■ CLINICAL INVESTIGATIONS

Effects of Low-flow Sevoflurane Anesthesia on Renal Function

Comparison with High-flow Sevoflurane Anesthesia and Low-flow Isoflurane Anesthesia

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Background: The safety of low-flow sevoflurane anesthesia, during which $CF_2=C(CF_3)-O-CH_2F$ (compound A) is formed by sevoflurane degradation, in humans has been questioned because compound A is nephrotoxic in rats. Several reports have evaluated renal function after closed-circuit or low-flow sevoflurane anesthesia, using blood urea nitrogen (BUN) and serum creatinine as markers. However, these are not the more sensitive tests for detecting renal damage. This study assessed the effects of low-flow sevoflurane anesthesia on renal function using not only BUN and serum creatinine but also creatinine clearance and urinary excretion of kidney-specific enzymes, and it compared these values with those obtained in high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia.

Methods: Forty-eight patients with gastric cancer undergoing gastrectomy were studied. Patients were randomized to receive sevoflurane anesthesia with fresh gas flow of 1 l/min (low-flow sevoflurane group; n = 16) or 6–10 l/min (high-flow sevoflurane group; n = 16) or isoflurane anesthesia with a fresh gas flow of 1 l/min (low-flow isoflurane group; n =

16). In all groups, the carrier gas was oxygen/nitrous oxide in the ratio adjusted to ensure a fractional concentration of oxygen in inspired gas (FiO_2) of more than 0.3. Fresh Baralyme was used in the low-flow sevoflurane and low-flow isoflurane groups. Glass balls were used instead in the high-flow sevoflurane group, with the fresh gas flow rate adjusted to eliminate rebreathing. The compound A concentration was measured by gas chromatography. Gas samples taken from the inspiratory limb of the circle system at 1-h intervals were analyzed. Blood samples were obtained before and on days 1, 2, and 3 after anesthesia to measure BUN and serum creatinine. Twenty-four–hour urine samples were collected before anesthesia and for each 24-h period from 0 to 72 h after anesthesia to measure creatinine, N-acetyl-β-D-glucosaminidase, and alanine aminopeptidase.

Results: The average inspired concentration of compound A was 20 ± 7.8 ppm (mean $\pm$ SD), and the average duration of exposure to this concentration was 6.11 ± 1.77 h in the low-flow sevoflurane group. Postanesthesia BUN and serum creatinine concentrations decreased, creatinine clearance increased, and urinary N-acetyl-β-D-glucosaminidase and alanine aminopeptidase excretion increased in all groups compared with preanesthesia values, but there were no significant differences between the low-flow sevoflurane, high-flow sevoflurane, and low-flow isoflurane groups for any renal function parameter at any time after anesthesia.

Conclusions: The only difference between the low-flow and high-flow sevoflurane groups was compound A formation, and postanesthesia laboratory data showed no significant effects of compound A formation during sevoflurane anesthesia on renal function. No significant effects on renal function were observed in either the low-flow or high-flow sevoflurane groups compared with the low-flow isoflurane group. (Key words: Anesthetic system: low-flow circuit. Anesthetics, volatile: sevoflurane; isoflurane. Carbon dioxide, absorption: Baralyme. Kidney: nephrotoxicity; urinary excretion of enzymes.)

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SEVOFLURANE has been administered to more than 10 million persons worldwide. However, most of the clinical data on this anesthetic agent were obtained with high fresh gas flow rates (greater than 3 l/min), and there have been few reports concerning low fresh gas flow rates.[1–4]

Sevoflurane reacts with soda lime and generates several degradation products.[5] Five degradation products of sevoflurane have been identified *in vitro*.[6] Among these, $CF_2=C(CF_3)-O-CH_2F$ (compound A) has been reported to be nephrotoxic in rats.[6-9] The compound A concentration in the anesthesia circuit is higher in low-flow sevoflurane anesthesia, at a flow rate of 1 l/min, than in relatively high-flow anesthesia, at a flow rate of 3 or 6 l/min.[10] Thus there has been some controversy regarding the safety of low-flow sevoflurane anesthesia.[11] Several reports have evaluated clinical laboratory data in closed-circuit or low-flow sevoflurane anesthesia, and no patients have shown evidence of renal dysfunction as assessed by blood urea nitrogen (BUN) and serum creatinine values.[1-4] However, these studies did not use more sensitive tests, such as measurement of the urinary excretion of kidney-specific enzymes, to detect renal damage.[12-14] Sevoflurane was recently marketed in the United States, and the Food and Drug Administration has stated that, due to limited clinical experience with sevoflurane in low-flow systems, fresh gas flow rates less than 2 l/min in a circle absorber system are not recommended.

