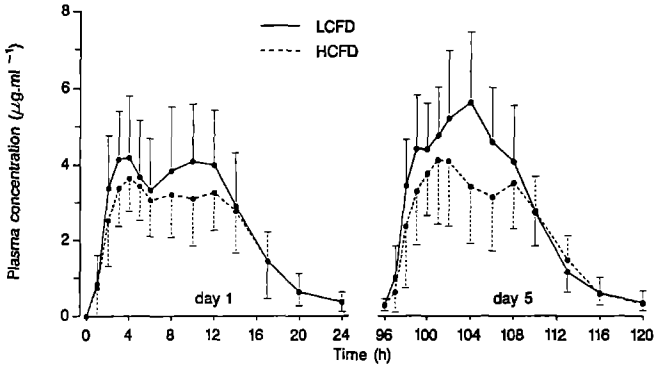

Fig. 1 Graphic presentation of the plasma concentration-time curves (mean with SD) of ketoprofen after oral administration of 200 mg sustained-release ketoprofen to 16 healthy males

Analytical method

Ketoprofen was determined in plasma and urine using the analytical methodology of Bannier et al [12] which is based on reversed-phase high-pressure liquid chromatography (HPLC) with UV detection at 254 nm. Briefly, this method involved ether extraction of ketoprofen from acidified plasma, evaporation of the ether under a gentle stream of nitrogen, reconstitution of the residue with mobile phase and injection of 20 µl of the resulting solution into the reversed-phase HPLC system. Ketoprofen was determined in urine following alkaline hydrolysis. Consequently, the sum of unaltered ketoprofen and its glucuronides was determined in the urine samples. The lower limit of quantitation (LOQ) for plasma and urine was about 0.02 $\mu g \cdot ml^{-1}$. The coefficient of variation for analysis in plasma and urine was about 7 %.

Pharmacokinetic analysis

The maximum plasma concentration (C_{max}), the apparent plasma elimination rate constant (K_β), the mean residence time (MRT), the area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) on days 1 and 5, the AUC_{0-4} on days 1 and 5, the AUC on day 1 extrapolated to infinity (AUC_{inf}), and the amount excreted into the urine during a 24-h collection period (A_e) on days 1 and 5 were calculated.

AUC_{0-4} and AUC_{0-24} were obtained by applying the linear trapezoidal method. AUC_{inf} was calculated from $AUC_{inf} = AUC_{0-x} + C_x/K_\beta$ where x represents the last time point with a concentration above the LOQ. K_β was obtained from the final linear portion of the semilogarithmic plasma concentration-time curve, i.e. from 14 h onwards. MRT was calculated from the ratio AUC_{inf}:$AUMC_{inf}$, in which $AUMC_{inf}$ is the area under the first moment curve extrapolated to infinity as described by Gibaldi and Perrier [13].

Statistical evaluations

Descriptive statistics were calculated for the pharmacokinetic parameters by diet and by day. Paired Student's t-tests were applied to compare the corresponding parameters of the two diets. Symmetrical 90 % and 95 % confidence intervals were also computed when necessary. Moreover, the General Linear Model (GLM) of variance analysis belonging to the Statistical Analysis System (SAS) package (SAS, SAS Institute, N. C., USA) was used to test the statistical significance of the interaction "treatment type by treatment order" (also called "treatment by period" interaction). Statistical significance was accepted at $P < 0.05$.

Results

In Fig. 1, the mean plasma concentration-time curves of ketoprofen are given for both diets, on day 1 (first dose) and on day 5 (steady state). The shape of the individual curves showed considerable variation, both between subjects and within subjects, particularly between 4 and 12 h after drug administration. For most subjects, that part of the curve was a slightly irregular plateau. For some subjects, there was a maximum in the first 4 h followed by a prominent second maximum 10–12 h after drug administration. Double peaks were observed with both diets on day 1 and on day 5. On average, plasma concentrations were higher with the LCFD than with the HCFD.

