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Tyramine Pharmacokinetics and Reduced Bioavailability with Food

Chad M. VanDenBerg, PharmD, Lawrence F. Blob, MD, Eva M. Kemper, and Albert J. Azzaro, PhD

Tyramine challenge studies have demonstrated that it requires approximately twice the amount of tyramine administered with a meal compared to administration after a fast to elicit the same effect, suggesting a reduction in bioavailability of tyramine when administered with food. The pharmacokinetics of tyramine when administered in a fasted versus a fed state were studied. A single 200-mg dose of tyramine was administered orally to healthy subjects both after an overnight fast and during a meal. Systemic exposure to tyramine was reduced by 53% ($p < 0.05$), and the maximum concentration of tyramine was reduced by 72% ($p < 0.05$) when the dose was administered during a meal. Tyramine maximum serum concentration was observed between 20 minutes and 1 hour when the dose was administered after an overnight fast and appeared to be delayed and/or prolonged by administration during a meal. Tyramine oral clearance was 135 ± 55.4 L/min, maximum observed serum concentration was 37.7 ± 26.01 ng/mL, and tyramine elimination half-life was 0.533 (range: 0.330-0.668) hours after administration to fasted subjects. Tyramine bioavailability was significantly reduced when administered with a meal compared to after a fast. The results suggest that larger amounts of dietary tyramine will be required to induce a pressor response equivalent to that following encapsulated tyramine administered in the fasted state.

Keywords: *Tyramine; pharmacokinetics; bioavailability*
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Tyramine is an indirectly acting sympathomimetic amine that mimics the effects of sympathetic adrenergic nerve stimulation through the release of neuronal stores of norepinephrine. At a mechanistic level, a cascade of events leading to the release of norepinephrine appears to occur.[1] The cascade begins with the active transport of tyramine across the neuronal membrane. Under normal circumstances, the small amount of tyramine entering the adrenergic neuron from the plasma is effectively deaminated by intraneuronal monoamine oxidase type A (MAO-A).

When administered systemically, the cardiovascular actions of tyramine include vascular constriction and an increase in cardiac rate and contractile force. These actions occur simultaneously in a dose-related fashion. Given sufficient tyramine, the resulting hypertension (referred to as the tyramine pressor response) can be severe enough to cause a myocardial infarction or stroke.

Dietary tyramine represents the major source of tyramine in the plasma. Normally, the ingestion of tyramine-rich food has no cardiovascular effect due to a series of highly effective enzymatic barriers that inactivate tyramine in the intestines and liver before it can reach the systemic circulation, in addition to another enzymatic barrier in the adrenergic neuron. Intestinal MAO-A plays a major role in preventing dietary tyramine from entering the systemic circulation.[2-4] Accordingly, transient hypertensive crisis similar to that observed in patients with pheochromocytoma has been occasionally observed in depressed patients treated with first-generation MAO inhibitors such as phenelzine and tranylcypromine.[5] The antidepressant effect of phenelzine or tranylcypromine is generally associated with the inhibition of MAO-A in the central nervous system.[6] At therapeutic doses, these first-generation MAO inhibitor antidepressants effectively inhibit more than 80% of MAO throughout the body, causing the enzymatic barrier to exogenous tyramine to be substantially less effective.[7] To evaluate the potential of amine-induced hypertensive reactions associ-

From Somerset Pharmaceuticals, Inc., Tampa, Florida (Dr. VanDenBerg, Ms. Kemper, Dr. Azzaro) and Potomac Clinical Trials, Jessup, Maryland (Dr. Blob). This work was supported by Somerset Pharmaceuticals, Inc. Submitted for publication November 27, 2002; revised version accepted February 22, 2003. Address for reprints: Chad VanDenBerg, PharmD, 2202 N. West Shore Blvd. Ste. #450, Tampa, FL 33607.
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ated with MAO inhibitors, tyramine challenges or amine blood pressure tests have been performed without serious sequelae.[3,8-13]

