Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 1229–1235 doi:10.1111/j.1365-2044.2009.06081.x

APPARATUS

Assessing the clinical or pharmaco-economical benefit of target controlled desflurane delivery in surgical patients using the Zeus® anaesthesia machine*

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Summary

The Zeus® anaesthesia machine includes an auto-control mode which allows targeting of end-tidal volatile and inspired oxygen concentrations. We assessed the clinical benefits and economic impact of this target-controlled anaesthesia compared with conventional manually controlled anaesthesia. Eighty patients were randomly assigned to receive desflurane either with a fresh gas flow set by the anaesthetist or in auto-control mode. Drug delivery was adjusted to maintain bispectral index between 40–60 units and systolic arterial pressure under 15 mmHg above its pre-induction value (upper limit) and over 90 mmHg (lower limit). Blood pressure was maintained in the desired range for 89% and 91% of the maintenance period for auto-control and manual control respectively ($p = 0.49$). Bispectral index was in the desired range for 82% and 79% of the maintenance period, for auto-control and manual control respectively ($p = 0.46$). Oxygen consumption was more than halved by the use of auto-control mode, and mean (SD) desflurane consumption during surgery was 0.07 (0.04) vs 0.2 (0.07) $ml.min^{-1}$ in auto-control and manual control respectively ($p < 0.0001$). The number of drug delivery adjustments per hour was significantly lower in auto-control mode (mean (SD) 7 (2) vs 15 (12); $p < 0.0001$). Thus, the auto-control mode provided similar haemodynamic stability and bispectral control as did conventional manually controlled anaesthesia, but led to a reduction in gas and vapour consumption with a more clinically acceptable workload.

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**This work was presented in part at the American Society of Anesthesiologists annual meeting in Atlanta, USA, October 2005.*
Accepted: 27 July 2009

Economic and environmental concerns have led to the development of semi-closed circuits for delivery of volatile anaesthetics in which a significant proportion of the volatile anaesthetic mixture is re-breathed [1], resulting in a difference between delivered and inspired concentrations depending on the fresh gas flow (FGF). At some times during a case, a high FGF is needed to enable rapid control of end-tidal anaesthetic concentrations (at the cost of greater expense and environmental pollution) and at other times a low FGF is acceptable when end-tidal concentrations are stable over sustained periods [2].

Several anaesthesia machines have emerged which offer algorithms for automatic closed-loop control of the end-tidal concentration [3]. The Zeus® anaesthesia machine (Dräger Medical, Lübeck, Germany) includes a blower-driven ventilator, an electronically-controlled gas and vapour delivery system and a servo-controlled valve system. Gas and vapour delivery can be controlled either manually (manually controlled anaesthesia, 'MCA') for conventional low and minimal flow anaesthesia or in a so-called 'auto-control mode' where the fresh gas flow and its composition are automatically adapted to the patient's uptake for both O_2 and volatile agent. The anaesthetist

initially sets a target end-tidal concentration and then manually adjusts this target according to the patient's needs. The inspired and expired concentrations are measured by sidestream infra-red technology and paramagnetic O_2 sensors. The sample gas flow is fed back to the system, so that the system is completely 'closed'. In addition, the fresh gas mixture is servo-controlled in order to keep the inspired O_2 concentration at the targeted level and to maintain a constant ambient pressure at the end of expiration in the manual breathing bag. If this pressure declines, FGF is automatically increased in response; conversely if the pressure rises, FGF is reduced. Thus, at steady state, there is little or no gas waste, typical of a closed system. As a consequence of this closed system, with a stable O_2 concentration, fresh O_2 flowing into the system can be regarded as a surrogate for the patient's O_2 consumption.

In the Zeus® machine, volatile anaesthetic is delivered by pure vapour injection, which facilitates an increase in concentration without the need to increase FGF. The amount delivered is calibrated to achieve the desired end-tidal concentration in < 3 min without overshoot, based on a pharmacokinetic model which includes a functional residual capacity estimate calculated from the patient's height and weight. For safety, the volatile agent concentration in the circuit is limited to inspired levels that are no higher than those obtainable with traditional vaporisers. The safety system uses independent sidestream sensors to measure the inspired volatile agent and inspired O_2 concentrations. This Target Controlled Anaesthesia® (TCA), is expected to

1 Minimise the time required to achieve a desired end-tidal anaesthetic concentration,
2 Reduce overshoot and fluctuations,
3 Reduce gas and vapour consumption and
4 Reduce the number of adjustments needed – all in a similar manner to target controlled infusion (TCI) for intravenous agents.

