ISAP 32nd Annual Meeting

2023 Syllabus

October 13th, 2023

Hilton Union Square
333 O'Farrell Street
San Francisco, California, USA

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32nd Annual Meeting

Mission Statement

The International Society for Anaesthetic Pharmacology (ISAP) is a nonprofit organization with an international membership, which is dedicated to teaching and research about clinical pharmacology in anesthesia, with particular reference to anesthetic drugs.

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Learners must complete an evaluation form to receive a certificate of completion. If you need MOC credit, you also need to pass a posttest with a score of at least 80%. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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Amedco LLC designates this live activity for a maximum of 5.50 AMA PRA Category 1 CreditsTM for physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Objectives

After Attending This Program You Should Be Able To:

1. Effectively understand the delivery and monitoring of anesthetic agents.
2. Recognize new methods of PKPD modeling including Kalman Filtering.
3. Obtain insight into the effects of inhaled anesthetics on the environment.

Disclosure of Conflict of Interest

The following table of disclosure information is provided to learners and contains the relevant financial relationships that each individual in a position to control the content disclosed to Amedco. All of these relationships were treated as a conflict of interest, and have been resolved. (C7 SCS 6.1-6.2, 6.5)

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Mohamed Naguib Lecture: General Introduction on the Role of Pro-resolving Medicators (SPMs)

Charles N. Serhan, PhD, DSc, Harvard University, Boston, MA USA

SENZIME

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ISAP has established the Mohamed Naguib Lecture to honor his many accomplishments, which will be presented at every ISAP Annual Meeting. The Inaugural Lecture was given at the 2021 ISAP Annual Meeting. ISAP has established a fund to endow the Mohamed Naguib Lecture and donations may be made at isaponline.org.

In the world of clinical pharmacology, Dr. Naguib was a renaissance man. As a man of many talents, his influential work has provided direction in many spheres of investigation and discovery. He made significant contributions to the scientific foundation and clinical applications of neuromuscular monitoring. He formed and led a coalition of thought leaders to prepare and disseminate expert consensus guidelines on neuromuscular monitoring. He had substantial interest in the mechanisms of and treatment for neuropathic pain. He led a laboratory that created molecules to treat neuropathic pain. At the time of his passing, he was a principal investigator on a NIH funded multi-center observational study focused on the discovery and validation of a biomarker signature for chemotherapy induced peripheral neuropathic pain. He was the co-founder of a company that is developing a novel therapy for neuropathic pain and Alzheimer's disease based on his research on the mechanisms of neuroinflammation. For each of these activities, he created a wake of opportunities for many that continue to have a vibrant and productive future. He was a prolific writer. He was the principal author or co-author of 130 peer-reviewed journal articles, 25 book chapters (including the premier Miller's Textbook of Anesthesia) and 150 abstracts.

By way of professional service, for years, he served on the editorial board of numerous anesthesia journals and was influential not only in his reviews but in preparing thought provoking editorials and commentary. He also served for many years in various leadership positions, including President of ISAP.

SAN FRANCISCO, CA

32nd Annual Meeting Schedule

0815–1800 Pacific Time Zone, USA

0815 – 0830 — **ISAP Welcome/Announcements**
Stuart Forman, MD

0830–1000 — **Session 1 – Pharmacology**

- **0830 – 0900** — **End-Tidal Anesthetic Concentration: Monitoring, Interpretation, and Clinical Application**
  Andre De Wolf, MD, Professor Emeritus, Northwestern University, Evanston, IL, USA
- **0900 – 0930** — **Gas Man® for Learning, Teaching, and Studying Inhalation Anesthesia Kinetics**
  James H. Philip, ME(E), MD, CCE, Anesthesiologist and Director of Clinical Bioengineering, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital; Medical Liaison for Anesthesia, Department of Biomedical Engineering, Partners HealthCare System, Professor of Anaesthesia, Harvard Medical School, Boston, MA, USA
- **0930 – 1000** — **Kalman Filtering in PKPD Modelling of Anaesthetic Drugs**
  Samaneh Nasiri, PhD, Harvard Medical School, Boston, MA, USA

1000-1015 — **Break**

1015 – 1145 — **Session 2 – Anaesthesia and the Environment**

- **1015 – 1045** — **Low Flow Anesthesia - 100 Years Later**
  Jeffrey Feldman, MD, MSE, Children's Hospital of Philadelphia, University of Pennsylvania, PA, USA
- **1045 – 1115** — **Climate Impact of Volatile Anesthetics: Vital Insights for Anesthetists in the Era of Climate Change**
  Prof. Alain Kalmar, MD, PhD, Sint-Jan Hospital Brugge-Oostende, Belgium; Ghent University, Belgium
- **1115 – 1145** — **Action Guidance for Addressing Pollution from Inhalational Anaesthetics**
  Jodi Sherman, MD, Yale School of Medicine, New Haven, CT, USA

