(Acta Anaesth. Belg., 2021, 72, 159-165)

Which sevoflurane wash-in rates towards 1.0 MAC ensure adequate anesthetic depth after a standardized intravenous induction before surgical incision?

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Abstract: *Background:* After intravenous (IV) induction of anesthesia, inhaled agent wash-in has to be titrated in such a manner that the combined effects of this agent and remaining opioid and propofol continue to ensure loss of consciousness (LOC) prior to incision. We assessed the effect of different sevoflurane wash-in rates on anesthetic depth.

Methods: Anesthesia was induced with sufentanil (0.2 µg/kg), followed 4 min later by propofol (1-2 mg/kg, depending on age), and rocuronium (0.6 mg/kg) in 33 ASA PS I-III patients. After tracheal intubation, sevoflurane wash-in towards 1 age-adjusted minimal alveolar concentration (MAC) was controlled to occur exponentially with a time constant of 2.5, 5.0, or 11.1 min, depending on the anticipated time of incision: FAST, MEDIUM, or SLOW, respectively. The effect-site MAC (MACe), sufentanil effect site concentration (CeSuf), Noxious Stimulation Response Index, Bispectral Index (BIS), and Brice questionnaire defined 3 probabilities of LOC (PLOC): extremely high, i.e. MACe > 0.63 and CeSuf > 0.17 ng/mL or NSRI < 50 and BIS < 65; high, i.e. 50 < NSRI < 70 and BIS < 65 or NSRI < 50 and BIS > 65; and insufficient, i.e. NSRI > 50 and BIS > 65 or recall elicited by the Brice questionnaire.

Results: The end-expired sevoflurane concentration rose towards 1 MAC with a time constant (95% con-fidence interval) of 2.6 (2.6; 2.7), 5.7 (5.3; 6.2), and 10.9 (9.6; 12.6) min in groups FAST, MEDIUM, and SLOW, respectively. 0.63 MACe was reached at 9.8 [9.8; 9.8], 12.3 [12.3; 12.6], and 18.5 [18.3; 18.7] min (median and interquartile range), for groups FAST, MEDIUM, and SLOW, respectively, with CeSuf > 0.17 ng/mL at the moment 0.63 MACe was reached in all but 2 patients in group SLOW. Before reaching 0.63 MACe, PLOC was high to extremely high in group FAST and MEDIUM patients, but insufficient in group SLOW, even though the modified Brice questionnaire did not elicit any recall.

Conclusion: An exponential end-expired sevoflu-rane wash-in rate towards 1.0 MAC with a time constant ≤ 5.7 min but not ≥ 10.9 min ensures hypnosis after IV induction with propofol (1-2 mg/kg), preceded 4 min earlier by sufentanil (0.2 µg/kg). Integrating these patterns into automated low-flow target controlled algorithms may help optimize anesthetic agent delivery.

Keywords: pharmacokinetics; inhaled agents; sevoflurane; synergy; anesthetic depth.

Introduction

There are few or even no guidelines on how fast wash-in of the inhaled anesthetic should occur after intravenous induction of anesthesia. Target-controlled anesthesia machines like the Aisys (GE, Madison, WI, USA) and Zeus (Dräger, Lübeck, Germany) aim to reach the target end-expired partial pressure (FA) as fast as possible, while the FLOW-i®'s® automated gas control with low flow (AGC®, Getinge Group, Göteborg, Sweden) prompts the clinician to select 1 out of 8 wash- in rates ("speeds") with which to attain the FA target (1, 2). How can one make a rational selection? As long as the inhaled agent is the sole hypnotic used to ensure unconsciousness, its (routinely measured) FA can be used to assess anesthetic depth (3).