The enzymatic barriers to tyramine in nonmedicated healthy volunteers are quite effective. The average person requires approximately 500 mg of tyramine administered orally in a fasting state to produce a minimal pressor response (systolic blood pressure increased from baseline ≥ 30 mmHg).[8,9,12] By contrast, similar pressor reactions are observed with oral tyramine doses of approximately 10 mg following steady-state treatment with the MAO inhibitor tranylcypromine.[9,10] Tyramine concentrations in typical meals are usually nominal (< 5 mg), but certain foods such as aged cheeses and improperly stored meats have higher tyramine concentrations. If eaten in sufficient quantities, these foods can increase the tyramine load of a meal to 20 to 40 mg.[1] Therefore, a tyramine-rich meal can provide enough tyramine to induce a hypertensive reaction in a patient taking a first-generation MAO inhibitor antidepressant such as tranylcypromine or phenelzine.

Previous tyramine challenge studies have demonstrated that subjects who ingest tyramine with a meal require approximately twice the amount of tyramine compared to administration after a fast to elicit the same effect.[8,14,15] It has also been demonstrated that tyramine doses up to 400 mg, given as food in the form of aged cheese, were insufficient to cause a clinically meaningful blood pressure response.[16] These data suggest a reduction in bioavailability of tyramine when administered with food or as a dietary constituent of food.

The present study was designed to characterize the pharmacokinetics of tyramine and confirm the clinical observations regarding the effects of food on the bioavailability of orally administered tyramine.

MATERIALS AND METHODS

This study was a single-center, open-label, two-period, two-treatment, single-sequence design to describe the pharmacokinetics of tyramine and evaluate the effect of tyramine administration during a meal. The study was performed at Potomac Clinical Trials (Jessup, MD), and the protocol was reviewed and approved by the Western Institutional Review Board. Study procedures and possible side effects were explained to all subjects, and written informed consent was signed prior to participation. This study was conducted in accordance with the Declaration of Helsinki.

Eight healthy male volunteers (3 Caucasian, 4 Black, and 1 Asian; 20 to 43 years of age; 55 to 84 kg in weight) were selected on the basis of general good health as confirmed by physical examination, medical history, and clinical laboratory evaluations. Seven subjects completed the study. Subjects were excluded if they had any disease or condition that could affect interpretation of study results. In addition, subjects were excluded if they had any of the following conditions: (1) used any prescription medication within 35 days, used over-the-counter medication within 14 days, or consumed alcohol within 24 hours of study initiation; (2) had a positive urine test for illicit drugs; (3) participated in a clinical investigation within 45 days; (4) followed a special diet; or (5) had any condition that might place them at increased risk of complications.

Tyramine was supplied as oral capsules containing 253 mg tyramine hydrochloride (from BASF Knoll, Lot No. 01967) by Watson Laboratories, Copiague, New York (Tyramine Hydrochloride Capsules 253 mg Lot No. 079802). Tyramine was administered as single oral doses of 200 mg containing 253 mg tyramine hydrochloride. The first dose was administered after an overnight fast with 180 to 240 mL water. One week later, the second dose was administered midway through a standard breakfast. There was a washout of 1 week between study periods. All subjects spent the night at the study facility before the tyramine dose of each period. Each volunteer was monitored for the occurrence of adverse events (AEs) and changes in vital signs.

Serial serum samples, for determination of single-dose tyramine pharmacokinetics, were collected 30 minutes predose and 10, 20, 30, 45, 60, 75, 90, 105, 120, 180, 240, 300, and 360 minutes following dosing. Serum samples were assayed for tyramine concentrations using a validated high-performance liquid chromatography method with tandem mass-spectrometric detection. The assay range was 1.00 to 100 ng/mL from a 0.5-mL aliquot. The assay precision, measured as the coefficient of variation of the mean result, was within 9.0%, and overall accuracy was within 2.0% of known concentration.