These expectations have been confirmed in vitro: TCA achieved equilibration as fast as conventional manual delivery with a high FGF, but without overshoot, and markedly reduced volatile agents consumption [4]. However, TCA performance has not been assessed in a clinical setting. This prospective randomised study was therefore conducted to assess the efficiency of desflurane TCA compared with manually controlled (MCA) low flow delivery during anaesthesia and to quantify the corresponding drug consumption and workload for the anaesthetist.

Methods

Following Institutional Review Board approval and written informed consent, 80 adult patients scheduled for major abdominal or urological procedures of > 1 h duration in two hospitals were included. Eligible patients were aged 18–75 years and had an American Society of Anesthesiologists (ASA) status 1 or 2. Patients were excluded if they received opioids before surgery, if they had a contra-indication to receive one of the components of the anaesthesia protocol, or if they had neurological disorders that would interfere with the interpretation of electroencephalographic (EEG) monitoring (such as previous stroke or psychiatric disorders requiring the use of psychoactive drugs, slowing baseline EEG).

Patients were randomly assigned to receive desflurane for anaesthesia maintenance using the Zeus® anaesthesia machine (Dräger Medical, software version 3.08) either by MCA or TCA, with or without N_2O (i.e. four groups). As one centre was doing mainly urology and the other gynaecological and bowel surgery, the randomisation list was stratified by centre to include a similar number of patients for each type of surgery in each randomisation group. All randomisation was done by the data centre of Institut Gustave Roussy using minimisation with a probability of allocating the treatment that minimises the imbalance of 100%. Advised by our ethics committee, we used an online, central randomisation service (http://tenalea.net), currently in deployment phase with a grant (grant number LSHC-CT-510736) from the e-TEN program of the European Union (http://ec.europa.eu/information_society/activities/eten).

Clinical protocol

The systolic arterial pressure (SAP) measured on the eve of surgery was used as the individual baseline value throughout the study. All patients received 1 $mg.kg^{-1}$ hydroxyzine orally 1 h before induction of anaesthesia.

Monitoring included electrocardiogram, non-invasive arterial pressure, heart rate, pulse oximetry, temperature and neuromuscular blockade (train of four). In addition, EEG bispectral index (BIS-XP™, A2000 monitor; Aspect Medical Systems, Natick, MA, USA) was used to estimate hypnosis. All patients had a warming blanket to maintain a body temperature > 36 °C throughout surgery. Desflurane consumption was recorded from the integrated Zeus® delivery system [4].

Anaesthesia was induced with thiopentone (5–8 $mg.kg^{-1}$), atracurium (0.5 $mg.kg^{-1}$) or cisatracurium (0.2 $mg.kg^{-1}$), and a remifentanil effect-site TCI (Base Primea™; Fresenius, Brezins, France, Minto's pharmacokinetic model [5]) set at an initial target concentration of 5 $ng.ml^{-1}$. This target was decreased after tracheal intubation to 1 $ng.ml^{-1}$ up to 1 min before incision when it was set at 2 $ng.ml^{-1}$.

After tracheal intubation, the patient's lungs were ventilated with the Zeus® in volume-controlled mode in

order to maintain an end-tidal CO_2 between 4–4.7 kPa, with O_2/N_2O in half of the patients in each group, and O_2/air in the other half, with an inspired O_2 concentration of 50%.

Desflurane administration was started immediately after intubation, in TCA or MCA mode according to the randomisation group, to achieve an initial end-tidal concentration of 4%.

Thereafter, end-tidal concentration of desflurane and remifentanil target concentration were adjusted every 5 min throughout the procedure in order to maintain the BIS value between 40 and 60 units and the SAP between 90 mmHg and baseline value plus 15 mmHg. Blood and fluid losses were compensated according to clinical needs.