1145-1300 — **Luncheon – ISAP Business Meeting**

1300 – 1400 — **Session 3 – Up and Coming Anesthetics & Research**

- **1300-1400** — **Clinical Effects of Site Concentration Guided Anesthesia**
  Henrik Öhrström, MD, DESA, Senior Consultant, Department of Anesthesia and Intensive Care, Örebro University Hospital and Lindesbergs Hospital, Sweden

  Pether Jildenstaal, PhD, Professor, Senior Consultant, Department of medical Sciences, Lund University, Lund, Sweden, Department of Anaesthesia, Operation and Intensive Care, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden, Department of Anesthesia and Intensive Care, Örebro University Hospital and Lindesbergs Hospital, Sweden

1400 – 1445 — **Mohamed Naguib Lecture** :
General Introduction on the Role of Pro-resolving Mediators (SPMs)
Charles N. Serhan, PhD, DSc, Gelman Professorship Harvard Medical School, Director Center for Experimental Therapeutics and Reperfusion Injury and Professor of Oral Medicine, Infection and Immunity, Brigham and Women's Hospital, Harvard University, Boston, MA, USA

1445-1500 — **Break**

1500– 1630 — **Moderated Poster Session 90 minutes**

1630-1645 — **Break**

1645 – 1730 — **Keynote Speaker & Lifetime Achievement Awardee**
Keynote: Anesthesia, the Eternal Loop Between Physiology and Pharmacology
Albert Dahan, MD, PhD, Full Professor of Anesthesiology, Head of Research, Head of the Anesthesia & Pain Research Unit, Staff Anesthesiologist, Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands

1730 – 1800 — **Gathering**

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Speakers & Moderators
Albert Dahan, MD, PhD
Full Professor of Anesthesiology, Head of Research, Head of the Anesthesia & Pain Research Unit, Staff Anesthesiologist, Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands

Andre De Wolf, MD
Professor Emeritus, Northwestern University, Evanston, IL, USA

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Charles N. Serhan, PhD, DSc
Gelman Professorship Harvard Medical School, Director Center for Experimental Therapeutics and Reperfusion Injury and Professor of Oral Medicine, Infection and Immunity, Brigham and Women's Hospital, Harvard University, Boston, MA, USA

Jodi Sherman, MD
Yale School of Medicine, New Haven, CT, USA

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MOHAMED NAGUIB LECTURE

Senzime

Senzime is a Swedish medical device company that develops, manufactures, and markets CE- and FDA-cleared patient monitoring systems. Senzime's employees worldwide are committed to the vision of a world without anesthesia- and respiratory-related complications.

The Contribution of Gap Junction and Claustral Dysfunction to General Anesthesia

Cameron Bosinski, Christopher Connor, Brigham and Women's Hospital

The most longstanding research question in anesthesiology is the mechanism of action of the volatile anesthetics. How do these agents, from ether through to modern fluorinated agents, induce an unconsciousness and unresponsiveness that is promptly reversible? Why do these agents work in essentially all multicellular creatures, even those without a brain? The anesthesiology literature has historically focused on anesthetic mechanisms involving chemical synapses such as GABA and NMDA, and on the disruption of either the cortex or thalamocortical loops. The recent elucidation of the BIS algorithm and its reliance on oscillations in the gamma range suggest that other neurologic structures may be involved. The presence of gamma oscillations has been associated with sensory perception in animal and human studies. There is no single mechanism of gamma oscillation production, as they can be created by multiple molecular mechanisms throughout various areas of the cortex. The binding problem is a longstanding problem in consciousness studies that refers to the question of how separate areas of the brain bind together to create a singular, unified sensory experience. The claustrum has previously been proposed to serve this function and may be the anatomic basis of volatile anesthetic action. Volatile anesthetic administration is associated with a loss of positively correlated neuronal activity in animal models. Gap junctions, a form of electrical synapse between cells, maintain neurologic synchrony and may serve as the molecular target of volatile anesthetics. Gap junctions are widely distributed throughout the brain and are evolutionarily conserved. This poster will review the contribution of gap junction and claustral dysfunction to the production of the state of general anesthesia induced by volatile anesthetics.

Several experiments can be performed to determine whether gap junctions, the claustrum or gamma oscillations are involved in the production of general anesthesia in humans. Genetic mutation and optogenetics would help to clarify the role of gap junctions in the induction of general anesthesia. One approach would be to make precise lesions in the claustrum while simultaneously monitoring gamma oscillations throughout the cortex and subcortical regions. The behavioral response to anesthetic exposure in a claustral lesioned animal could then be quantified. Maintenance of the awake state in spite of gap junction and claustral dysfunction would falsify this theory of general anesthesia.