Pharmacokinetic Analysis

Parameters were determined from each subject's serum tyramine concentration versus time (actual sampling times) data for each dose. The peak concentration (C_{max}) and the corresponding peak time (t_{max}) were the observed values. The elimination rate constant (λ_z) was obtained by log-linear regression analysis of the terminal phase of the serum concentration versus time decay curve. The apparent elimination half-life ($t_{1/2}$) was determined by taking the ratio of the natural log of 2 and

λ_z. The area under the curve from time 0 to infinity (AUC_∞) was obtained through summation of the area under the curve from time 0 to the last measurable concentration (AUC_T), calculated by linear interpolation, and the ratio of the last measurable concentration and λ_z. Oral clearance (CL/F) was determined from the ratio of dose and AUC_∞, where F represents oral bioavailability. Mean residence time (MRT) was calculated from $AUMC_\infty/AUC_\infty$. Area under the first moment curve ($AUMC_\infty$) was computed by linear interpolation of the time by serum concentration versus time data from time 0 to the last measurable concentration (C_T) plus $TC_T/\lambda_z + C_T/(\lambda_z)^2$, where T = time of the last measurable concentration. Lag time (t_{lag}) for serum tyramine to reach measurable concentrations was set equal to the time of the preceding sample.

Statistical Analysis

Descriptive statistics were computed for pertinent pharmacokinetic parameters. The effect of food on tyramine pharmacokinetics was determined by a paired *t*-test of AUC_T, AUC_∞, and C_{max} after logarithmic transformation. In addition, t_{max}, λ_z, $t_{1/2}$, t_{lag}, and MRT observed with and without food were compared by the Wilcoxon signed rank test.

RESULTS

One subject was withdrawn from the study for noncompliance after completing the first period, and all others completed the study in its entirety. The results of all 7 subjects who completed the study were included in the analysis. No subject withdrew due to the occurrence of an adverse event (AE). The treatments were generally well tolerated, and no consistent, clinically meaningful changes in vital signs were observed.

Safety

No reported adverse event was serious, and all resolved completely without any sequelae. The most frequently reported AE was hypertension, defined as a semirecumbent systolic blood pressure greater than 160 mmHg and observed in 3 subjects. In 1 subject, hypertension was observed after tyramine was administered during a fast and was possibly treatment related. In 2 subjects, hypertension was observed after tyramine was administered during a meal but was not considered to be treatment related. A total of 6 AEs were reported by 4 of 8 volunteers, and no other AE was considered related to treatment. Therapeutic intervention to control elevated blood pressure was not required for any subject.

Table I Tyramine Pharmacokinetics When Administered after an Overnight Fast and during a Meal

Parameter	Fasting (*n* = 7)	With a Meal (*n* = 7)
C_{max} (ng/mL)	37.7 ± 26.01	8.23 ± 9.13[a]
t_{max} (h)	0.50	1.25[b]
t_{lag} (h)	0	0.75[b]
λ_z (h^{-1})[c]	1.32	0.70
$t_{1/2}$ (h)[c]	0.533	0.922[d]
AUC_T (ng•h/mL)	25.1 ± 10.17	7.80 ± 3.397[a]
AUC_∞ (ng•h/mL)[c]	28.0 ± 9.85	11.4 ± 3.28[a]
CL/F (L/min)[c]	135 ± 55.4	
MRT (h)[c]	0.849	2.19

Arithmetic mean ± *SD* except median was reported for t_{max}, $t_{1/2}$, t_{lag}, λ_z, and MRT. C_{max}, peak concentration; t_{max}, corresponding peak time; t_{lag}, lag time to measurable concentrations; λ_z, elimination rate constant; $t_{1/2}$, apparent elimination half-life; AUC_T, area under the curve from time 0 to last measurable concentration; AUC_∞, area under the curve from time 0 to infinity; CL/F, oral clearance; MRT, mean residence time.

a. Significantly different from fasting result, paired *t*-test ($\alpha = 0.05$).

b. Significantly different from fasting result, Wilcoxon signed rank test ($\alpha = 0.05$).

c. $n = 6$ for each treatment and $n = 5$ for paired statistical tests.

d. Three of the estimates were obtained over less than one half-life.