Protocols for control of desflurane in the two groups

The adjustment rules for desflurane were as follows. In the TCA group, the desired end-tidal concentration was simply set on the Zeus® machine (i.e., only one setting had to be made) and volatile agent delivery and fresh gas mixture were automatically calculated by the Zeus®. The minimum FGF needed to maintain the desired inspired O_2 concentration of 50% was delivered ('uptake mode').

In MCA group, the adjustments were made by the anaesthetist on both the delivered desflurane concentration and the total FGF (with a minimum value of 1 $l.min^{-1}$). The adjustment rule to achieve a chosen end-tidal concentration of desflurane as fast as possible was based on a pilot study performed in one centre [6] and on a recommendation given by Coetzee in closed circuit [7]. Thus, to increase the end-tidal concentration of desflurane, the delivered desflurane concentration was set at 18% without modifying the FGF (1 $l.min^{-1}$). When the desired value was reached, the delivered desflurane concentration was decreased to this value (meaning that two adjustments had to be made by the anaesthetist for each increase in desflurane concentration). Conversely, to decrease the end-tidal concentration of desflurane, the delivered desflurane concentration was set at the desired value, and the FGF was increased to 8 $l.min^{-1}$ and then decreased again to 1 $l.min^{-1}$ when the desired end-tidal concentration of desflurane value was reached (meaning that three settings had to be made by the anaesthetist for each decrease in desflurane concentration).

Protocols for adjustments of remifentanil and neuromuscular blockade

Adjustments for remifentanil were made by changing the target on the TCI pump. The amplitude of each change for end-tidal desflurane concentration and remifentanil target concentration was at the discretion of the physician in charge of the patient.

During maintenance, adequate neuromuscular blockade was maintained and guided by regular assessments of the response to train-of-four stimulation at the adductor pollicis.

Protocols for analgesia

Forty-five to sixty minutes before the expected end of surgery, intravenous morphine 0.1 $mg.kg^{-1}$, paracetamol 1 g, tramadol 100 mg and ondansetron 4 mg were administered. During skin closure, at 25% recovery of the first response to train-of-four stimulation, neuromuscular blockade was reversed by neostigmine (40 $\mu g.kg^{-1}$) and atropine (15 $\mu g.kg^{-1}$).

Recovery

At the end of skin closure, the remifentanil infusion was stopped without any modification of the desflurane end-tidal concentration. When the predicted remifentanil effect site concentration reached 1 $ng.ml^{-1}$, ventilation was switched to pressure support mode. When efficient spontaneous ventilation was achieved (tidal volume > 250 ml and respiratory rate > 6 min^{-1}), the respiratory rate was considered as a criterion of adequate analgesia [8]. If the respiratory rate was above 16 $breaths.min^{-1}$, 3 mg morphine i.v. boluses were administered every 5 min. If the respiratory rate was under 16 $breaths.min^{-1}$, desflurane was discontinued as well as N_2O if appropriate and the patient received pure O_2. In the MCA group, the circuit was opened to 10 $l.min^{-1}$. The tracheal tube was removed as soon as the patient was able to respond to simple orders and the train-of-four ratio was superior to 0.9.

Data recording

Variables including delivered, inspired and expired breathing gas composition, fresh gas flow, ventilator settings, remifentanil target and predicted concentrations as well as infusion rate, BIS and haemodynamic monitoring, were recorded online on a computer using RUGLOOP™ software (T. De Smet and M. Struys, http://www.demed.be).

Clinical end-points such as the start of thiopental injection, intubation, incision, end of surgery, resumption of spontaneous ventilation, eyes opening and removal of tracheal tube were marked online on the recorded file.

Data analysis

The intra-operative data were limited to the time when desflurane was administered (maintenance). This period was studied both globally and as two distinct phases: from

intubation to incision (pre-incision period) and from incision to end of desflurane administration (surgery).

The primary end-points were the median fractions of time spent in the desired BIS and SAP range. Secondary end-points were:

1 The delay in achieving the desired level of anaesthesia. At induction, this delay was assessed by the time necessary to achieve an end-tidal concentration of desflurane of 4% and the magnitude of overshoot. At recovery, the delay in achieving the desired level (i.e. the recovery from anaesthesia) was assessed by the time from end of desflurane delivery to eyes opening and removal of tracheal tube.
2 The work load as indicated by the number of anaesthetic drug delivery setting adjustments per hour (for each of desflurane, fresh gas flow or remifentanil target concentration) and
3 The volatile agent and O_2 consumption.

