Acta Anaesth. Bel., 2023, 74 | Suppl. 1: *107-114*

Master thesis | Original study

Comparison of the intentions of residents and licensed anesthesiologists to adapt propofol, sufentanil and sevoflurane titration according to the patient's age

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Abstract

Background: **This study uses pharmacokinetic-pharmacodynamic (PKPD) simulations, identical to those applied in SmartPilot® View (SPV) (Dräger, Lübeck, Germany), to compare whether residents adapt the dose of propofol, sufentanil and sevoflurane to the patients age in a similar effective way as licensed anesthesiologists. By comparing the drug titration intentions, we aim to identify gaps in knowledge or suboptimal performance for drug titration, so to improve future educational strategies using PKPD simulations.**
Objectives: **The aim is to develop, implement and evaluate a protocol for the application of FIB in the emergency department for patients with hip fractures at the University Hospital of Antwerp. Additionally, a survey was conducted on analgesia policies for hip fractures in hospitals in Flanders.**
Materials and Methods: **After EC approval (AZ Sint Jan Brugge-Oostende AV, nr B0492021000026) a survey was conducted in four Belgian hospitals, inquiring for titration intentions by residents and anesthesiologists when managing laparoscopic procedures of demographically identical ASA 1 patients, apart from age (18 versus 80 years). Propofol, sufentanil, rocuronium and sevoflurane were available for use. SPV simulates the effect-site concentrations of propofol (CePROP), sufentanil (CeSUF) and sevoflurane (CeSevo), the "probability of tolerance to laryngoscopy" (PTOL), and its derivative: the "noxious stimulation response index" (NSRI). Appropriate T tests explore significant differences ($p<0.05$) within and between groups.**
Results and Discussions: **38 residents and 30 anesthesiologists were compared. In young and old patients, high doses of propofol and sevoflurane led to near maximal values of PTOL and NSRI in both groups. Residents target higher CePROP, CeSUF en CeSEVO in young patients compared to anesthesiologists. Both groups reduce doses in elderly but without reducing PTOL values.**
Conclusions: **PKPD simulations could assist in drug titration training programs to optimize the adaptation of the drug dose to patients' age, both for residents and anesthesiologists.**

Keywords: **Pharmacodynamics, simulation training, drug titration.**

Ethics Committee approval and informed consent: Ethics approval was granted on October 21, 2021 by the Ethics Committee of AZ St. Jan Brugge Oostende AV (Ruddershove 10, 8000 Bruges). The chair of this committee is dr. L. Vanopdenbosch. The study registration number is BUN B04920210000026. Inclusion of participants started on 22/03/2022 and ended on 31/05/2022.

Introduction

Anesthesiologists are responsible for administering drugs to patients to achieve a desired level of sedation, analgesia and immobility during surgery. However, the optimal dose of a drug can vary depending on the patients' age, weight, medical history and other factors. The recommended dose can be derived from drug manufacturers recommendations or from pharmacokinetic-pharmacodynamic (PKPD) and drug interaction models. PKPD models describe a demographically adjusted mathematical relationship between an administered drug dose and the subsequent clinical effect, as observed in a historical population of patients. In addition, response surface interaction models can predict the time course of clinical effects (such as the probability of tolerance to laryngoscopy (PTOL)) when multiple anesthetic drugs are combined[1,2]. However, in daily practice, it remains unclear whether the clinical decision to adapt a dose according to demographic variation of the patient is affected by these recommendations and to what extent the dose adjustments are in line with PKPD model calculations.

The current learning process to optimize drug titration for anesthesiology residents is predominantly based on empirical imitation of clinical practices from licensed anesthesiologists. Subsequently, the resident can only master and refine the titration technique in a personal trial-and-error fashion, during which an unknown number of patients will inevitably be submitted to risks of over- or underdosing. It may therefore be advantageous to include bedside calculations of PKPD and interaction models to improve the safety of the current learning process for residents and to improve the clinical decision for dose adaptations by the anesthesiologist[3].