Tyramine Pharmacokinetics

The pharmacokinetic results for tyramine administered alone and with food are shown in Table I. The serum tyramine concentration profiles after a single oral dose of 200 mg tyramine administered to each subject after an overnight fast and during a meal are shown in Figure 1. No tyramine was measured in serum samples obtained prior to administration of any dose. Concentrations above the assay lower limit (1 ng/mL) were detected sooner and at higher concentrations, when the dose was administered to fasting subjects. Tyramine concentrations higher than 1 ng/mL were observed in only a few samples obtained 3 or more hours after a dose. The maximum serum concentration ranged from 13.6 to 85.7 ng/mL when 200 mg tyramine was administered to fasting subjects and from 2.96 to 27.9 ng/mL when the same dose was administered to subjects during a meal. The decrease ranged from 21% to 96% (average = 72%) ($p = 0.0056$). The maximum concentration of tyramine administered after an overnight fast was observed 20 minutes to 1 hour after the tyramine dose and was observed 0.5 to 4.0 hours after the dose

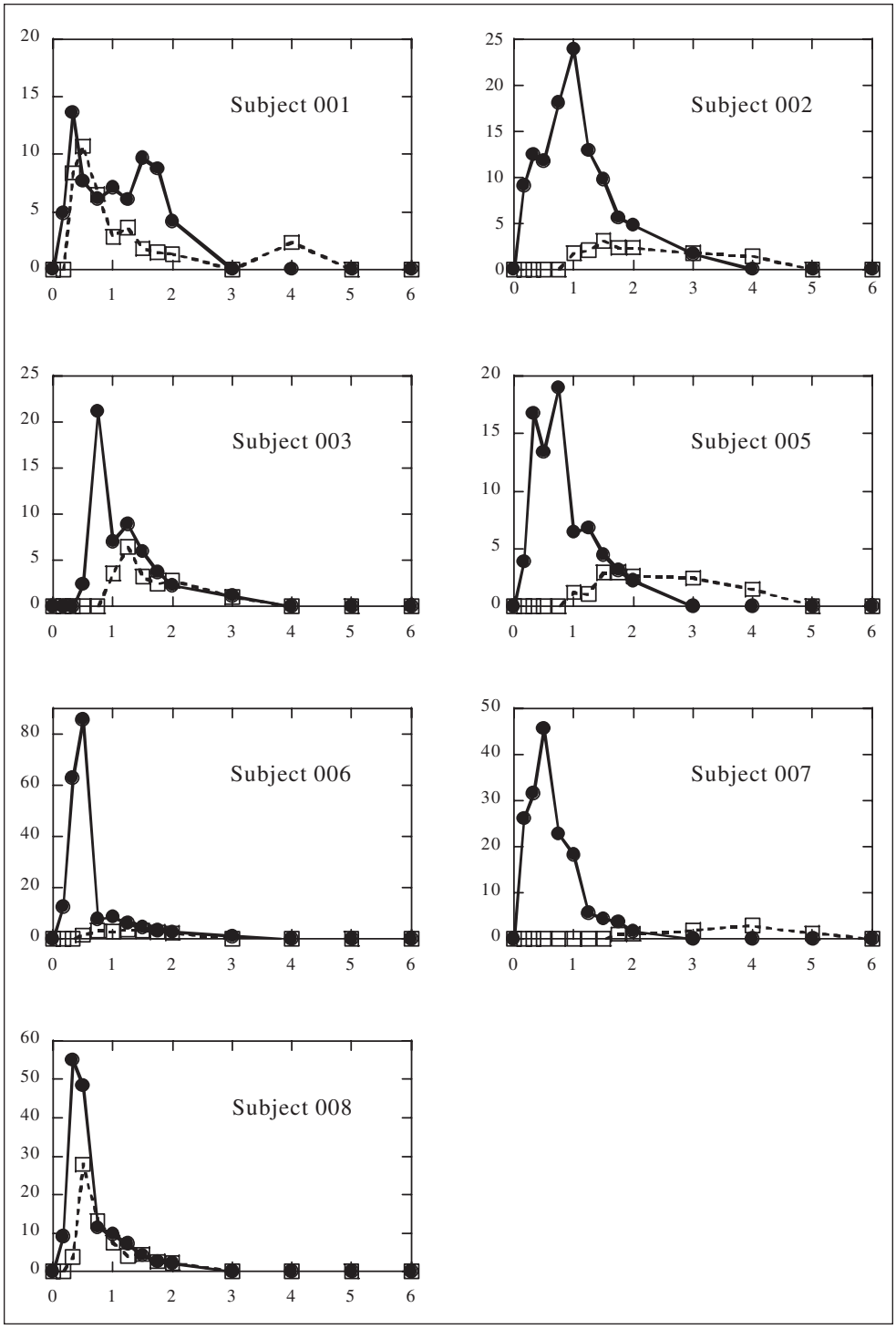

Figure 1. Individual tyramine serum concentrations (ng/mL) versus time (h) after administration of 200 mg tyramine after a fast and during a meal. Filled symbol = dose after a fast; open symbol = dose during a meal. Note: the tyramine concentration scale differs by subject. No figure is shown for subject 004, who did not complete the study.

when administered during a meal. Administration during a meal resulted in a median delay in time of maximum concentration of 0.5 hours ($p = 0.0156$). The lag time before the observation of quantifiable tyramine concentrations was evident when tyramine was administered during a meal and ranged from 10 minutes

to 1.5 hours. A lag time (20 min) was observed for only 1 subject when tyramine was administered to fasting subjects. The difference was statistically significant (p = 0.0156).