This study examined the effects of low-flow sevoflurane anesthesia on renal function in patients having surgery. We measured not only BUN and serum creatinine concentration but also creatinine clearance and the urinary excretion of kidney-specific enzymes in low-flow sevoflurane anesthesia, and we compared these values with those obtained in high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. We also measured compound A concentrations during low-flow and high-flow sevoflurane anesthesia.

Materials and Methods

The study was approved by our institution's committee on human research, and informed consent was obtained from all patients. The study group included 48 patients categorized as American Society of Anesthesiologists physical status class 1 or 2 who had gastric cancer and were scheduled for gastrectomy. Patients in whom the medical history, laboratory data, or physical examination showed evidence of abnormal hepatic or renal function or severe cardiovascular disease were excluded from the study. Patients who received chemotherapy for cancer before or as much as 3 days after anesthesia were also excluded. Patients were randomly selected to receive low-flow sevoflurane anesthesia (low-flow sevoflurane group; n = 16), high-flow sevoflurane anesthesia (high-flow sevoflurane group; n = 16), or low-flow isoflurane anesthesia (low-flow isoflurane group; n = 16).

Fresh Baralyme (Allied Healthcare Products, St. Louis, MO) was placed in the canister in the low-flow sevoflurane and low-flow isoflurane groups immediately before the anesthetics were administered. Instead of carbon dioxide absorbent, glass balls were placed into the canister in the high-flow sevoflurane group. The anesthesia machine used was a Modulus CD Anesthesia System (Ohmeda, Madison, WI).

Patients were premedicated with 50 mg hydroxyzine and 0.5 mg atropine injected intramuscularly 45 min before anesthesia was induced. After administration of 100% oxygen for several minutes, anesthesia was induced by 4 or 5 mg/kg thiopental and 0.10–0.15 mg/kg vecuronium. After tracheal intubation, the fresh gas flow rate was set to 1 l/min in the low-flow sevoflurane and low-flow isoflurane groups and to 6–10 l/min in the high-flow sevoflurane group. In the high-flow sevoflurane group, the fresh gas flow rate was adjusted so that rebreathing did not occur (inspired carbon dioxide concentration = 0). The ratio of the oxygen to nitrous oxide flow rates was adjusted to maintain the oxygen concentration in the inspiratory limb at more than 30%. The anesthetic concentration was adjusted to maintain systolic blood pressure within 20% (±) of baseline. The lungs were ventilated mechanically with a tidal volume of 10–12 ml/kg, with the ventilatory rate adjusted to maintain an end-tidal carbon dioxide concentration (partial pressure) of 30–40 mmHg. Postoperative antibiotics were restricted to 2 g/day of cefotiam hydrochloride for as long as 3 days after anesthesia.

During anesthesia, the end-tidal carbon dioxide concentration and the inspired and end-tidal anesthetic concentrations were monitored by mass spectrometry (Medical Gas Analyzer 1100; Perkin Elmer, Pomona, CA). The mass spectrometer was calibrated using known concentrations of sevoflurane and isoflurane that were verified by calibration with a gas chromatograph (model GC-9A; Shimadzu, Kyoto, Japan).

The concentration of compound A in the inspiratory limb of the circle system was measured using a gas chromatograph (model GC-9A, Shimadzu) equipped with a gas sampler (model MGS-5, Shimadzu). Samples were drawn from the circuit at 1-h intervals throughout the period of anesthesia into a gas-tight syringe. The temperature of a glass column with a length of 5 m and an internal diameter of 3 mm packed with 20% dioctyl

phthalate on a Chromosorb WAW (Technolab S.C. Corp., Osaka, Japan) 80/100 mesh was maintained at 100°C. The temperature in the injection port was maintained at 140°C. A carrier stream of nitrogen flowing at 50 ml/min was delivered through the column to a hydrogen flame ionization detector.