The commercially available bedside simulation software SmartPilot® View (SPV, Dräger, Lübeck, Germany) translates the drug administration history of propofol, opioids, volatile agents and neuromuscular blockers into a time course of the respective effect-site concentrations for each drug and also adds a measure of drug potency of the combined effect of propofol, opioids and volatile agents, called probability of tolerance to laryngoscopy (PTOL). The use of SPV simulations can affect clinical outcome through streamlining titration decisions, but the effects on the educational process for residents is less well explored[4].

The primary purpose of this observational study is therefore to explore and compare the intentions for dose adaptations of propofol, sufentanil and sevoflurane by residents versus licensed anesthesiologists, when they are asked to manage anesthesia for a laparoscopic procedure in demographically identical ASA1 cases, except for age (being either 18 or 80 years). The hypothesis is that licensed anesthesiologists adapt the drug dose more accurately according to the patients age compared to residents. We use SPV simulator software to evaluate whether drug titration is performed in concordance with predictions of effect of the PKPD and interaction models and identify potential gaps in titration skills in either group, such to guide future educational efforts in clinical practice and during training.

Methods

Following approval of the institutional ethics committee (AZ Sint Jan Brugge-Oostende AV, Bruges, Belgium, BUN B04920210000026, 21st of October 2021), a survey was conducted in four Belgian hospitals to inquire for respective dosing intentions of board-certified anesthesiology specialists versus anesthesia residents. Questionnaires were distributed on a voluntary basis in the anesthesia departments of two Belgian university hospitals (respectively the University of Ghent and Leuven) and two large non-university centers (AZ Sint-Jan Brugge-Oostende AV, Bruges and AZ Damiaan Oostende, Ostend). The survey was designed and distributed using the SurveyMonkey platform (momentive.ai, San Mateo, CA, USA) and conducted between March and May 2022.

The survey

Each participant of the survey was challenged to provide a personal anesthetic plan for four healthy patients, all categorized ASA class 1, and scheduled for a diagnostic laparoscopy with a surgical time of 30 minutes, following a similar time-course of events. The patients are randomly presented to the participants, but each survey contained two pairs of patients, differentiated by only one demographic characteristic: age (18 versus 80 years), body mass index (+/-18 versus +/-33) or gender (male/female). In order not to extend the length of the survey, we only provided four cases per participant in total. This manuscript only presents the results of the age variations.

The choice of drugs was restricted to sufentanil, propofol, rocuronium and sevoflurane. Intravenous drugs could be administered in single or repeated bolus throughout the case. The dose and timing of each administered anesthetic drug is registered for induction (between first administered drug and incision) and for maintenance of anesthesia (between incision and the end of surgery). Participants are urged to provide doses that reflect their clinical

habits, rather than to aim for the dose proposed by the drug manufacturer or academic guidelines.

The intended timing of intubation of the trachea was decided at the discretion of the participant and expressed as minutes and seconds after the last induction agent. After intubation, the desired target end-tidal vol% of sevoflurane vapor pressure was queried in the assumption that the fresh gas flow was set in open flow (>10L fresh gas flow) to ensure the fastest onset of effect. The combined administration of drugs should aim for an immobile patient (even without the addition of neuromuscular blocker effect) at the time of incision. Incision was set at 10 minutes after intubation in all patients.

The expected probability of a movement response at incision (in absence of neuromuscular blocking agents) was surveyed, considering the drug administration history and assuming that the stimulus intensity of incision is similar to laryngoscopy. Participants could select one out of four categories of probability of movement response: >90%, 51-90%, 10-50%, <10%.

This can be transformed in a probability of tolerance (=immobility) to incision of respectively: <10%,10-49%,50-90%,>90%.

We informed the participants that no clinical arousal or hemodynamic or movement event occurred throughout the case. We inquired also for intended tapering strategies towards the end of surgery to reduce the extubation time.

Data handling and endpoints

The current paper only presents a subset of results of the survey, being the dose adaptations according to age differences. Subsequent publications will report on the differences in titration when BMI and sex differ between patients.