A summary of statistics on the pharmacokinetic parameters are presented in Table 3. The parameters C_{max} and AUC_{0-24} (AUC_{inf}) were significantly higher with the LCFD, both after the first dose and in steady state. The same tendency could be observed for AUC_{0-4} and A_e, but the difference was statistically sig-

Table 3 Pharmacokinetic parameters (mean with SD) of ketoprofen in a low-calorie/low-fat diet (LCFD) and high-calorie/high-fat diet (HCFD) in 16 healthy males

	LCFD	HCFD	P Value
Single dose			
C_{max} ($\mu g.ml^{-1}$)	5.8 (1.2)	4.6 (0.7)	0.001
K_β (h^{-1})	0.22 (0.04)	0.21 (0.05)	NS
MRT (h)	9.9 (1.7)	10.3 (1.8)	NS
AUC_{0-24} ($\mu g.ml^{-1}.h$)	59.7 (10.9)	51.8 (7.8)	0.007
AUC_{0-4} ($\mu g.ml^{-1}.h$)	10.5 (3.5)	8.5 (2.7)	NS
AUC_{inf} ($\mu g.ml^{-1}.h$)	61.4 (11.2)	53.8 (8.2)	0.008
A_e (mg)	145 (20.3)	127 (16.3)	0.003
Multiple dose			
C_{max} ($\mu g.ml^{-1}$)	6.5 (1.4)	5.3 (1.4)	0.010
K_β (h^{-1})	0.16 (0.03)	0.18 (0.05)	NS
MRT (h)	9.7 (1.3)	10.2 (1.5)	NS
AUC_{0-24} ($\mu g.ml^{-1}.h$)	67.4 (10.4)	54.4 (9.3)	< 0.001
AUC_{0-4} ($\mu g.ml^{-1}.h$)	11.2 (3.1)	8.3 (3.2)	0.015
A_e (mg)	135 (21.3)	129 (24.2)	NS

NS not statistically significant ($p > 0.05$)

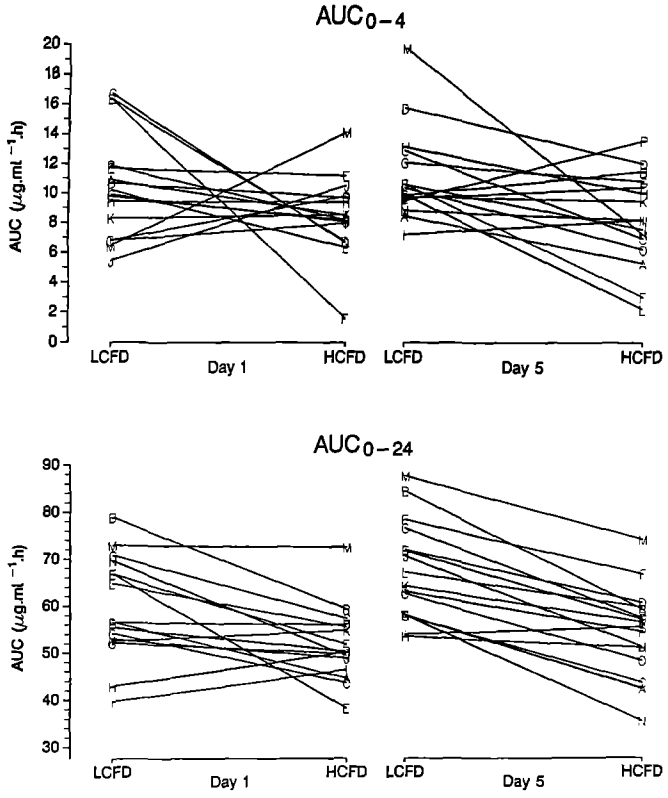

Fig. 2 Graphic presentation of the individual results of AUC_{0-4} (*top*) and AUC_{0-24} (*bottom*) of ketoprofen after oral administration of 200 mg sustained-release ketoprofen to 16 healthy males

nificant only after the first dose (A_e) or only at steady state (AUC_{0-4}). Taking into account the individual plasma concentration-time curves, it appears that the lower AUC_{0-4} for the HCFD on day 5 is mainly due to longer absorption-lag times for several subjects. The results of K_β and MRT were very similar for the two diets.

The individual results of AUC_{0-4} and AUC_{0-24} are graphically presented in Fig. 2. This figure indicates that the difference between means of AUC_{0-4} for the two diets on day 1 was mainly due to one subject with exceptional results. Concerning the AUC_{0-24}, the difference between the two diets was most consistent on day 5.