Blood samples were obtained before and on days 1, 2, and 3 after anesthesia to measure BUN and serum creatinine. Twenty-four–hour urine samples were collected before anesthesia and for each 24-h period from 0 to 72 h after anesthesia to measure creatinine, N-acetyl-β-D-glucosaminidase (NAG), and alanine aminopeptidase (AAP) concentrations. Urinary NAG and AAP activity (units/l) were determined colorimetrically using a commercially available method (Shionogi & Co., Osaka, Japan). N-acetyl-β-D-glucosaminidase and AAP activity were expressed in relation to creatinine. The normal range of NAG and AAP activity was less than 6.3 and 1.4 to 12 U/g creatinine, respectively.

Measured values are expressed as means ± standard deviation. The minimum alveolar anesthetic concentration (MAC) hour exposure was calculated as the product of inspired anesthetic concentration and duration of exposure, determined at 5-min intervals. Values of 1.71% and 1.15% MAC were used for sevoflurane and isoflurane, respectively.[15,16] Intergroup comparison of patient characteristics, anesthesia time, MAC hour, and maximum compound A concentration was performed using one-way analysis of variance with Fisher's test of protected least significant difference. Inter- and intragroup comparisons of laboratory data were performed using two-way repeated measures analysis of variance. A probability value less than 0.05 was considered significant.

Results

There were no significant differences in age, height, body weight, anesthesia time, or MAC hour exposure among the study groups (table 1).

In the low-flow sevoflurane group, the individual maximum concentration of compound A [CF_2=$C(CF_3)$-O-CH_2F] was 28.8 ± 11.1 ppm (range, 12.2 to 46.5; table 1). In the high-flow sevoflurane group, the concentration was 0.3 ± 0.1 ppm (range, 0.2 to 0.5; $P < 0.01$; table 1). The average inspired concentration of compound A was 20.0 ± 7.8 ppm (range, 9.2–35.9), and the average duration of exposure to this concentration was 6.11 ± 1.77 h (range, 3.68–9.47) in the low-flow

sevoflurane group, whereas the average inspired concentration of compound A was 0.2 ± 0.1 ppm (range, 0.1–0.4) and the average duration of exposure to this concentration was 5.90 ± 0.85 h (range, 4.70–7.93) in the high-flow sevoflurane group. In the low-flow sevoflurane group, the concentration of compound A measured at 1-h intervals was 26.5 ± 11.3 ppm 2 h after anesthesia and tended to decrease thereafter (fig. 1). In the high-flow sevoflurane group, the concentration of compound A measured at 1-h intervals was 0.3 ± 0.1 ppm at 1 h and remained at comparable levels thereafter (data not shown). The concentration of compound A measured at 1-h intervals was significantly higher in the low-flow sevoflurane group than in the high-flow sevoflurane group.

Blood urea nitrogen concentrations decreased after anesthesia in all three groups, and no significant differences were observed between the groups at any time after anesthesia (table 2). Serum creatinine concentrations decreased on postanesthesia day 3 in the low- and high-flow sevoflurane groups but not in the low-flow isoflurane group (table 2). There were no significant differences in serum creatinine concentrations between the groups. No patients in any of the three groups had BUN or serum creatinine concentration values higher than the upper limit of the normal range (BUN, 22 mg/dl; serum creatinine, 1.3 mg/dl). On postanesthesia day 1, only one patient in the low-flow isoflurane group had a serum creatinine concentration greater than 0.2 mg/dl, which is higher than the preanesthesia value. Creatinine clearance increased after anesthesia in all three groups, and there were no significant differences among the three groups (table 2). Twenty-four–hour urinary NAG and AAP excretion, expressed as U/g creatinine, also increased after anesthesia in all three groups, and no significant differences were observed on days 1, 2, and 3 among the groups (table 2).