All answers from the SurveyMonkey output file were organized according to patients' age (respectively 18 versus 80 years) and to the participants' experience level (respectively "residents" versus "licensed anesthesiologists") using Microsoft® Excel 16.0 (Microsoft, Redmond, USA). SmartPilot® View simulator software (Dräger, Lübeck, Germany) simulates the time course of the drug effect-site concentrations and the corresponding noxious stimulation response index, which corresponds to probability of tolerance to laryngoscopy[1].

All simulations use identical PKPD and interaction models as applied in the commercially available SmartPilot® View advisory screen (software version 2, Dräger, Lübeck, Germany)

The effect-site concentration of sufentanil (CeSUF) is calculated using the pharmacokinetic model of Gepts5 and a ke0 of 0.112 min-1 derived from Scott et al[6]. For the effect-site concentration of propofol (CePROP), the Schnider PKPD model was used[7,8]. For the effect-site concentration of rocuronium(CeROC), the pharmacokinetic model of Wierda was used and correlated to corresponding train-of-four percentage (TOF) using the parameters of Masui et al[9]. The effect-site concentration of sevoflurane (CeSEVO) was calculated using the Bailey model[10].

For the calculation of the PTOL, CeSUF was converted to remifentanil equivalents (CeREMIeq)[11] using the conversion factor as described by Scott[6], Gilron[12] and Brunner[13]. Next, CeREMIeq, CePROP and CeSEVO are the input variables for an interaction model that yields the NSRI and PTOL. NSRI is a derivative of PTOL and therefore, both measures serve as an effect potency measure of a combination of propofol, opioids and volatile agents to evoke tolerance (=immobility in response) to laryngoscopy. An NSRI of 100, 50, 20, and 0 corresponds respectively to an estimated PTOL of 0, 50, 90 and 100 percent.

Our primary outcome is the mean (SD) or median (25-75 percentile range) of the total dose of administered drugs at induction, the effect site concentration of propofol, sufentanil and sevoflurane, the maximum PTOL and NSRI reached during induction, at the time of intubation, incision and at the end of surgery. Secondary outcomes were timing between the first and last administered drug during induction and timing between last drug administration during induction and the intubation.

The prediction accuracy of the participants for the risk of a movement response at incision was assessed as follows: the category of probability of movement response at incision selected by the responder was inverted to probability of tolerance of incision (=absence of movement response). As we postulated that incision is assumed equally stimulating as laryngoscopy, we used the model predicted PTOL at the time of incision as a reasonable estimation of the probability of movement at that time. As such, the prediction accuracy of the respondents is defined as the number of categories between the model predicted PTOL and the respondent's selected category of "probability of tolerance to incision". A positive or negative score indicates that the participant selected respectively a number of categories above or below the category identified by the model derived PTOL. A score of 0 indicates a correct estimation of the risk of tolerance to incision/ laryngoscopy.

Statistical tests

All primary and secondary endpoints were imported and analyzed in Microsoft® Excel 16.0 (Microsoft,

Redmond, USA). The statistical significance was set to $P<0.05$.

We did not perform an a priori power analysis as it was initially unknown how large the expected titration differences could be, and because our results depend on the voluntary response rate, in line with European GDPR privacy regulations.

Characteristics of the responders are compared using appropriate T-tests in Microsoft® Excel 16.0 after an F test confirmation of the comparability of the variance between samples. The T test was modified depending on the result of the F test so to compensate for the asymmetric characteristics of the samples. We compared all primary and secondary endpoints and the accuracy of the prediction of movement response to incision within and between groups.

Results

289 surveys, each containing four cases were sent to residents and anesthesiologists working in 4 Belgian hospitals. A total of 87 questionnaires were returned, yielding a 30.1% response rate. Figure 1 shows the inclusion and exclusions in a CONSORT flow diagram. After exclusions, 68 surveys were analyzed, respectively 38 residents and 30 anesthesiologists. This paper only focusses on the effect of an age difference between cases, analyzing respectively 92 and 44 cases of respectively 18- and 80-year-old patients (Table I).