Pharmacokinetics and pharmacodynamics of remimazolam for procedural sedation in children and adolescents

Presenting author: Michel M.R.F. Struys[1,7]

Co-authors: Pieter J. Colin[1], Keira Mason[2], RJ Ramamurthi[3], Kumar Belani[4], Lynn Bichajian[5], Valentin Curt[5], Jeroen V. Koomen[1], Thomas Stöhr[6], and Michel M.R.F. Struys[1,7]

[1] Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands., [2]Department of Anesthesiology, Boston Children's Hospital, Boston, Massachusetts., [3]Department of Anesthesiology, Stanford University Medical Center, Palo Alto, California., [4]Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota., [5]Department of Clinical Drug Development, Eagle Pharmaceuticals, Inc., Woodcliff Lake, New Jersey., [6]Department of Development and Regulatory Affairs, PAION AG, Aachen, Germany., [7]Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium

Background/Introduction: Remimazolam, a short-acting benzodiazepine is currently not approved for use in patients <18 years of age. As part of the pediatric study plan agreed with the U.S.-F.D.A. a clinical trial was initiated in 2021 to assess the efficacy and safety of IV remimazolam in inducing and maintaining appropriate sedation levels in pediatric patients undergoing diagnostic and/or therapeutic procedures. This study reports on an interim analysis of the pharmacokinetics and pharmacodynamics of remimazolam and a subsequent model-based optimization of the dosing regimen that was studied in the trial.

Methods: 31 patients ≥ 6 years and ≤ 18 years of age were included in the trial. Patients were stratified across 4 treatment arms: repeated bolus administration, continuous infusion and repeated bolus administration, repeated bolus + fentanyl co-administration or continuous infusion and repeated bolus + fentanyl co-administration. The University of Michigan Sedation (UMSS) scale was used to assess the level of sedation. Blood samples were drawn to measure remimazolam and CNS7054, the main metabolite of remimazolam. Population pharmacokinetic pharmacodynamic modelling was performed in NONMEM®. Optimization of the dosing regimen and power/sample size calculations were performed in R®.

Results: A joint population pharmacokinetic model was developed describing the concentration-time profile of remimazolam and CNS7054 in the absence or presence of fentanyl. Size-adjusted typical PK parameters were similar to PK parameters previously reported in adults. A proportional odds logistic regression PD model combined with a simplified Minto model, assuming an additive interaction between remimazolam and fentanyl, described the observed UMSS well. The steady-state exposure response relationship according to our model is shown in Figure 1. Clinical trial simulations confirmed that the dosing regimen which was tested in our trial was unlikely to lead to appropriate sedation in a large proportion of patients. An optimized dosing regimen consists of higher per kg remimazolam bolus doses (200 vs. 150 $\mu g.kg^{-1}$) and infusion rates (up to 80 instead of 20 $\mu g.kg^{-1}.min^{-1}$), an extended titration scheme for continuous infusion dosing (10 – 80 instead of 7.5 – 20 $\mu g.kg^{-1}.min^{-1}$), shorter inter-dose intervals for top-up bolus doses (at least 2 min gap vs. 3 min gap between bolus doses), removal of the

maximum dose cap which had been based on adult dosing and a more frequent fentanyl co-administration at higher (per kg) bolus doses (2 $\mu g.kg^{-1}$ vs. 1 $\mu g.kg^{-1}$). Finally, clinical trial simulations showed that a trial with 30 patients ≥3 years and <18 years receiving the optimized dosing regimen has a high probability of demonstrating that >70 % of patients achieve a UMSS ≥3 15 min after the first remimazolam bolus dose.

Conclusions: This study has shown that the pharmacokinetics of remimazolam are likely not different in children ≥6 years old and adults (after correcting for size differences) while the pharmacodynamics are perhaps different, although this difference may be in part (or wholly) due to investigators' deeper desired level of sedation in children compared to adults for procedural sedation. At the same time, the exposure response relationship shows that the currently studied dosing regimen is insufficient to meet the protocol specified primary endpoint. In order to effectively use remimazolam for procedural sedation in children ≥6 years it's dosing schedule has to be modified to allow for higher remimazolam exposures.