Statistical analysis

Data are presented as mean (standard deviation, SD) or median [range] when normal distribution was not verified. A sample size of 40 in each group was calculated as having at least 80% power and an alpha risk of 5% to detect a difference in the concentration of anaesthetic time spent in the desired BIS and SAP range of 15% between TCA and MCA.

Differences in continuous variables between MCA and TCA mode with or without N_2O were first tested by analysis of variance (ANOVA), followed if statistically significant by protected *t*-test to compare groups of patients two by two, or by Kruskall–Wallis's nonparametric test as appropriate. The lack of difference in O_2 or desflurane consumption between N_2O vs air mixture allowed us to group these patients together and express only TCA vs MCA differences. A p value < 0.05 was considered to be significant.

Results

The patients' characteristics are described in Table 1. Groups were similar as regards age, body mass index, sex ratio, duration of anaesthesia and type of surgery. One centre mainly performed major urological procedures in middle-aged men and used cisatracurium, while the other mainly performed major intra-abdominal gynaecological procedures in rather younger women and used atracurium.

Time spent in the desired systolic arterial pressure (SAP) and BIS ranges

SAP remained in the desired range for 89% and 91% of the maintenance time (median values) for TCA and MCA groups respectively (p = 0.49). Bispectral Index was in the range 40–60 for 82% of the time in the TCA group and 79% of the time in the MCA group (p = 0.46). Both variables were in the desired range simultaneously for 75% and 74% of the study time for TCA and MCA respectively (p = 0.61). No difference was found between TCA and MCA groups or between N_2O and air mixture in the time spent in each BIS/SAP status.

Table 1 Patient characteristics and details of the procedures. Values are mean (SD) or number of patients.

	TCA groups *n* = 40	MCA groups *n* = 40
Age; years	55 (15)	55 (15)
Sex ratio; M/F	17/23	20/20
Body mass index; kg.m^{-2}	26 (5)	25 (5)
Baseline SAP; mmHg	133 (20)	133 (16)
Surgical procedure (urological/gynecological)	20/20	20/20
Duration of anaesthesia; min	219 (75)	226 (90)
Duration of surgery; min	190 (74)	195 (85)

TCA, target controlled anaesthesia; MCA, manually controlled anaesthesia; SAP, systolic arterial pressure.

Time to achieve the desired level of anaesthesia upon desflurane introduction and at recovery

There was no difference between the TCA and MCA groups as regards the time to reach the desired 4% end-tidal concentration of desflurane after its introduction (2.8 (1.2) min vs 3.0 (0.7) min respectively; p = 0.49). There was no statistically significant difference in overshoot between MCA and TCA groups: the maximum end-tidal concentrations of desflurane achieved were 4.6 (0.7)% vs 4.2 (0.2)% respectively (p = 0.07).

Time to eye opening and removal of tracheal tube from the end of desflurane and N_2O administration were similar in both groups (3.9 (2.9) min and 5.3 (2.8) min in the TCA group vs 4.6 (3.2) min and 6.0 (3.0) min in the MCA group; p = 0.29 and 0.27 respectively).

Anaesthetist workload

Far more adjustments per hour were necessary in the MCA group than in the TCA group (15.2 (11.6) vs 6.7 (2.5); p < 0.0001; Fig. 1). Conversely, the number of remifentanil target concentration adjustments per hour was not different (2.1 (1.5) with MCA vs 2.6 (1.5) with TCA; p = 0.18).

Drug requirements

TCA achieved considerable savings of all gases (O_2, N_2O) and volatile agent.