Unconsciousness is virtually guaranteed once the measured FA (at steady state) has reached 2 x MACawake, or 0.70 MAC (4). This threshold can be reduced to about 0.63 MAC in the presence of an opioid (equivalent to an effect-site concentration [Ce] of 2 ng/mL fentanyl) (5). But to assess the

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Paper submitted on May 24, 2021 and accepted on May 26, 2021.
Conflict of interest: None.
This work was presented at the 25th annual meeting of the International Society of Anaesthetic Pharmacology in Chicago, 2016.

probability of loss of consciousness (PLOC) induced by a combination of sevoflurane, propofol, and an opioid before the above MAC thresholds are reached (6, 7), the FA alone no longer provides sufficient information. In other words, the required rate of rise of the inhaled agent in the presence of a decreasing propofol and opioid concentration remains poorly defined. To determine anesthetic depth in the immediate post-induction period after a standardized intravenous induction, we measured the noxious Stimulus Response Index (NSRI) (to calculate the effect of triple drug interactions (8, 9)) and the Bispectral Index (BIS®) (10) (to intercept possible NSRI outliers due to model misspecification. In addition, we used the modified Brice questionnaire to elicit recall (11).

We tested 3 different speeds of inhaled agent wash-in towards 1 MAC after a standardized, commonly used intravenous induction sequence and hypothesized all ensure hypnosis and provide similar hemodynamic control (while immobility is ensured by muscle relaxants).

Methods

After obtaining IRB approval (OLV study number 2015/129) and written informed consent, 33 ASA PS I-III adult patients undergoing abdominal surgery were enrolled. Exclusion criteria were those imposed by the pharmacokinetic and pharmacodynamics (PK/PD) models incorporated in the SmartPilot®View (height < 150 cm or > 200 cm, weight < 40 or > 140 kg, BMI > 35, and age < 18 or > 90 years), and benzodiazepine administration the morning of surgery. Non-invasive mean arterial blood pressure (MAP, mm Hg) and heart rate (HR, beats/min) were measured the evening before and the morning of surgery on the surgical ward, and the lowest of the two values defined baseline MAP and HR.

In the operating room, routine monitors and the BIS® (Bispectral Index Technology, Covidien, Medtronic, Minneapolis, MN, USA) were applied. NSRI data were collected by the SmartPilot®View (software version 2.0, Dräger, Lubeck, Germany). The anesthesia provider was blinded to the SmartPilotView® and BIS® monitor. Patients were preoxygenated with 80% O2 in air (8-15 L.min-1) via an adult circle breathing system (Covidien, Medtronic, Minneapolis, MN, USA) attached to a Zeus® anesthesia machine (software version 4.03, Dräger, Lubeck, Germany) empowered with the SmartPilot®View. Anesthesia was induced intravenously with sufentanil (0.2 of consciousness (defined as the moment the patient stopped counting from 1 to 30) and adequate mask ventilation, rocuronium (0.6 mg/kg) was administered, followed by intubation of the trachea within 2.5 min. All drugs were injected via a three-way stopcock located 10 cm from the intravenous catheter insertion site, while a Hartmann's solution was running at its maximum gravity-mediated infusion rate. Sufentanil and propofol doses were manually entered in the SmartPilot®View at the time of injection.

After securing the airway (confirmed by the presence of sustained end-expired CO^2) and performing a lung recruitment maneuver (40 cm H^2O for 4 sec), controlled mechanical ventilation was started (tidal volume 500 mL, respiratory rate 10/min, 5 cm H2O PEEP). Ventilation was adjusted to maintain the end-expiratory CO^2 partial pressure between 32-45 mmHg.

Anesthesia was maintained with sevoflurane in O2/air with the Zeus® used in target- controlled mode. The target FIO2 was set at 50%. Sevoflurane administration was started within 4-5 min after propofol injection and progressively increased towards 1.0 age-adjusted MAC (=100*0.0254*10 (-0.00326*age), in %, with age in years (12)) by adjusting the sevoflurane target control dial (dialed target FAsevo, in %) every minute according to one of the following three exponential equations:

– group FAST dialed target FA(t)sevo = (100*0.0254*10(-0.00326*age)) (1 – e(-t/2.5))

– group MEDIUM dialed target FA (t)sevo = (100*0.0254*10(-0.00326*age)) (1 – e(-t/5.0))

– group SLOW dialed target FA (t)sevo = (100*0.0254*10(-0.00326*age)) (1 – e(-t/11.1)), with t = time (min).

These rates (or time constants) were derived from clinical studies that tested 3 different speeds with the AGC system (1, 13). The FLOW-i® itself could not be used for this study because only the SmartPilot®View can calculate the NSRI, an index of anesthetic depth that reflects the probability that the patient no longer responds to various stimuli based on drug dosing history and drug interactions (see below for details). Patients were assigned to one of these 3 groups depending on whether incision was expected to occur within 10 min, within 20 min, or > 20 min after propofol administration, respectively.