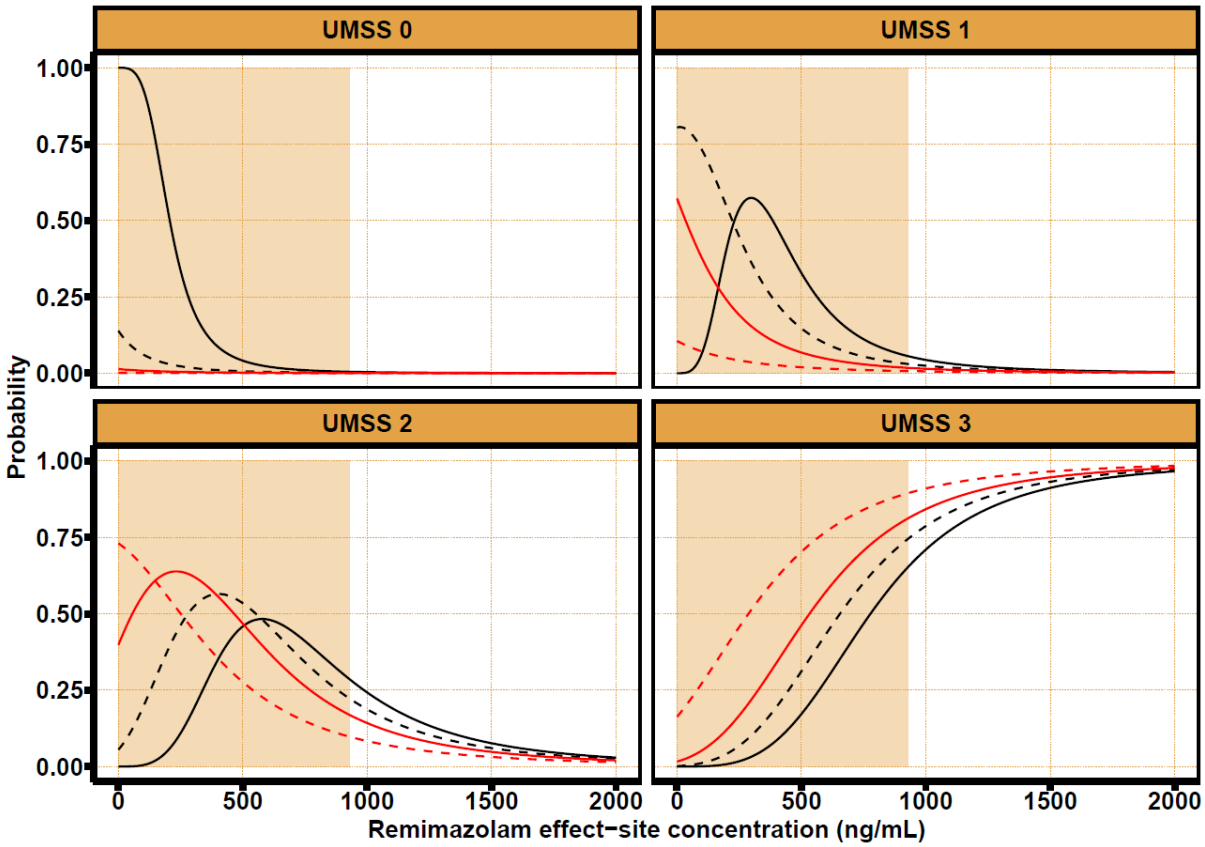

Figure 1. Steady-state pharmacodynamic interaction between fentanyl and remimazolam. *The predicted probability for UMSS = k with k ∈{0, 1, 2, 3} for different combinations remimazolam – fentanyl according to our final pharmacodynamic model. The remimazolam effect-site concentration driving the pharmacodynamic effect is depicted on the x-axis. The background fentanyl regimens, expressed as predicted effect-site concentrations, are depicted by different line types: no fentanyl co-administration (solid black line), 1 ng.mL-1 (dashed black line), 2 ng.mL-1 (solid red line) and 4 ng.mL-1 (dashed red line). The range of predicted remimazolam effect-site concentrations from this study are denoted by the orange shaded area.*

Human Abuse Potential of HSK3486 Injection in Nondependent, Recreational Central Nervous System Depressant Users: Trial in Progress

Presenting Author: William L. Daley, MD, MPH[1]
Co-Authors: Ahad Sabet, MD[2]; Lisa Doria, MS[1]; Yu-Ling Lai, MS[1]; Rong Zhou, PhD[3]

[1]Haisco-USA Pharmaceutical Company, Inc., Bridgewater, New Jersey; [2]ICON, Salt Lake City, UT; [3]Haisco Pharmaceutical Group Co., LTD., Shannan, China

Background/Introduction: Propofol is an intravenous (IV) anesthetic associated with hypotension, respiratory depression, and injection site pain. HSK3486 is a phenol derivative, non-barbiturate injectable emulsion with fast onset and quick, stable recovery. HSK3486 and propofol have the same mechanism of action and function as direct agonists of the γ-aminobutyric acid receptor subtype A. Prior clinical studies support HSK3486 as an effective, safe anesthetic with substantially less injection site pain than propofol. The phase 1 human abuse potential (HAP) study is planned to address the US Food and Drug Administration requirement that any new chemical entity targeting the central nervous system (CNS) needs to be evaluated for substance abuse potential.

Methods: This single center study (NCT05614544) consists of 2 parts. Part 1 was an open-label, dose-finding study of HSK3486 and propofol conducted in 44 participants (n=24, HSK3486; n=20, propofol) to determine the appropriate doses for use in part 2. Part 2 is a randomized, double-blind, placebo- and active-controlled, 4-period, 4-way crossover study in approximately 42 participants. All participants in the study will be healthy, nondependent, recreational CNS depressant drug users.

Both parts 1 and 2 will consist of an outpatient screening visit, an in-clinic IV naloxone challenge, an in-clinic treatment phase, and follow-up (**Figure 1**). In part 2, participants who successfully complete the qualification phase will be randomized to 1 of 8 treatment sequences according to two 4×4 William squares. The 4 treatments are: HSK3486 dose 1 (highest dose meeting criteria in part 1), HSK3486 dose 2 (second highest dose meeting criteria in part 1), propofol (highest dose meeting criteria in part 1), and placebo (treatment A matched). Each treatment will be separated by approximately 24 hours. Serial pharmacodynamic (PD)/pharmacokinetic (PK) assessments will be performed (**Table 1**). Participants will also undergo safety assessments.