Table II shows results of the induction doses of propofol, sufentanil and the target of end-tidal partial pressure of sevoflurane initiated after intubation. When inducing anesthesia in elderly, residents and licensed anesthesiologists reduce the induction dose of propofol by respectively 44% and 35%, sufentanil by respectively 19% and 21% and sevoflurane by respectively 25% and 25% compared to young patients with identical BMI. The mean (standard deviation) induction dose of propofol in elderly is therefore significantly lower when administered by residents (106 (28) mg) compared to licensed anesthesiologists (122 (28) mg). However, this lower dose of propofol by the residents does not evoke a significant difference in CePROP in elderly, neither at the peak value after induction, nor at intubation, incision or at the end of surgery (Table III).

When evaluating all three drugs combined at incision, with similar targets of sevoflurane by residents and licensed anesthesiologists, the residents reach a maximal PTOL of 100 for both age groups, despite the 44% propofol dose reduction. Licensed anesthesiologists also reach this maximum PTOL value at incision, both in young and elderly patients. At the end of surgery, the NSRI and PTOL are lower than at incision, because of tapering strategies in some cases, mainly by reduction of sevoflurane during maintenance. Within each experience level, there were some small statistically significant differences in PTOL target between the 18- and 80-year patients, but these are clinically insignificant.

Secondary outcomes of timing are shown in Table IV. Timing between first and last drug administered during induction and the time delay to intubation were not significantly different between

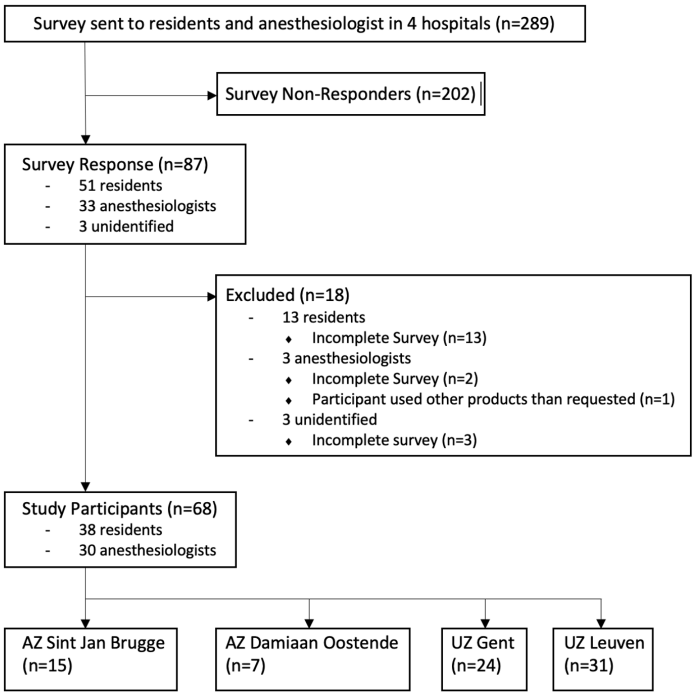

Fig. 1 — CONSORT flow chart of survey study responders.

Table I. — Number of respondents and cases included in data analysis.

	Residents	Licensed Anesthesiologists	Total
Number of cases included (%)	152 (56)	120 (44)	272
Number of cases with different age (%)	76 (56)	60 (44)	136
Number of cases: - 18 years old (%) - 80 years old (%)	 55 (60) 21 (48)	 37 (40) 23 (52)	 92 44

Table II. — Induction doses and the initially set end-tidal sevoflurane target concentration.

		Propofol (mg) Mean (SD)	Sufentanil (mg) Mean (SD)	Sevoflurane (%) Mean (SD)
Residents	18 years 80 years	189 (22) $ 106 (29) $*	16 (8) $* 13 (3) $*	2.4 (0.4) $ 1.8 (0.3) $
Licensed Anesthesiologists	18 years 80 years	187 (20) $ 122 (28) $*	14 (4) $* 11 (3) $*	2.4 (0.6) $ 1.8 (0.3) $
SD =standard deviation; $p<0.05 between young and elderly patients; * p<0.05 between residents and licensed anesthesiologists.				