Discussion

To evaluate the renal effects of low-flow anesthesia with sevoflurane, we performed low-flow sevoflurane anesthesia in patients having surgery and compared postanesthesia renal function against that of patients having surgery who received high-flow sevoflurane anesthesia or low-flow isoflurane anesthesia. When the renal effects of anesthetic agents and anesthesia methods are investigated in such patients, surgical invasion and the administration of postoperative medications

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Table 1. Patient Characteristics, Anesthesia Time, MAC Hour, and Compound A Concentration

	Low-flow Sevoflurane (n = 16)	High-flow Sevoflurane (n = 16)	Low-flow Isoflurane (n = 16)
Age (yr)	59 ± 10 (42–73)	64 ± 10 (36–76)	63 ± 11 (43–76)
Height (cm)	158.6 ± 12.7 (136.2–185.2)	156.8 ± 7.9 (140.5–173.1)	159.7 ± 7.1 (146.2–175.0)
Weight (kg)	54.9 ± 10.1 (33.8–67.0)	53.6 ± 8.0 (39.0–64.8)	54.7 ± 9.1 (37.5–74.1)
Anesthesia time (h)	6.11 ± 1.77 (3.68–9.47)	5.90 ± 0.85 (4.70–7.93)	6.33 ± 1.49 (3.13–8.75)
MAC hour	7.13 ± 2.22 (4.53–13.00)	6.36 ± 0.96 (4.21–7.72)	7.22 ± 1.55 (5.23–11.70)
Maximum compound A concentration (ppm)	28.8 ± 11.1* (12.2–46.5)	0.3 ± 0.1 (0.2–0.5)	— —

Values are mean ± SD (range).

MAC hour = minimum alveolar concentration (MAC) hour exposure.

* Significantly higher than high-flow sevoflurane group.

such as antibiotics may complicate interpretation of the results. Therefore, in this study, we compared three groups in whom all experimental conditions were identical except for the fresh gas flow rate and the anesthetic agent used. All patients had gastric cancer and underwent gastrectomy. Because postoperative antibiotics tend to affect renal function,[17,18] all patients received the same antibiotic at the same dose until 3 days after surgery. The delivered anesthesia dose, calculated as

MAC hour exposure, and the anesthesia time also did not differ among the three groups.

Postanesthesia laboratory tests were performed on days 1, 2, and 3. We chose this time frame because 1) in rat studies, the renal impairment caused by compound A became evident on day 1 after anesthesia, followed by recovery on the fourth day[7]; 2) in rat and human studies, elevation of urinary enzymes is not seen immediately after renal injury occurs, but rather after a delay of 12 to 48 h[19,20]; and 3) in the study of humans by Higuchi et al.,[21] a small elevation in NAG after sevoflurane anesthesia was observed on day 2. Thus we concluded that tests done on days 1, 2, and 3 after anesthesia should detect the presence or absence of renal injury caused by anesthetics.

Low-flow and high-flow sevoflurane anesthesia were compared because we thought that to assess the toxicity of compound A it was necessary to compare two groups of patients in whom all experimental conditions, other than the concentration of compound A in the circuit, were identical. In our study, we placed glass balls into the canister instead of carbon dioxide absorbent in the high-flow sevoflurane group to prevent the generation of degradation products. Thus this semiclosed circuit represented a non-rebreathing circuit in which there was no possibility of reaction between sevoflurane and carbon dioxide absorbent. Nevertheless, compound A was detected (although at minute concentrations) because sevoflurane in its commer-
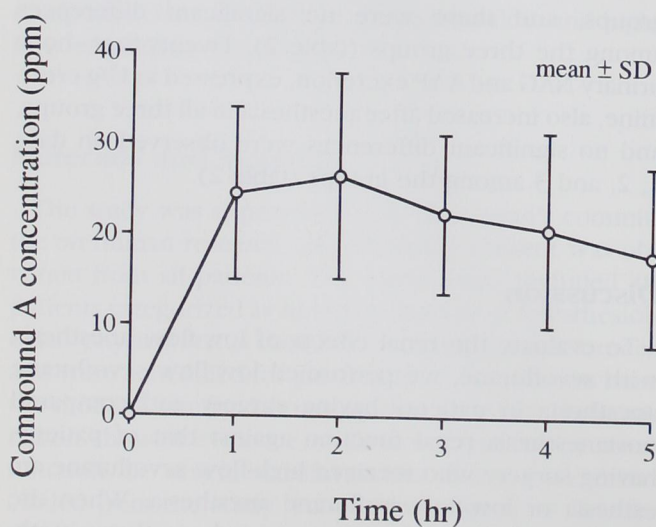

Fig. 1. Compound A concentrations in the low-flow sevoflurane group (n = 16 for 1 h, 2 h, and 3 h; n = 14 for 4 h; n = 12 for 5 h). Values shown are means ± standard deviation.