Patients displaying spontaneous respiration or movement received an extra bolus of sufentanil (0.1 µg/kg). Hypotension (MAP < 65 mmHg or 30% below baseline) that persisted for > 2 min was treated with a phenylephrine bolus (100 µg), or with an ephedrine bolus (6 mg) if accompanied by

bradycardia. Bradycardia (HR < 50 bpm or 20% below baseline HR) that persisted for > 2 min was treated with an atropine bolus (0.4 mg). Finally, hypertension (MAP > 10% above baseline MAP) and/or tachycardia (HR > 100 bpm) that persisted for > 2 min was treated with a sufentanil bolus (0.1 µg/kg).

In order to elicit recall, the patients were asked (MVT) to orally answer the Brice questionnaire, one hour after they left the theatre. FAsevo, BIS® (excluding data with a signal quality index < 50), MAP and HR were downloaded every 5 sec, and converted into Excel® files using RUGloop® (Demed, Temse, Belgium). Effect-site concentrations (Ce of sufentanil, propofol, sevoflurane) and NSRI were downloaded from the SmartPilot®View, converted into an Excel® file, and synchronized with the other data. Time zero was defined as the moment propofol was injected. All results are presented as raw data and median, unless mentioned otherwise.

FAsevo was expressed as a fraction of age-adjusted MAC, and a one-exponential fit to these age-adjusted MAC values for each group yielded the time constants that define the exponential rise of the partial pressures in the 3 groups.

The effect-site sevoflurane partial pressures obtained from the SmartPilotView®, which take into account hysteresis, were expressed as a fraction of age-adjusted MAC (MACe). We considered the probability of loss of consciousness (PLOC) to be extremely high if MACe > 0.63 and CeSuf > 0.17 ng/mL [5,14] or NSRI < 50 and BIS < 65; high if 50 < NSRI < 70 and BIS < 65 or NSRI < 50 and BIS > 65; and insufficient, i.e. NSRI > 50 and BIS > 65 or recall elicited by the Brice questionnaire.

Patient demographics, and time to first appearance of end-expired sevoflurane, were compared using ANOVA, followed by Bonferroni for inter-group comparisons. Sufentanil and vasoactive agent use were compared among the groups using odds ratios. Differences were considered to be statistically significant if $p < 0.05$.

Results

Of the 33 patients enrolled, 7 were excluded for a variety of reasons: sufentanil dosing error (n = 1), delay in propofol administration (n = 1), error in sevoflurane target setting (n = 2) and prolonged intubation sequence leading to additional drug administration and an excessive delay in starting sevoflurane administration (n = 3), leaving 9, 8, and 9 patients in the FAST, MEDIUM, and SLOW group, respectively.

Table 1.

Patient demographics

	Group FAST	Group MEDIUM	Group SLOW
Age (y)	65 [53; 74]	66 [63; 69]	68 [65; 69]
Height (cm)	171 [170; 175]	180 [176; 182]	176 [173; 187]
Weight (kg)	84 [76; 92]	78 [75; 81]	85 [80; 101]
Sex (m/f)	7/2	6/2	8/1

Data presented as median and quartiles; groups do not differ

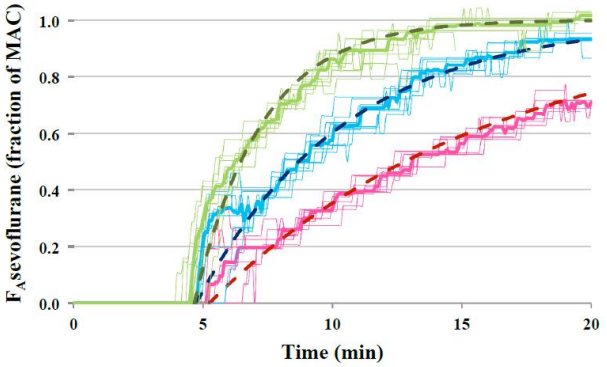

Fig. 1. — End-expired sevoflurane partial pressure (FA sevoflurane), expressed as fraction of MAC.
Thin lines = raw, thick lines = median, thick broken lines = fit. Group FAST in green, MEDIUM in blue, and SLOW in pink. See text for details.