PD/PK endpoints will be analyzed using a mixed-effect model. Stepwise hypothesis testing will be conducted for PD treatment differences. The relationship between PK and PD may be evaluated using correlational analysis or similar methodology. Descriptive statistics or incidence/frequency counts, as applicable, will be used to describe safety parameters.

The primary objective of this study (part 2) is to evaluate the HAP of HSK3486 compared with propofol, with the null hypothesis that HSK3486 has greater abuse potential than propofol (**Table 1**). Secondary objectives are to evaluate the safety and tolerability of HSK3486 alone (part 1) and compared with propofol (part 2). An additional secondary objective (part 2) is to evaluate the PK profile of HSK3486.

Results: Part 1 of the HSK3486 HAP study has been completed. Part 2 is estimated to be completed in September 2023.

Conclusions: This study was designed to evaluate abuse potential, safety, and tolerability of HSK3486 as compared with propofol. Enrollment is ongoing, and the results will inform future HSK3486 clinical development. This study is sponsored by Haisco-USA Pharmaceuticals, Inc.

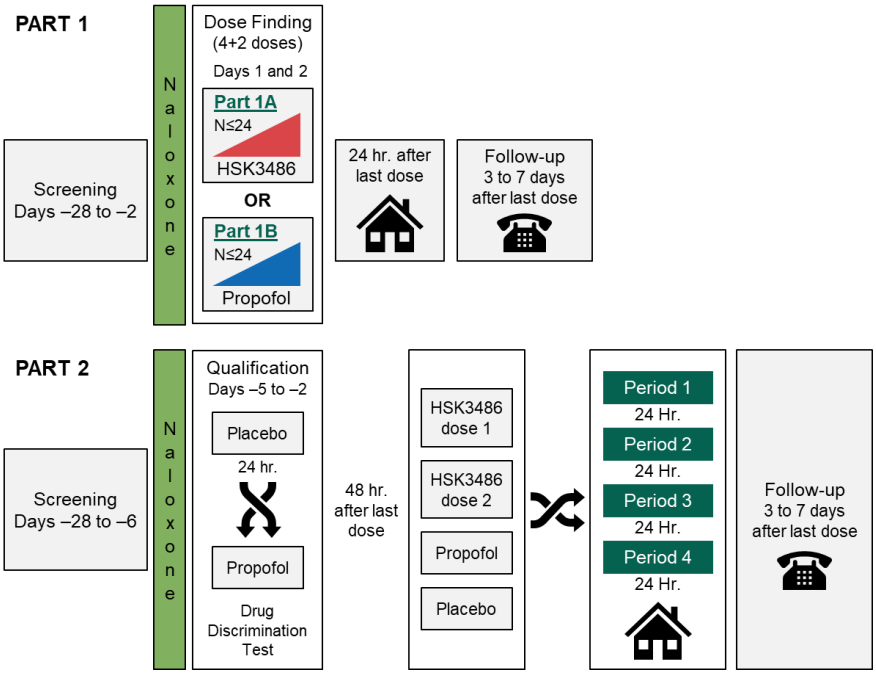

Figure 1. HSK3486 HAP Study Design. Key inclusion criterion: nondependent, nontreatment-seeking recreational CNS depressant user. Key exclusion criteria: drug, alcohol, or opioid dependence; history of mental illness. A naloxone challenge will be administered on the day of admission to ensure that participants are not opioid dependent. Only participants who do not have signs or symptoms of opioid withdrawal (Clinical Opioid Withdrawal Scale score <5) will be eligible for further participation in the study. Doses to be used in part 2 will be determined during dose finding in part 1. Groups of 4 participants will receive 1 dose level. Enrollment will be halted after the doses to be used in part 2 have been determined. The drug discrimination test during the qualification phase will ensure that participants can differentiate between the effects of active control (propofol) and placebo. Participants will receive each of the 4 treatments in a randomized, double-blind, 4-way crossover manner.

PD: parts 1 and 2	
Drug Liking ("at this moment") VAS (E_{max})[a]	
Drug Liking ("at this moment, I feel high") High VAS (E_{max})[b]	
Drowsiness/Alertness VAS (E_{min}, TE_{min}, TA_AUE_{0-1}, and TA_AUE_{0-2})[c]	
Modified Observer's Assessment of Awareness/Sedation scale	
Ability to complete battery of human abuse potential assessment questions for 1 hour	
PD: part 2	**PK: part 2**
Overall Drug Liking VAS (12- and 24-hour score)[b]	C_{max}
Take Drug Again VAS (12- and 24-hour score)[b]	T_{max}
Drug Liking VAS (TE_{max}, TA_AUE, E_{min}, TE_{min}, and percent reduction)	C_{max}/T_{max}
DEQ: Any Drug Effect VAS (E_{max}, TE_{max}, and TA_AUE_{0-1})	AUC
DEQ: Good Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE_{0-1})[c]	k_{el}
DEQ: Bad Drug Effects VAS, Sick-Nausea (E_{max}, TE_{max}, and TA_AUE_{0-1})[c]	$t_{1/2}$
Relaxation/Agitation VAS (E_{max}, TE_{max}, E_{min}, TE_{min}, and TA_AUE_{0-1})	
Drug Similarity ("How similar is the drug you most recently received [drug 1] to drug you just took [drug 2]?") VAS[c]	