Table 2. Clinical Laboratory Values

	Group	Preanesthesia	Day 1	Day 2	Day 3
BUN (mg/dl)	Low-flow sevoflurane	14.7 ± 3.7	9.6 ± 2.9*	6.9 ± 2.6*	10.7 ± 4.1*
	High-flow sevoflurane	14.7 ± 3.0	10.7 ± 3.9*	8.6 ± 3.4*	12.1 ± 4.0*
	Low-flow isoflurane	13.2 ± 2.5	10.4 ± 3.5*	7.6 ± 2.5*	11.2 ± 4.3
Serum creatinine (mg/dl)	Low-flow sevoflurane	0.74 ± 0.18	0.68 ± 0.15	0.66 ± 0.16	0.59 ± 0.18*
	High-flow sevoflurane	0.79 ± 0.15	0.71 ± 0.14	0.70 ± 0.14	0.64 ± 0.13*
	Low-flow isoflurane	0.72 ± 0.13	0.72 ± 0.22	0.64 ± 0.16	0.60 ± 0.11
Creatinine clearance (ml/min)	Low-flow sevoflurane	97 ± 28	123 ± 44	147 ± 52*	127 ± 58
	High-flow sevoflurane	92 ± 16	118 ± 31*	121 ± 28*	105 ± 25
	Low-flow isoflurane	92 ± 19	140 ± 39*	134 ± 41*	114 ± 34
Urinary NAG (U/g creatinine)	Low-flow sevoflurane	2.3 ± 1.6	4.6 ± 4.1	6.4 ± 8.2	8.4 ± 6.9*
	High-flow sevoflurane	3.1 ± 2.0	7.8 ± 7.8	6.0 ± 5.5	10.8 ± 8.3*
	Low-flow isoflurane	2.8 ± 1.6	5.9 ± 3.7	10.5 ± 9.4*	10.1 ± 8.1*
Urinary AAP (U/g creatinine)	Low-flow sevoflurane	6.3 ± 3.3	13.2 ± 13.7	12.2 ± 11.4	19.9 ± 12.6*
	High-flow sevoflurane	7.2 ± 3.4	13.2 ± 9.7	14.7 ± 12.0*	21.0 ± 13.0*
	Low-flow isoflurane	7.1 ± 3.3	12.8 ± 11.4	17.5 ± 14.5*	16.8 ± 8.8*

Values are mean ± SD.

BUN = blood urea nitrogen; NAG = N-acetyl-β-D-glucosaminidase; AAP = alanine aminopeptidase.

* Significantly different from preanesthesia value ($P < 0.05$).

cially available form contains 13 or 14 ppm of compound A (personal oral communication, Nobukatsu Satoh, Managing Director, Central Research Laboratories, Maruishi Pharmaceutical Co., June 1996).

However, the differences in compound A concentrations in the anesthesia circuit between the low-flow and high-flow sevoflurane groups were clear, and thus comparison of these two groups was considered adequate for evaluating the effects of compound A on renal function.

We also compared sevoflurane with isoflurane anesthesia because isoflurane is a volatile anesthetic agent that has enjoyed a good safety record for more than 15 yr. Higuchi et al.[21] compared postanesthesia urinary NAG values after sevoflurane and isoflurane anesthesia in high-flow systems and reported that postanesthesia urinary NAG values were three times higher for the sevoflurane group with high serum fluoride concentration ($> 50 \mu$M) than for the isoflurane group. This difference was attributed primarily to a single patient and was not generally considered to be clinically significant. This observation suggests that urinary NAG may be elevated after sevoflurane anesthesia even at high fresh gas flow rates. Therefore, we thought it necessary to confirm whether sevoflurane alone causes renal dysfunction by comparing it with isoflurane. In the present

study, isoflurane anesthesia was performed using a low-flow system. The reasons for this were 1) to permit comparison with low-flow sevoflurane anesthesia, a fresh gas flow rate of 1 l/min was used in both groups to minimize the differences in experimental conditions between the groups; and 2) because isoflurane rarely reacts with carbon dioxide absorbent, low-flow isoflurane anesthesia can be administered without problems.[22,23]