BIS® capture did not succeed in 2 patients in the MEDIUM group (other data were included). NSRI data could not be retrieved from the SmartPilot®View in 4 patients: failure to capture sevoflurane information (n = 1 in group MEDIUM; other data were included); gender entree error (1 each in group FAST and MEDIUM, therefore Ce of sufentanil and propofol were excluded from analysis). One extra sufentanil bolus was not entered (n = 1 in group SLOW; data prior to bolus were included).

Prior to intubation, one patient in the MEDIUM group received an extra bolus of sufentanil because of movement. Sufentanil was administered post-intubation for hypertension in groups MEDIUM (n = 3) and FAST (n = 2) (all within 6.5-12 min after propofol administration), for tachycardia in group FAST (n = 1) and SLOW (n = 1) (all within 6 min after propofol administration), and for movement in group FAST (n = 1, within 4 min after propofol administration). Sufentanil usage for each of these indications did not differ among the groups.

Patient demographics did not differ among the groups (Table 1). FAsevo was first detected at 5.3 [5.2; 5.9] min in group SLOW, which was later

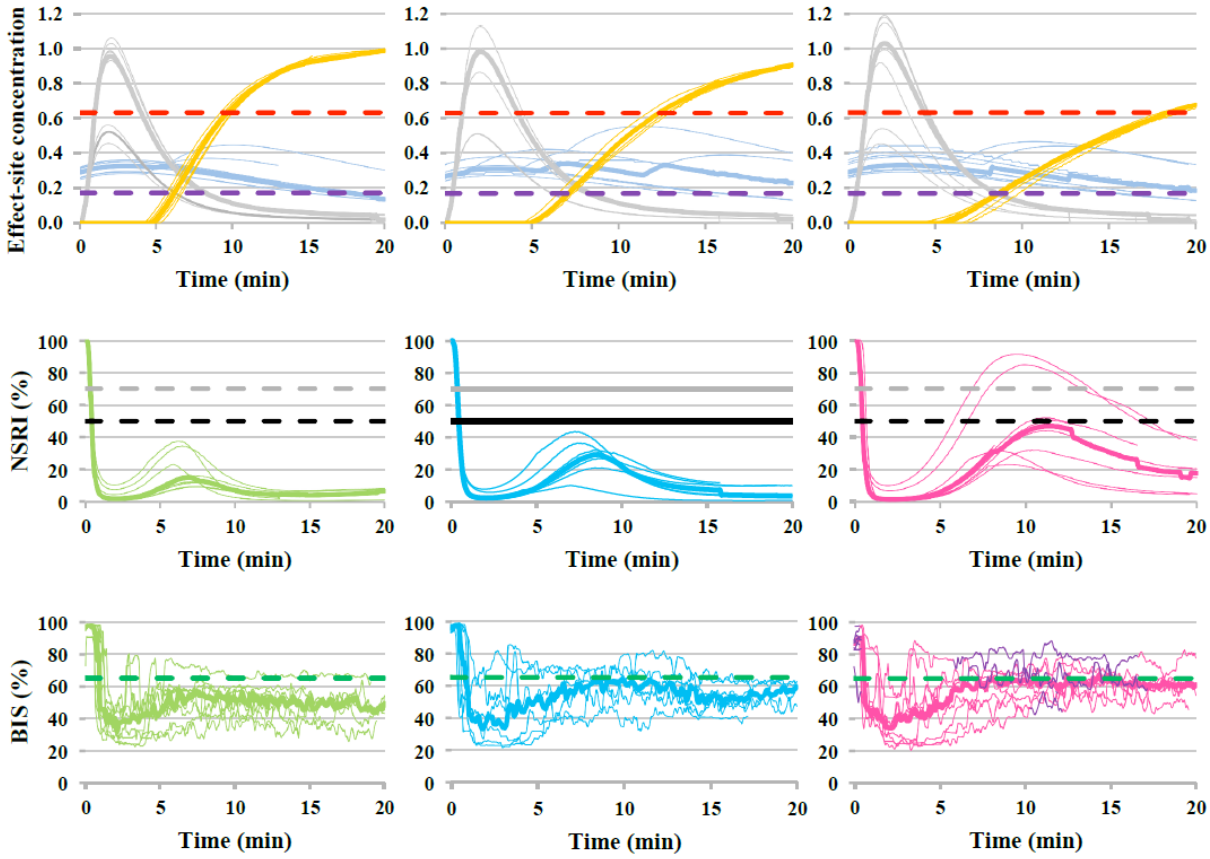

Fig. 2. — Effect-site concentrations (upper panes) of sufentanil, propofol, and sevoflurane, NSRI (middle panes), and BIS (lower panes) for study groups (from left to right) FAST (green), MEDIUM (blue), and SLOW (pink), with thin lines representing raw data and thick lines median values.
Upper panes: blue line = sufentanil (ng/mL); grey line = propofol (value*10 µg/mL); orange line = sevoflurane (MAC equivalent); red broken line = 0.63 MACe (effect-site MAC); purple broken line = 0.17 ng/mL sufentanil effect-site concentration. Middle panes: grey line = NSRI 70, black line = NSRI 50. Lower panes: green line = BIS 65, purple lines indicates BIS® values if NSRI > 50. See text for details.

($p < 0.05$) than in the FAST group (4.7 [4.4; 4.8] min) but not the MEDIUM group (4.8 [4.7; 5.0] min) (Figure 1). The time constants (with the 95% confidence interval) of the one-exponential curve fit to the FAsevo (normalized to age- adjusted MAC) were 2.6 (2.6; 2.7), 5.7 (5.3; 6.2), and 10.9 (9.6; 12.6) min in groups FAST, MEDIUM, and SLOW, respectively. Effect-site concentrations of all drugs, NSRI and BIS® (raw and median) for the three groups are presented in Figure 2. Time to reach 0.63 MACe was 9.8 [9.8; 9.8], 12.3 [12.3; 12.6], 18.5 [18.3; 18.7] min in groups FAST, MEDIUM, and SLOW, respectively.