The area under the curve of observed tyramine concentrations (AUC_T) was 14.1 to 40.1 ng•h/mL, when 200 mg tyramine was administered to fasting subjects, and 4.46 to 14.6 ng•h/mL, when tyramine was administered during a meal. For individual subjects, the decrease ranged from 34% to 89% (average = 64%) (p = 0.0027, n = 7). It was not possible to estimate tyramine elimination half-life for subject 001, when the dose was administered fasting, or for subject 007, when the dose was administered during a meal, because no exponential decay of concentrations was observed. Thus, the AUC_∞ was computed after both doses in only 5 subjects. AUC_∞ was 15.1 to 41.1 ng•h/mL (n = 6) when tyramine was administered to fasting subjects and 7.47 to 16.3 ng•h/mL (n = 6) when tyramine was administered during a meal. The ratio of AUC_∞ when administered with a meal compared to fasting ranged from 0.19 to 0.68 in individual subjects (p = 0.0171, n = 5). Results from 5 subjects for whom AUC_∞ was calculated after both treatments did not differ from relative bioavailability based on AUC_T from 7 subjects. Thus, the effect of administration of tyramine during a meal was a decrease in the oral bioavailability by an average of 53% (range: 32%-81%).

The oral clearance of tyramine estimated when it was administered after an overnight fast was 81.0 to 221 L/min for the 6 subjects in whom an elimination rate constant could be estimated. All estimates of half-life were based on at least three concentration-time observations that decreased in an exponential manner. The tyramine elimination half-life was 0.330 to 0.668 hours when calculated from concentrations observed after tyramine was administered to fasting subjects. The half-lives were estimated from data observed over two to four half-lives. In contrast, when tyramine was administered during a meal, the estimated half-life was 0.503 to 3.00 hours. However, three of the six half-lives were calculated from concentrations observed over less than one half-life and are less reliable estimates. The three more reliable estimates ranged from 0.503 to 0.910 hours.

The tyramine mean residence time was 0.692 to 1.38 hours when administered after an overnight fast. When tyramine was administered during a meal, the MRT was calculated to be 1.01 to 5.29 hours. The MRT for tyramine administered during a meal was longer by 1.4-fold to 4.8-fold for all 5 subjects for whom both were available, and the median increase was 3.1-fold. This change was not statistically significant by the Wilcoxon signed rank test.