In Table 4 are given the values (mean with SD) of urinary excretion of ketoprofen (non-conjugated + glucurono-conjugated) measured every day, from day 1 to day 6, for both diets. In addition, the P value of the paired t-test comparison (HCFD versus LFCD) and the confidence limits are mentioned. There is only one statistically significant difference ($P = 0.0034$), seen on day 1, which indicates that urinary excretion is transiently greater with the LCFD than with the HCFD; however, there is no statistically significant ($P = 0.38$ and $P = 0.79$) change in the amount of ketoprofen excreted at the end of each diet period (days 5 and 6 on which the residual urinary excretion of ketoprofen represents only around 3 % of the last administered dose).

Discussion

The present study was primarily designed to detect possible indirect effects of diet on ketoprofen pharmacokinetics by means of changes in physiological conditions. The possibility of direct interaction of the food with the medication was minimised by timing the food intake with regard to drug intake. The measurements on day 1 were intended to detect the influence of any acute physiological changes (e.g. gastric emptying rate, intestinal motility and splanchnic blood flow). The measurements on day 5 were intended to detect the influence of any long-term physiological changes, such as changes in metabolism and urinary composition. The AUC_{0-4} is a key parameter in this respect, because any short-term influence of food can be excluded.

Ketoprofen was administered as a sustained-release formulation. For most sustained-release formulations, the slow release of the drug represents the rate-limiting factor in the process of absorption [15]. As a consequence, the effective intestinal transit time of the controlled-release preparation and factors directly or indirectly affecting the release rate may influence the absorption. Gastric emptying rate and intestinal motility (both determining the transit time), the nature of the gastrointestinal contents (pH, ionic strength, viscosity), and splanchnic blood flow may also play a role [6].

The medication on day 1 was taken in fasting conditions following a period of usual diet. For this reason, the difference between the AUC_{0-4} values for day 1 must be considered as an experimental variation, which is confirmed by the graphic presentation of the individual data in Fig. 2 (upper left panel). On the other hand, the total AUC (AUC_{0-24} and AUC_{inf}) is significantly different on day 1, suggesting an acute effect of diet.

The results concerning AUC_{0-4} and absorption-lag times on day 5 suggest that the HCFD decreases the gastric emptying rate as a long-term adaptive effect. However, it seems likely that the consistently higher AUC_{0-24} with the LCFD on day 5 is mainly due to an acute effect of the meal taken.

From the AUC data it is not possible to conclude whether this acute effect is only on the extent of absorption, or also on the rate of absorption (bioavailability). In this connection, additional information can be derived from the mean residence time (MRT) data. The MRT after oral drug administration is the sum of the MRT after intravenous administration and the mean absorption time (MAT). Although it was not possible to calculate $MRT_{i.v.}$ in this study, it is very likely that this parameter was not influenced by diet, as K_β was similar with the LCFD and the HCFD. From the fact that the MRT was very similar with the two diets, one can conclude that MAT is also not influenced by diet. Nevertheless, it is possible to consider that the excess of fat (and calories) decreases the bioavailability of ketoprofen when given as a sustained-release formulation. Since the MRT and the minimal concentration measured 24 h

Table 4 Day-to-day urinary excretion (mean with SD) of ketoprofen with LCFD and with HCFD in 16 healthy male volunteers (NC not computed; NS not statistically significant)

Day:h	LCFD	HCFD	Pvalue	Confidence interval (mg)
	A_e (mg)	A_e (mg)		90 %/95 %
1: 0–24 h	145 (20.3)	127 (16.3)	0.0034	8.9–27.1/7.0–29.0[a]
2: 24–48 h	126 (30.5)	133 (24.5)	NS (0.53)	NC
3: 48–72 h	134 (26.0)	120 (40.6)	NS (0.29)	NC
4: 72–96 h	129 (44.7)	136 (38.7)	NS (0.71)	NC
5: 96–120 h	135 (21.3)	129 (24.2)	NS (0.38)	2.8–8.5/2.2–9.1
6: 120–144 h	6.08 (4.76)	6.41 (3.63)	NS (0.79)	NC

[a] For the difference (LCFD-HCFD)

after dosing are very stable whatever the diet, there is no fast or irregular release of ketoprofen from the pharmaceutical matrix during the transit of the tablet along the gastrointestinal tract.