In all patients, except for 2 in group SLOW, Ce of sufentanil was higher than 0.17 ng/mL at the time MACe reached 0.63 and its decrease was gradual, resulting in an extremely high likelihood of loss of consciousness from that moment.

In group FAST, NSRI remained < 40 after securing the airway in all patients, with BIS® being < 65, except for one patient in whom BIS® remained borderline > 65, even after MACe reached 1.0. This patient had the lowest NSRI (and corresponding the highest Ce of sufentanil and propofol) of all patients in this group. Thus, in the period between securing the airway and reaching 0.63 MACe, PLOC in this group was considered high to extremely high.

In group MEDIUM, the NSRI remained < 45 in all patients after securing the airway, with BIS® < 65, except for two patients in whom BIS® was > 65 in the period between securing the airway and reaching 0.63 MACe. Therefore, PLOC in this group was considered extremely high to high.

In the SLOW group, only 3 patients had a combination of NSRI < 50 and BIS® < 65, resulting in an extremely high PLOC. In 2 patients with a NSRI 50-70, and BIS® < 65, and in another 2 patients with a NSRI < 50 and BIS® > 65, PLOC was high. Two patients had an NSRI >50 and BIS® > 65, resulting in a PLOC that was insufficient. By the time MACe reached 0.63, the NSRI decreased in both patients, while the BIS® was increasing in one patient.

The Brice questionnaire did not elicit recall in any patient. The use of vasoactive agents did not differ amongst the groups: two patients each in groups SLOW and MEDIUM received phenylephrine, 1 patient in group SLOW received atropine.

Discussion

Unconsciousness is the very essential component of general anesthesia and is expected in at least 99.99% of our patients. If inhaled agents are used exclusively, and hysteresis (15) is accounted for, FAsevo, which is routinely measured, is an excellent tool to assess PLOC, especially because of the steep dose-response curve with narrow spread (16, 17). This is applied by the MACawake concept: 0.70 MACe (2 times MACeawake) of a potent inhaled agent ensures unconsciousness in 99.99% of patients (1). However, most anesthetics start with the administration of intravenous agents, followed by the wash-in of potent inhaled anesthetics at variable speeds. The rate of wash- in should be fast enough to ensure that the combination of propofol, sufentanil, and the rising partial pressure of sevoflurane continues to guarantee unconsciousness in the period before reaching a sevoflurane partial pressure of 0.70 MACe.