Table III. — Simulated pharmacokinetic-pharmacodynamic primary endpoints.

Residents		Ce_{PROP} Median (range)	Ce_{SUF} Median (range)	Ce_{Sevo} Median (range)	P_{TOL} Median (range)	NSRI Median (range)
Peak value after induction	18 years 80 years	7.4 (4.0) $ 5.8 (1.8) $	0.29 (0.12) $ 0.22 (0.08) $		100 (0) 100 (0)	2 (2) * 2 (2)
Intubation	18 years 80 years	7.4 (3.8) $ 5.8 (1.8) $	0.26 (0.10) $ 0.21 (0.05) $		99 (3) $ 98 (5) $	4 (6) $* 7 (9) $
Incision	18 years 80 years	1.0 (0.3) $ 0.4 (0.1) $	0.22 (0.08) $ 0.17 (0.05) $	2.3 (0.3) $ 1.7 (0.2) $	100 (0) 100 (0)	2 (2) * 2 (2)
End of surgery	18 years 80 years	0.4 (0.1) $ 0.1 (0.0) $	0.06 (0.02) $ 0.05 (0.02) $		88 (19) 93 (10)	22 (19) 17 (13)
Licensed Anesthesiologists						
Highest or lowest value after Induction	18 years 80 years	6.4 (2.7) 6.6 (2.7)	0.29 (0.10) $ 0.19 (0.08) $		100 (1) 100 (0)	3 (4) * 1 (2)
Intubation	18 years 80 years	6.4 (2.7) 6.5 (2.9)	0.26 (0.10) 0.19 (0.10)		98 (2) 97 (6)	8 (6) * 9 (10)
Incision	18 years 80 years	0.9 (0.2) $ 0.5 (0.1) $	0.19 (0.07) 0.16 (0.03)	2.2 (0.7) $ 1.9 (0.5) $	100 (1) 100 (0)	3 (4) * 1 (2)
End of surgery	18 years 80 years	0.3 (0.1) $ 0.1 (0.0) $	0.06 (0.02) 0.05 (0.02)		82 (28) $ 95 (8) $	28 (23) $ 13 (13) $
Effect-site concentration of respectively propofol (CePROP), sufentanil (CeSUF) and sevoflurane (CeSEVO), Probability of tolerance to laryngoscopy (PTOL) and Noxious stimulation Response Index (NSRI). SD = standard deviation. $ p<0.05 between young and elderly patients; * p<0.05 between residents and licensed anesthesiologists.						

age groups. In young patients, the timing between the last administered drug and intubation was significantly longer in the licensed anesthesiologist group.

The 1-PTOL calculations predict a probability of movement of <10% at incision. Both residents and licensed anesthesiologists overestimate the probability of movement at incision with a mean (standard deviation) number of categories of respectively 0.53(0.56) and 0.62(0.68) in young patients and 0.43(0.51) and 0.57(0.58) in elderly. Figure 2 shows the distribution of the overestimated categories of probability of movement at incision.

Table IV. — Results of timing of dosing and intubation.

Residents	18 years	80 years
Timing between first and last drug during induction (s; mean(SD))	187.16 (90.74)	191 (100.44)
Timing between last administered drug and intubation (s; mean(SD))	125.18 (44.28)*	133 (37.51)
Licensed Anesthesiologists		
Timing between first and last drug during induction (s; mean(SD))	181.19 (62.62)	165.91 (94.01)
Timing between last administered drug and intubation (s; mean(SD))	141 (42.64)*	127.65 (51.96)
S =seconds, SD =standard deviation. * p<0.05 between residents and licensed anesthesiologists.		