Table 1. Summary of PD and PK Parameters. [a] Primary endpoint for the study; with α=.05, a sample size of 27 will provide 98% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than a margin of δ_2=11 in a 1-sided t-test. This assumes a mean (SD) of the difference in Drug Liking E_{max} between HSK3486 and propofol of 0 (15). [b] Secondary endpoints for the statistical hypothesis testing. [c] Secondary endpoints for the descriptive analysis. AUC, area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration; C_{max}/T_{max}, abuse quotient; DEQ, Drug Effects Questionnaire; E_{max}, maximum effect; E_{min}, minimum effect; k_{el}, terminal elimination rate; $t_{1/2}$, terminal elimination half-life; TA_AUE, time-averaged area under the effect curve; T_{max}, time to attain maximum observed plasma concentration; TE_{max}, time to maximum effect; TE_{min}, time to minimum effect; VAS, visual analog scale.

Δ9-tetrahydrocannabinol Pharmacokinetics of Inhaled Cannabis Market Products in Occasional and Daily Users

Presenting Author: Thomas K. Henthorn[1,2]
Co-Authors:, Michael Kosnett[3], George Sam Wang[4], Greg Dooley[6], Julia Wrobel[3], Sarah Limbacher[5], Ashley Brooks-Russell[5]

[1]Department of Anesthesiology, [2]Department of Pharmaceutical Sciences, [3]Colorado School of Public Health, [4]Department of Pediatrics, [5]Injury and Violence Prevention Center University of Colorado Anschutz Medical Campus and [6]Department of Environmental and Radiological Health Sciences Colorado State University

Background/Introduction: Population pharmacokinetic models of Δ9-tetrahydrocannabinol (THC) have been developed for THC plasma concentration data following protocol-driven inhalation regimens with NIDA-supplied, low THC potency cannabis products. Since, most cannabis consumption is now of high concentration, market-derived cannabis and most consumption is *ad libutum*, we performed a pilot study of the population pharmacokinetics of THC in users of high potency flower, (occasional and daily), and users of high concentration THC concentrates.

Methods: THC concentration data were obtained for 135 minutes from 30 subjects stratified to three groups: 10 occasional users (no more than three times per week) and 10 daily users all of whom normally smoked high concentration flower (15-30%) and 10 daily users who normally inhaled THC concentrates (60-90%). On the day of the study, all subjects were instructed to smoke/inhale the product they supplied themselves, *ad libitum,* in the manner they usually employed, and to the endpoint they usually desired. Parameters for a 3-compartment population pharmacokinetic model were estimated along with an estimate of the bioavailable inhaled dose which were compared to the physically measured dose used during the study session.

Results: Central and rapidly equilibrating volumes of distribution of a 3-compartment model were estimated (19.9±1.2 L, 51.6±4.7 L, respectively) as well as intercompartmental clearances to rapid and slow equilibrating peripheral compartments (1.65±0.14 L/min and 1.75±0.10 L/min, respectively). The slow volume of distribution and elimination clearance were fixed to estimates we determined previously from the population pharmacokinetic model of data in other subjects in which blood samples were collected for one week following a single inhalation session (3372 L and 0.72 L/min, respectively). Covariate analysis revealed that occasional cannabis users inhaled significantly less THC than daily users despite similar used, physically weighed THC.

Conclusion: 3-compartment pharmacokinetics of THC did not differ among the 3 groups and the early phase (first 135 minutes after inhalation) kinetics were similar to those previously described using low potency cannabis products. These analyses suggest covariate-driven adjustments can be made to weighed THC doses, based both on product and usage pattern, that would improve the accuracy of THC exposure estimates based on weighed product alone.