To study this, we anesthetized patients with 3 different wash-in rates of sevoflurane after a standardized intravenous induction, and we then used the SmartPilot®View to derive effect-site concentrations of sufentanil and propofol, sevoflurane partial pressure, and the NSRI, while simultaneously measuring BIS®. In addition, the Brice questionnaire was used to determine whether recall was present. Finally, usage of vasoactive agents was compared between the groups.

When sevoflurane is co-administered with intravenous drugs (opioid, propofol), direct measurement of FAsevo no longer suffices to assess anesthetic depth. The contribution of the intravenous drugs to the hypnotic effect is harder to assess: we cannot measure the concentration of intravenous drugs routinely, their dose-response curves are less steep (16), and drug interaction with sevoflurane needs to be taken into account.

The interaction between the remaining opioid and sevoflurane is described in the reduction of MACawake to induce unconsciousness; in the presence of a sufentanil effect-site concentration > 0.17 ng/mL, 0.63 MACe or higher is very likely to induce unconsciousness because of a 10-15 % synergistic effect on MACawake (5). We used a 10% synergistic effect to take into account inter-individual variability.

If, in addition, propofol is present, triple drug interactions have to be taken into account. Here the NSRI is extremely useful because it estimates the PLOC based on the effect-site concentration of the opioid, propofol, and inhaled agent (8, 9). However, the PK/PD models underlying the NSRI have an inherent degree of misspecification, causing predicted drug concentrations to differ from actual concentrations. This will cause the NSRI to mis-estimate the PLOC to some degree. A direct measure of drug effect (BIS® or other EEG-derived index) may help detect these instances. To complicate matters further, in the presence of opioids, the BIS® number is less reliable to estimate anesthetic depth (18). When opioids are added to sevoflurane, BIS values above the classically suggested 40-60 range have been shown to be associated with a high PLOC in the absence of surgical stimulation, suggesting BIS values of the 40- 60 in the presence of sevoflurane and 5 ng/mL remifentanil equivalent may actually represent an excessive depth (in the absence of surgical stimulation) (18). Therefore, the combination of a calculated measure of drug effect based upon dosing history and drug interactions, and a direct monitor of drug effect may more precisely reflect the level of anesthesia compared with monitoring based on one of these aspects alone [19]. To the best of our knowledge, no study has ever combined an EEG- derived index and a calculated index to address the question raised in this study. Individual outliers of BIS® > 65 might make some clinicians feel uncomfortable, suggesting that the used rate of rise of the inhaled agent is not sufficient in these patients. The NSRI however reveals a high PLOC in all patients, except for two in group SLOW.

Based on a limited number of patients, we could preliminary recommend the following: reaching 0.63 MACe within 13.4 min after a propofol bolus (2 mg/kg if age < 70y, 1 mg/kg if age ≥ 70y), itself preceded 4 min earlier by a 0.2 µg/kg sufentanil bolus, should result in a high PLOC, although this does not necessarily mean that a patient may not react (movement, hemodynamic change) to a noxious stimulus. Because the 13.4 min threshold reflects the fastest drop in Ce sufentanil to 0.17 ng/mL in any of our patients, the Ce opioid might not be sufficient anymore to produce the 10% reduction in MACe that virtually guarantees unconsciousness if it takes longer to reach 0.63 MACe after propofol injection.

Were the other components of anesthesia ensured with the three different wash-in rates? Immobility was mostly ensured by muscle relaxants, regardless of the wash-in rate. The use of vasoactive