This study had an open, one-way, cross-over design, but with no randomisation of the two 5-day treatment periods (either LFCD or HFCD). Theoretically speaking, this trial design might be considered as having a weakness due to the risk of treatment order bias. However, it is known that adaptation of the gastrointestinal tract to a specific diet takes many days, especially when the diet changes from a high-fat/high-calorie diet to a low-fat/low-calorie one. As it was considered too difficult to prolong the trial period with a pre-inclusion period consisting of randomised allocation of each diet with placebo before the administration of ketoprofen with the scheduled diet regime, it was decided not to randomise the treatment order and to design the study with the low-fat/low-calorie diet at the beginning, followed by a washout period with a normal diet, and finally the high-fat/high-calorie diet. The GLM statistical model indicates that there is no statistically significant ($P = 0.456$) "treatment order" interaction, which shows that the lack of randomisation of the diets is not a relevant bias in the present study. In addition, the 90 % and 95 % symmetrical confidence limits for the differences between the AUC values for each diet on day 1 and day 5 are: 3.49–12.4 and 2.54–13.3, and 9.95–16.1 and 9.29–16.8 $h \cdot \mu g \cdot ml^{-1}$, respectively. Conversely, the urinary excretion of ketoprofen (Table 4) was greater with the LCFD for both measurements performed on day 1 and day 5, corresponding to the measures of ketoprofen AUCs: indeed, the 90 % and 95 % confidence intervals for A_e are 8.9–27.1 mg and 7.0–29.0 mg on day 1, respectively, and 2.8–8.5 mg and 2.2–9.1 mg on day 5, respectively.

To our knowledge there is no publication that demonstrates the influence of lipid and glucid amounts in the diet on the pharmacokinetic profile and bioavailability of medications, particularly of multiple-dose non-steroidal anti-inflammatory drugs (NSAIDs). Most of the published studies [15–17] have evaluated the influence of food during a single administration of drug in fasting state and then after a calibrated meal (glucids, proteins and lipids). Bogentoft et al. [18] showed that acetylsalicylic acid oral absorption is incomplete when enteric-coated formulations (i.e. Premasin) are given with food. This is partly due to the fact that tablets stay longer in a full stomach than in an empty one [19]. This pattern is not seen with ketoprofen. For diclofenac, food intake decreases the oral absorption rate [20], but this feature is not always observed [21]. Food intake does not induce any significant modification in the bioavailability of fendosal [22]. On the contrary, when nabumetone is given with food, the resorption in the gastrointestinal tract is significantly increased [23]. A similar pattern is seen with tiaprofenic acid [24].

Transit through the gut and colon is mainly affected by diet. One of the major determinants of the absorption of a drug from the colon is the residence time in any particular segment of the colon. The time taken for food to pass through the colon accounts for most of the time the food is in the gut. In normal subjects, this is about 78 h for expulsion of 50 % ingested markers [25], but may range from 18 to 144 h. Steady-state measurement of mean transit time after injection of markers for several days gave a mean transit time of 54.2 h [26], which represents about 5.6 times the mean residence time of ketoprofen in plasma with an LCFD [MRT = 9.7 (1.3) h] and about 5.3 times when it is taken with an HCFD [MRT = 10.2 (1.5) h]. In order to minimise interindividual variability, it was decided not to include women in this trial. In effect, men have slightly shorter transit times than women, and this is most apparent in the proximal colon [27]; in the rat, this is related to circulating steroid hormones, but the menstrual cycle does not seem to have an effect in women [28, 29]. Thus, it is logical to assume that is was correct to avoid the possible effect of gender on transit time in the present study by recruiting only male volunteers.

An acute, indirect effect of diet could be demonstrated when a meal was taken 4 h after intake of sustained-release ketoprofen. This resulted in a 15–20 % greater extent of ketoprofen absorption with an LCFD than with an HCFD. The absorption rate was not influenced by this acute effect. The longer gastric residence time of ketoprofen with the HCFD may be the result of a long-term indirect effect on gastric emptying rate.

If the extreme difference between the diets in this study is taken into account, it seems unlikely that the

observed indirect effects have any implications for clinical practice.

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