During surgery, desflurane consumption in the TCA group was reduced by 65% (0.07 (0.04) ml.min^{-1} in TCA vs 0.20 (0.07) in MCA; Fig. 2) Oxygen consumption

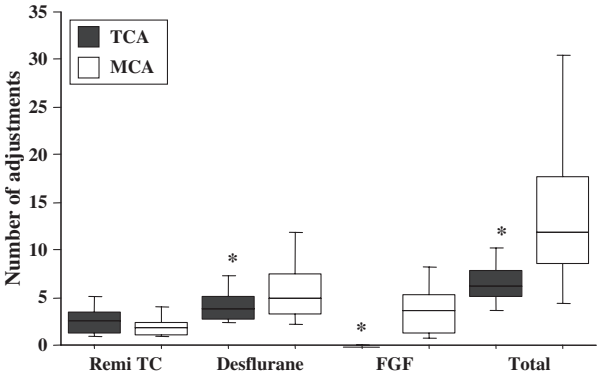

Figure 1 Number of adjustments made to drug delivery per hour of anaesthesia in the TCA group and the MCA group for: the target-controlled remifentanil (remi TC), desflurane, fresh gas flow (FGF), total. Results are presented as box plots. The lower edge of the box corresponds to the 25th percentile, the upper edge the 75th percentile, the horizontal line the median and the error bars display the 10th and 90th percentiles. *$p < 0.05$ compared with MCA group.

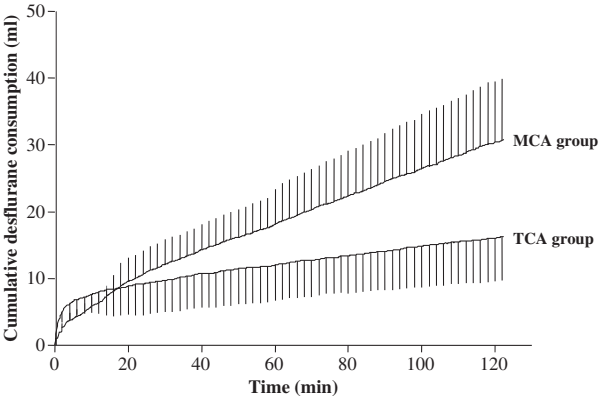

Figure 2 Mean (SD) cumulative desflurane consumption in ml for 40 patients/mode (for clarity, SD bars are displayed only every 2 min).

decreased by 65% (163 (51) vs 483 (78) $ml.min^{-1}$) and N_2O by more than 80% (118 (91) vs 637 (113) $ml.min^{-1}$; $p < 0.001$ for all three comparisons).

Remifentanil consumption was similar in both groups (0.10 (0.07) $\mu g.kg^{-1}.min^{-1}$ with TCA vs 0.08 (0.03) $\mu g.kg^{-1}.min^{-1}$ with MCA; $p = 0.17$).

Discussion

This study showed that both TCA and MCA offer good control over both BIS and blood pressure, but that TCA can achieve this with the additional benefit of a reduced drug consumption and workload. In the MCA group, the anaesthetist had to adjust settings on average every 4 min, compared with an adjustment every 10 min with TCA. This workload saving may be important in moments (e.g., critical incidents or crises) when the anaesthetist's attention is diverted elsewhere.

Our result that TCA did not reach a chosen target (i.e. the initial end tidal target of 4% desflurane) faster than MCA differs from the finding of Struys et al.'s [4] in vitro study, where TCA reached its target more than 1 min faster than did manual mode. However, Struys et al. simulated volatile anaesthetic uptake by a continuous, fixed sampling of the breathed mixture of 0.2 $l.min^{-1}$ and assumed a constant uptake over time and between patients, which is not true in clinical practice where uptake varies both in time (Fig. 2) and between patients. Other authors have described a model-based assisted sevoflurane delivery which reached a desired end-tidal target faster than classical fresh gas flow control delivery [9]. The difference between this and the Zeus® system is that the latter uses feedback control based on variables measured from the patient, rather than refer to a typical model. Nonetheless, comparison of efficacy between the Zeus® and the model-based methods would be interesting.

Like both Struys et al. [4] and Kennedy et al. [9], we could not demonstrate a significant difference in the magnitude of the initial overshoot between both delivery modes. This result may be due to an insufficient statistical power or because MCA was especially carefully executed in our study. Nevertheless, one of the expected advantages of the feedback control offered by TCA in clinical practice is to prevent a dangerous overshoot that may occur in MCA mode if the operator is distracted from drug delivery settings while overshooting the delivered concentration.