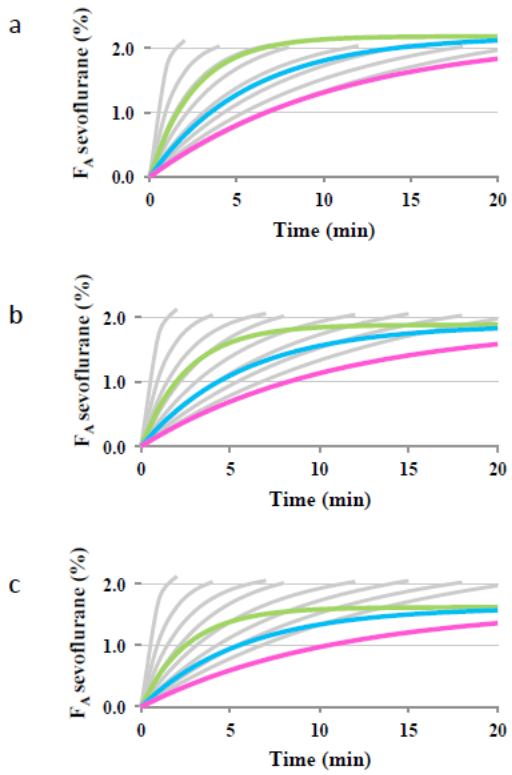

Fig. 3. Preprogrammed, fixed sevoflurane wash-in rates or "speeds" of the Automated Gas Control feature of the FLOW-i® are superimposed on the median end-expired sevoflurane concentration in groups FAST (green line), MEDIUM (blue line), and SLOW (pink line) for three different age groups – from top to bottom: 20 year old (a), 40 year old (b), and 60 year old (c).
Because anesthetic depth was judged adequate in groups FAST and MEDIUM, the area above MEDIUM represents an area in which AGC® speeds are acceptable in the three groups (within the boundaries of the study protocol – see text for details).

agents and sufentanil to control HR and MAP did not differ. Blood pressure and heart rate have previously been found to be poor indicators of anesthetic depth (20).

Several limitations apply to our study. First, the number of patients in this study is small, prompting restraint in interpreting its results. The absence of awareness in only a small patient population does not necessarily mean that the used sevoflurane wash-in regimens will guarantee unconsciousness in all patients after a standardized induction technique. Second, there was no noxious stimulus during the study period (except for the intubation process and the presence of an endotracheal tube), which causes a 0.3% increase of the sevoflurane partial pressure required to maintain the same BIS (21).

Figure 3 applies our findings to the speed feature of the automated low flow feature of the FLOW-i® (AGC®) by superimposing our wash-in rates on those of the AGC® (22). Because the rate of rise of the FAsevo for a particular AGC® speed is fixed, one particular speed does not represent the same increase in anesthetic depth for patients of different ages, thus we superimpose our study wash-in rates towards 1 MAC on those of the AGC® for three different age groups, 20, 40, and 60 years old. All AGC® rates above our MEDIAN wash-in rate are deemed acceptable (i.e. high to very high PLOC), rates below our SLOW wash-in rate unacceptable (i.e. insufficient PLOC), and the AGC® area in between our SLOW and MEDIAN wash-in rates an area of uncertainty requiring further study. Combined, our findings suggest all speeds to be acceptable in the 3 age groups, except speeds 1 and 2 in the 20 and 40 year old and speed 1 in the 60 years old for one specific (yet frequently used) sufentanil – propofol induction sequence, which require further study. Our fastest wash-in rates were slower than the fastest AGC® speeds, precluding us from making any recommendations on anesthetic depth and hemodynamic repercussions of these AGC® speeds.

To summarize, an exponential rise of the end-expired sevoflurane concentration towards 1.0 age-adjusted MAC with a time constant (95 % confidence interval) of 2.6 (2.6; 2.7) and 5.7 (5.3; 6.2), but not 10.9 (9.6; 12.6) min, is very likely to ensure continued unconsciousness if started 4 to 5 min after intravenous induction of anesthesia with propofol (2 mg/kg if age < 70y, 1 mg/kg if age ≥ 70y) given 4 min after sufentanil (0.2 µg/kg). Evolving PK/PD models that incorporate multiple drug interactions into a depth of anesthesia index like the NSRI can be combined with direct monitors of drug effect to start making personalized anesthetic drug titration a reality - and this in a cost-efficient manner. Integrating these techniques and/or their derived administration patterns with automated low-flow target controlled anesthesia will help revolutionize anesthetic agent delivery.

Acknowledgements

The study has not been funded. Jan Hendrickx has received lecture support, travel reimbursements, equipment loans, consulting fees and/or meeting organizational support from a number of companies involved with inhaled agent delivery (alphabetically): AbbVie, Acertys, Air Liquide, Allied healthcare, Armstrong Medical, Baxter, Draeger, GE, Hospithera, Heinen und Lowensein, InnoMediq, Intersurgical, Maquet, MDMS, MEDEC, Micropore, Mindray, Molecular, NWS, Philips, Quantum Medical.

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