Discussion

In this observational study, we found that both residents and anesthesiologists reduce the dose of propofol, sufentanil and sevoflurane significantly in elderly patients compared to young patients with an identical BMI. Despite these dose adjustments, the PKPD simulations indicate that both residents and licensed anesthesiologists intend to administer drugs towards a combined drug effect compatible with a simulated PTOL that reaches near maximal values (close to 100) at incision, in both 18- and 80-year-old patients. Question remains whether this high PTOL reached in all patients is a necessary or even safe approach to ensure the adequate anesthesia without excessive risk for side effects?

We simulated PKPD endpoints, such as drug specific effect-site concentrations and PTOL as a measure of combined drug effect, to allow a more objective demographically adjusted comparison between the different dosing strategies and the different expertise levels of the responders. We decided to use similar simulations as applied in SPV, as this provides a commercially available educational tool that might be applied in future training programs. PTOL is a population derived measure of combined anesthetic drug effect. It should be interpreted in a similar fashion as the minimal alveolar concentration for volatile agents. For example: if a population of patients with similar demographic characteristics as the current patient is titrated to a combination of anesthetic drugs that yields a PTOL of e.g. 90%, than 90% of that population will be tolerant for laryngoscopy, while only 10% of the population will still respond to the stimulus and need to receive a higher target of PTOL before continuing to intubation. However, due to the uncertainty of how sensitive each individual patient is to an administered drug, we can assume that an unknown fraction of the 90% unresponsive patients

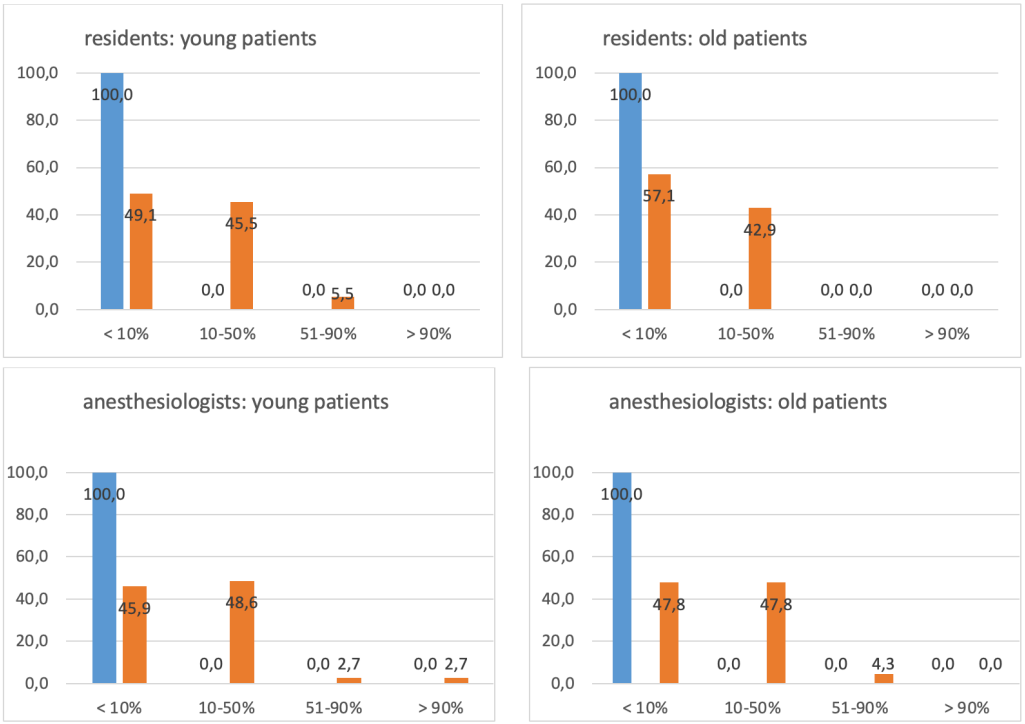

Fig. 2 — The orange bars show the percentage of responders (Y axes) selecting a category of probability of movement at incision (X axes). The blue bar indicates the 100% of cases with a probability of movement response <10% at incision, as predicted by the 1-PTOL model.
PTOL = probability of tolerance of laryngoscopy.

probably would have been unresponsive at lower PTOL as well. Therefore, this unknown fraction of patients has received a relatively excessive dose in relation to their personal needs. A higher target of PTOL will inevitably increase this fraction of the population that is relatively overdosed in relation to their individual need, and vice versa. It has been postulated before that a reasonable target for induction of anesthesia would be a PTOL of 90% as this will lead to adequate anesthesia in a reasonable majority of the population, without maximizing the fraction of the population that is relatively overdosed[14]. The disadvantage of this proposed target is that we will need to intervene in (only) 10% of the cases, by adjusting the drug target concentrations appropriately.