DISCUSSION

Currently, there are no reports of studies of the serum pharmacokinetics of tyramine and the effect of administration with a meal in the absence of other drug treatments. There are reports from which the pharmacokinetics of tyramine might be inferred. For example, after oral doses to fasting subjects, Schultz et al[3] reported a dose-normalized tyramine AUC of 1.3 ± 0.6 nmole•h/L per 1-mg dose. This is equivalent to 36 ± 16 ng•h/mL for a 200-mg dose and is within two standard deviations of the mean AUC_T (25.1 ± 10.17 ng•h/mL) or mean AUC_∞ (28.0 ± 9.85 ng•h/mL) observed in this study. The maximum concentrations of tyramine observed when 200 mg was administered after an overnight fast in this study ranged from 13.6 to 85.7 ng/mL and were comparable to the range of 20 to 50 ng/mL reported by Korn et al[14] when 200 mg was administered 1 hour after placebo to fasted subjects.

The oral clearance of tyramine was 135 ± 55.4 L/min based on serum concentrations. This very high clearance is consistent with the expected high first-pass elimination of tyramine by gut wall and hepatic MAO. A large first-pass elimination of oral tyramine was also expected based on the much higher doses of tyramine required to produce a pressor response when it was administered orally compared to intravenously. For example, Korn et at[14] reported a pressor response after 4.1 ± 0.4 mg (mean ± *SEM*) tyramine administered intravenously but a negligible response after a 200-mg oral dose (in the absence of any other drug treatment), consistent with an oral bioavailability of less than 2%.

The effect of administration of tyramine during a meal was to decrease systemic exposure by 53%. This corresponds closely to the reported 2.13-fold decrease in tyramine AUC (no specific AUC values were reported) when administered with a meal compared to a fasting state.[14] These observations were made during treatment of healthy volunteers with moclobemide. The same investigators reported maximum concentrations of tyramine administered to subjects treated with moclobemide. The median maximum concentration was 54 ng/mL after 200 mg tyramine administered during a fast. It was much lower at 26 ng/mL after the same dose administered with a meal. Similar effects of food on the bioavailability of oral tyramine can be inferred from the work of Berlin et al,[8] who demonstrated that 2.8 times higher oral tyramine doses were required to produce the same pressor response in the fed versus the

fasted state. Overall, these results demonstrate that there is a greater margin of safety in clinical practice regarding the potential for an acute hypertensive reaction to MAO inhibitors than may be demonstrated from tyramine challenges performed in the fasted state. The present study also supports this argument since tyramine exposure was reduced by 53% when the tyramine dose was administered during a meal.

When administered to fasting subjects, tyramine concentration reached a maximum of 37.7 ± 26.0 ng/mL between 20 minutes and 1 hour after the dose and then decreased rapidly with a median half-life of 0.533 hours. Thus, by 2 hours after the dose, the concentrations had decreased to 2.84 ± 1.19 ng/mL. When administered during a meal, tyramine reached a maximum concentration of 8.23 ± 9.13 ng/mL between 0.5 and 4 hours, and by 2 hours after the dose, the average concentration was 2.10 ± 0.63 ng/mL, which is very similar to that observed 2 hours after tyramine was administered to fasting subjects. Systemic exposure to tyramine was delayed when it was administered during a meal, as indicated by the observed lag time (median 0.750 h vs. 0 h) ($p = 0.0156$). It is possible that the longer apparent elimination half-life observed when tyramine was administered during a meal was a result of prolonged absorption rather than an effect on elimination. There was no statistically significant change in the MRT of tyramine administered during a meal. This may have been a result of the low power of the test since paired data were available in only 5 subjects. However, the time from the first to the last quantifiable concentrations of tyramine showed no trend to be longer when tyramine was administered during a meal. It ranged from 1.83 to 2.83 hours when tyramine was administered after an overnight fast and from 1.5 to 3.25 hours when tyramine was administered during a meal.

The results of this study provided explicit measures of tyramine pharmacokinetics and the effect of administration with a meal. The results are consistent with what can be inferred from reports of tyramine pressor response studies. The high oral clearance of tyramine corresponds to low oral bioavailability and the potential for increased exposure when the enzymes responsible for first-pass metabolism are inhibited. Systemic exposure to tyramine administered with a meal was decreased by approximately half. Therefore, systemic exposure to tyramine from foods is expected to be lower by approximately half compared to that obtained when tyramine is administered to fasting subjects in an experimental situation.

The tyramine serum samples were assayed at Pharmakinetics Laboratories, Baltimore, Maryland.

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