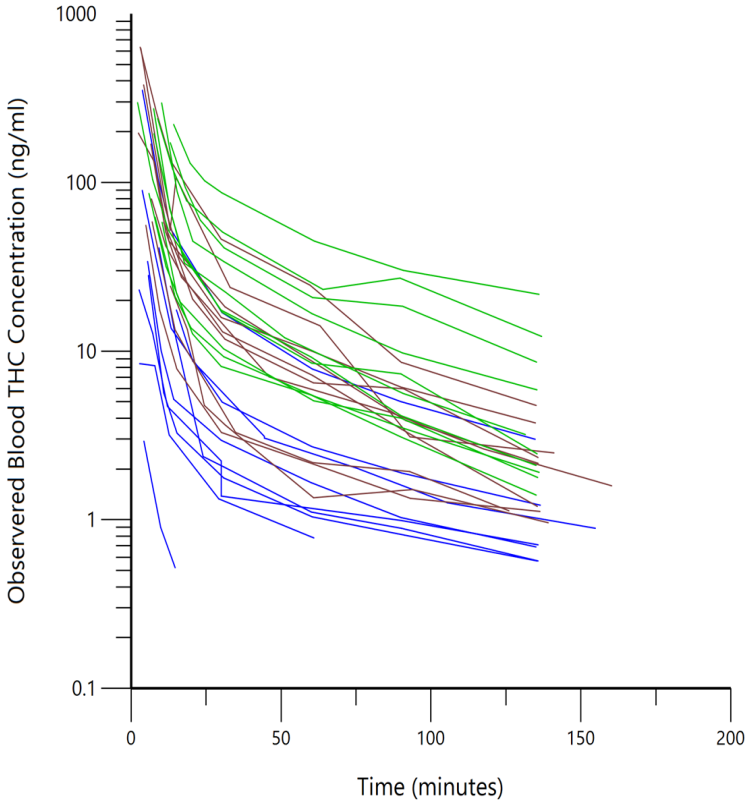

Figure 1. Observed blood THC concentration versus time for all 29 subjects (each line connects the measured concentrations from one subject) after subtraction of the baseline (before inhalation) blood THC concentration. Blue lines are occasional flower users, brown lines are daily concentrate users and green lines are daily flower users.

Validating the two-box model: overall fresh gas flow and characteristics of the initial high flow period are both useful markers of volatile anaesthetic consumption.

Presenting Author. R Ross Kennedy [1,2]

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Introduction: Volatile anesthetics are unique in that much of the agent admistered doesn't reach the patient. This waste has long been a concern, driven initally by economics but more recently by environmental concerns.
We have monitored fresh gas flow (FGF) rates as a marker of efficiency of volatile delivery for over two decades, while recognising that this is a surrogate for the actual vapour consumption. In 2017 we introduced the concept of the "two-box model" of FGF which emphasises the large contribution of FGF in the initial high flow period to overall average FGF (1). Over the past five years we have used GE Insights to monitor FGF patterns in many of our OR. This provides data on actual vapor consumption, FGF and a range other parameters. This allowed us to investigate the relationship between actual vapor consumption and 1) FGF and 2) the characteristics of the initial high flow period – the first box.

Methods: From the Insights data set we extracted cases between August 2018 and July 2023 lasting > 30min where sevoflurane was delivered for at least 1/3 of the case. Since actual sevoflurane use is the variable of interest, these cases were grouped by the total sevoflurane useage into 150 equal sized groups. We then explored the relationship between the group means of sevoflurane useage and 1) mean FGF and 2) the product of initial FGF and duration of the initial flow, defined in Insights as the period until FGF first falls below 5 l/min.

Results: We found 28,000 cases meeting our criteria. These had a mean duration of 95min and an overall time-weighted mean FGF of 0.934 l/min. Average consumption was 14.2ml of sevoflurane (2.8kg CO2-equiv). We have data for 77 cases from the same period using desflurane with an average useage of 31.6ml (117kg CO2-equiv).
As shown in the Figures, we found a strong positve correlation between sevoflurane consumption and both mean FGF ($r^2 = 0.83$) and [initial gas flow x initial flow duration] ($r^2 = 0.92$).

Conclusions: These results validate the use of fresh gas flow rates as a marker for efficiency of delivery of sevoflurane. They also support the concept behind the "two-box model": that both intial high flow rates and the time at these flows (area of the first box) are major drivers of overall vapor consumtion.
The lines of best fit suggest that changing the average FGF by 100ml/min alters sevoflurane consumption by 5ml and that a 1min change in duration or 1L/min change in FGF in the initial period equates to 1.7ml sevoflurane, or 20% of our average.
These results are not desgined as a comprehensive model, but to reinforce important, measureable, and modifiable factors influence vapour consumption.

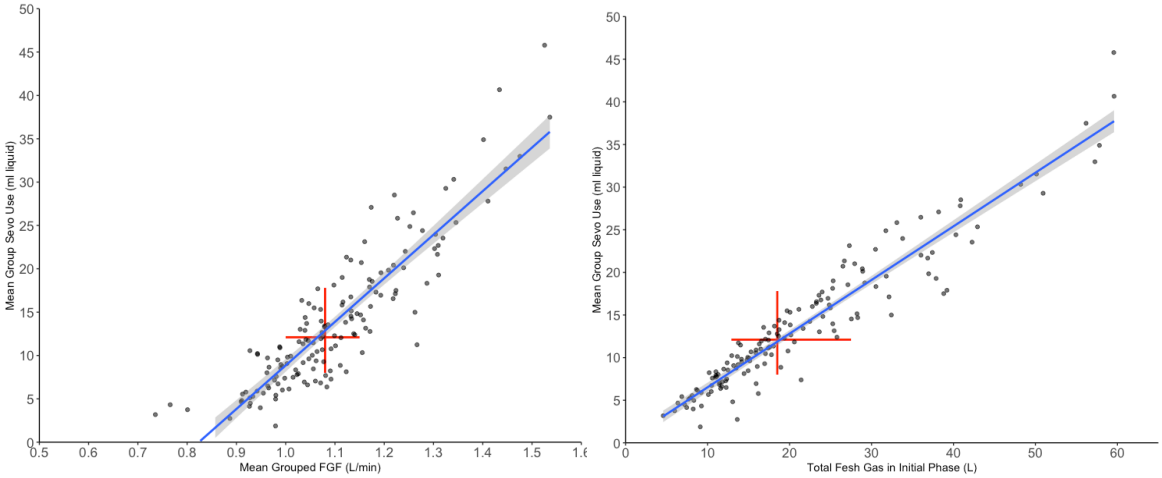

Figure: The relationship between mean FGF and ml of sevoflurane used (Left panel) and the product of FGF and time for the initial period with FGF above 5l/min(Right panel).
Blue line is the linear best fit: R^2 = 0.83 for overall FGF (left); R2 =0.91 for inital flows (right)
Red lines show the medians and interquatile ranges