In our study, we systematically found a near maximal PTOL in all cases, independent of age and despite dose reductions in the elderly. Using high PTOL as a goal indicates a maximized fraction of relatively overdosed patients, and therefore, we can define this habit of titration as a gap in performance, both for residents and licensed anesthesiologists. In the future, educational training programs, including PKPD and PTOL simulations could assist to improve the awareness of this problem and initiate dose reduction programs towards more optimal dosing habits.

Since PTOL can be calculated simultaneously with the administration at bedside, this opens educational and clinical perspectives for advisory screens such as SPV. A recent study of Kuizenga et al. shows that PTOL via SPV calculations could significantly improve the severity of perioperative hypo- and hypertension and the severity of low BIS trends, without however seeing significant differences in postoperative outcome[4]. At the other hand, these results also suggest that titration according to SPV information may have benefits for some (sensitive) patients without increasing the risk for adverse events per- and postoperatively.

Our study has some limitations. A main limitation is that we used a survey, which only inquired for dosing intentions in hypothetical cases. Many decisions on dose adjustments in clinical practice are evoked by clinical observations and individually monitored measures. This could not be simulated in our study setting. Nevertheless, the administration of an induction dose remains a decision without knowing the patient's responsiveness in advance. Our study therefore remains an adequate tool to inquire for dosing intentions. Also, as the limitation is identical for residents and licensed anesthesiologists, the comparison between both groups remains valid.

PTOL is a population-based parameter which does not exclude that individual responses may differ significantly from the predicted (population average) behavior. Therefore, we cannot make strong claims on whether the proposed titration schedules are unsafe in any way. It would be sensible to repeat this study using interaction models that quantify the effect of combined drugs on hemodynamics, e.g. blood pressure and heart rate. However, such validated models are currently lacking.

Another limitation is that we used an F test to determine whether the variances of the samples were statistically significant different or not, but F tests may not be an optimal test to distinguish between parametric/nonparametric data. The T test was modified depending on the result of the F test so to compensate for the asymmetric characteristics of the samples. By doing so, we identified which data was parametric or not. The T test gave identical significance results regardless of whether we adjusted it for asymmetry/symmetry in the samples. This suggests that nonparametric tests will presumably also give the same result.

We did not find significant difference in timing of drug administration between studied groups, except that residents intubate more rapidly after the last administered drug in the young patients. We did not inquire for the speed of injection for each drug as this is not a metric that affects the calculation of the effect-site concentrations nor PTOL, so we didn't investigate the effect of the time frame of drug injection.

There was a rather low response rate (30%) to our survey, leading to a higher risk for nonresponse bias and a reduced external validity of our findings. One of the consequences of the low response rate is that we were unable to collect enough comparisons from the different hospitals to investigate behavioral differences between a university and non-university hospital.

Conclusion

Dose reductions in elderly do not lead to a reduced PTOL compared to young patients, suggesting that large proportions of both populations remain at risk for excessive drug effects. Our study suggests that bedside PKPD simulations, as also applied in the commercially available SPV advisory screen, could assist in dose reduction training programs, both for residents and licensed anesthesiologists, independent of the age of the patient.

Declaration of interest: None declared.

Funding: Dräger (Lübeck, Germany) provided the SmartPilot® View Simulator software complimentary, all funding was done by the department of

anesthesiology, AZ Sint-Jan Brugge-Oostende (Bruges, Belgium).

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doi.org/10.56126/75.S1.21