In our previous study of low-flow sevoflurane anesthesia using Baralyme as the carbon dioxide absorbent, the compound A concentration was 32.0 ± 2.3 ppm (range, $23.5 - 41.3$),[24] which is similar to that observed in the present study. When Baralyme is used as the carbon dioxide absorbent, the concentration of compound A is higher than that obtained with soda lime.[1,24] Therefore, because Baralyme was used in this study, the difference in compound A concentrations between the low-flow sevoflurane group and the high-flow sevoflurane group was probably greater than would have been the case if soda lime had been used.

The median lethal concentration of compound A in rats is 331 ± 7 ppm for a 3-h exposure, 203 ± 4 ppm for a 6-h exposure, and 127 ± 9 ppm for a 12-h exposure, and severe renal damage is observed.[7,8] Morphologic abnormalities are seen in rats after exposure to

50 ppm of compound A for 3 h.[7] In the present study, the average compound A concentration was 20.0 ± 7.8 ppm, and the duration of exposure was 6.11 ± 1.77 h, which is less than the median lethal concentration in rats but close to the value that causes morphologic abnormalities. Although compound A is a dose-dependent nephrotoxin in rats, the mechanism is controversial,[25-28] and the nephrotoxicity caused by compound A formation during low-flow sevoflurane anesthesia has not been established in humans. The Food and Drug Administration has stated that, due to limited clinical experience with sevoflurane in low-flow systems, fresh gas flow rates less than 2 l/min in a circle absorber system are not recommended.

Several studies have reported that low-flow sevoflurane anesthesia is not associated with abnormalities in renal function as assessed by routine laboratory tests,[1-4] but further research is still needed. The conclusions of previous studies were based only on clinical laboratory tests on blood samples (BUN and serum creatinine). In this study, not only were tests on blood samples performed but creatinine clearance and the urinary excretion of kidney-specific enzymes (NAG and AAP) were also evaluated. Urine testing for the enzymes that are present in the renal tubular cells is used to assess the nephrotoxicity of drugs or to investigate the pathophysiologic characteristics of renal dysfunction.[12-14] In the present study, BUN and creatinine concentrations did not increase after anesthesia compared with values before anesthesia, but NAG and AAP values did increase. However, the increases in NAG and AAP were observed in all three groups, with no significant differences observed among the three groups, and these postanesthesia values were not sufficiently high to indicate clinically significant renal dysfunction.[17,29] Therefore, with regard to the compound A concentrations and exposure times during low-flow sevoflurane anesthesia as performed in the present study, there was no evidence of renal injury, at least compared with high-flow sevoflurane and low-flow isoflurane anesthesia.

Higuchi *et al.*[21] reported that postanesthesia NAG values were significantly higher after sevoflurane anesthesia than after isoflurane anesthesia, which does not correspond with our results. The differences between our experimental methods and those of Higuchi *et al.* are as follows: 1) We studied patients having gastrectomy, whereas Higuchi *et al.* studied patients having peripheral orthopedic surgery; 2) we used a low-flow system (1 l/min), whereas Higuchi *et al.* used a high-flow system (6 l/min), resulting in a lower inhaled compound

A concentration in their study; and 3) we used nitrous oxide concomitantly, whereas Higuchi *et al.* did not, resulting in a higher inhaled anesthetic concentration in their study. However, it is not clear how these differences led to the observed differences in results.

In conclusion, the effects of low-flow sevoflurane anesthesia on renal function in patients having gastric resection, as assessed by conventional renal function tests and highly sensitive tests to detect renal cellular injury, were similar to those of high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. Blood urea nitrogen and creatinine concentrations did not increase, and creatinine clearance did not decrease after anesthesia compared with values before anesthesia, but NAG and AAP did increase. However, these increases in NAG and AAP were similar in all groups and not clinically significant. Low-flow sevoflurane anesthesia did not show evidence of renal injury compared with high-flow sevoflurane or low-flow isoflurane anesthesia.

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