Despite tight adjustment rules, high and low BIS episodes lasting several minutes were observed in both groups. This may have been due to a delay to change ventilator settings, and might have been optimised by using a closed-loop system directly adjusted to BIS as has been described with isoflurane [10]. Another improvement might involve targeting desflurane to the effect site concentration, rather than simply to the end-tidal concentration because the time this agent takes to reach the brain from the alveoli induced a delay between changes in end-tidal concentration and corresponding changes in the brain as represented by BIS [11]. TCA control over hypnosis might be further improved by modeling alveolar to blood then to brain transfer and including it in the feed-back algorithm. Finally, as desflurane has the fastest equilibration rate, as represented by the percent fraction of alveolar:inspired ratio, sophisticated drug delivery systems as described in our study are probably less relevant to achieve a chosen target with this

drug than with more soluble volatile agents. In other words, one might expect a greater benefit of TCA on the control of volatile anaesthesia when using sevoflurane or isoflurane.

TCA appeared extremely cost effective: desflurane and O_2 consumption during surgery were halved and N_2O consumption was reduced to a fifth. Because of the initial wash-in phase, the benefit of TCA on total volatile consumption is likely negligible for short duration surgery and the longer the procedure lasts, the more cost-effective TCA is likely to be [12, 13].

The reduction of desflurane consumption in the TCA group appeared mainly due to large reductions in FGF, which minimised the amount of drug vented from the breathing system [7] and kept the desflurane consumption close to the patient's uptake [12]. This notion is supported by Struys et al. [4] who found that automatic FGF adjustment on uptake was the only setting which decreased significantly the volatile agent consumption. Conversely, when the minimal FGF was fixed at 1 or 3 $l.min^{-1}$, the volatile consumption was similar in TCA and MCA modes.

De Cooman et al. [13] have argued that FGF fixed at 0.7 $l.min^{-1}$ in MCA mode would decrease the volatile consumption below that obtained in TCA mode with the Zeus®. However, in their study, the desflurane end-tidal concentration chosen in the Zeus® TCA group was higher than the concentration chosen for MCA group, thus biasing their results in favour of the latter. Also, since they did not employ a BIS monitor, it was not possible to determine if a similar depth or quality of anaesthesia was achieved in both groups.

The measured O_2 delivery in TCA during periods of stable anaesthesia could be used as an upper bound estimate of the patient's O_2 consumption since it includes both metabolic O_2 consumption and leaks (albeit likely trivial) from the circuit. An O_2 flow < 0.5 $l.min^{-1}$ (i.e. FGF of 1 $l.min^{-1}$ with an inspired O_2 concentration of 50%) cannot therefore be recommended when the manual fresh gas flow control mode is used because O_2 consumption may exceed this value in some patients (in fact, five of our patients had an O_2 consumption > 400 $ml.min^{-1}$) thus increasing the risk of administrating a hypoxic mixture. It was for this reason that we used 0.5 $l.min^{-1}$ oxygen flow (i.e., FGF 1 $l.min^{-1}$) in manual control. This upper bound estimate is rather higher than reported in many physiological studies and there are possibly at least two reasons for the differences. First, many physiological studies that calculate O_2 consumption on a breath-by-breath basis use sophisticated corrections for nitrogen balance between inspired and expired gas and also estimate changes in lung volume within one breath; the Zeus® system does not use the same methods to calculate patient O_2 consumption. Second, physiological methods rigorously eliminate any leaks in the system (e.g., the volunteers breathe through tight mouthpieces and wear noseclips) while in clinical practice leaks are inevitable and indeed included in the Zeus® estimate of 'consumption' [14, 15]. Further studies on this topic are obviously required, but one may speculate that very low flow anaesthesia cannot be safely achieved without feedback control on the patient's O_2 consumption.

Our unblinded study design may have introduced some bias but we feel this bias was small as the adjustment algorithm was based on very precise values of BIS and arterial pressure measured every 5 min. Furthermore, the same anaesthetists (the three clinician authors, BLJ, VB, FS) were involved, thus reducing the risk of deviation from protocol.

It would be important to assess if the potential of the Zeus® system in reducing volatile agent and O_2 consumption and reducing anaesthetic workload is translated into significant cost savings or improved outcomes.

Conflicts of interest and acknowledgement

This work was supported by a grant from Dräger Medical. Two Zeus® machines were provided to the investigating centres. WB works for Dräger in charge of Zeus® machine development. V Billard and F Servin have received consulting fees from Dräger in 2005 and 2006.

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