Reference Kennedy RR, French RA, et al. The effect of fresh gas flow during induction of anaesthesia on sevoflurane usage: a quality improvement study. Anaesthesia. 2019;74:875-882.

Can remimazolam become an alternative agent of propofol in orthognathic surgery?

Kyotaro Koshika, Toshiya Koitabashi, Tatsuya Ichinohe

Introduction

Postoperative nausea and vomiting (PONV) after general anesthesia is one of the major postoperative complications and a distressing and unpleasant symptom for patients. The incidence of PONV in orthognathic surgery is estimated at approximately 40-67%, because the distinctive population showing the large number of young female patients is undergoing this surgery and the bleeding from the surgical field often runs into the stomach during and after surgery. Especially, the vomiting after an orthognathic surgery may cause serious complications such as an airway obstruction or aspiration pneumonia. Therefore, general anesthesia for orthognathic surgery is commonly maintained with propofol to prevent these risks. Although propofol has an anti-emetic effect, intraoperative hypotension is likely to occur during propofol anesthesia. Remimazolam besilate (remimazolam), a new intravenous anesthetic, has less negative inotropic effect. However, its anti-emetic effect is unknown. The purpose of this study was to evaluate the incidence of PONV and the average blood pressure between remimazolam and propofol in patients who underwent orthognathic surgery.

Methods

This study was approved by the Ethics Committee of Tokyo Dental College (approval number: 1065). Patients who underwent orthognathic surgery under total intravenous anesthesia with either propofol (P group) or remimazolam (R group) from January 2021 to March 2022 were enrolled. The medical, anesthesia, and nursing records were reviewed retrospectively. Primary end point was the incidence of PONV (up to 2 h and 2-24 h after surgery). Secondary end points were the incidence of intraoperative hypotension which consists of average mean arterial pressure (MAP) and the incidence of intraoperative hypotension (MAP < 65 mmHg). Statistical analysis was performed using the chi-square

test and the Mann-Whitney U-test. A p-value of less than 0.05 was considered significant. Data were expressed as mean ± standard deviation.

Results

A total of 125 patients (P group: 84 patients; R group: 41 patients) were included. There were no significant differences between two groups in terms of patient characteristics, surgical procedure, anesthesia time, the amount of the intraoperative bleeding, total remifentanil and fentanyl doses, and postoperative opioid use. The incidence of PONV up to 2 h after surgery was significantly lower in the P group than in the R group. However, there was no difference regarding the incidence of PONV from 2-24 h after surgery. The incidence of intraoperative hypotension was significantly lower in the R group (61.0%) than in the P group (89.3%), and the average MAP was significantly higher in the R group (76.7 ± 7.1 mmHg) than in the P group (68.0 ± 6.1 mmHg).

Conclusion

The results of this study demonstrate that intraoperative hypotension occurred less frequently during remimazolam anesthesia. On the other hand, the incidence of PONV in the early postoperative period was shown to be higher after remimazolam anesthesia. The further study will be needed to evaluate the efficacy of the multimodal strategy to reduce PONV after remimazolam anesthesia.

High Frequency Signals in Frontal Cortex at Loss of Consciousness

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Background/Introduction: Brain oscillations have rarely been studied at frequencies beyond 200 Hz, and it remains unknown what the highest frequency of brain bioelectric activity is. We used the volatile anesthetic, isoflurane, to depress activity at behavioral endpoints of loss of righting reflex (LORR) and loss tail clamp responses (LOTC). These endpoints provide surrogate measures of loss of consciousness (LORR) and surgical anesthesia (LOTC) in rats. We recorded signals from DC to 20 KHz; extending analysis of oscillatory cortical activity well beyond traditional ranges.

Methods: Following IRB approval, local field potentials were recorded from layer 2/3 of frontal cortex in rats using chronically implanted electrodes. Rats were placed in an air-tight chamber with a controlled atmosphere of room air that was slowly replaced with increasing concentrations of isoflurane in oxygen, delivered from a calibrated vaporizer. Body temperature was maintained using a heat lamp. Animal behavior was carefully monitored to determine LORR and LOTC responses. Rats recovered following each experiment after replacing isoflurane with room air.

Results: Isoflurane produced a characteristic profile of effects, consistent with previous reports. At LORR high amplitude slow wave activity was evident that transitioned to a burst suppression pattern at LOTC. Spectral analysis revealed that increased slow wave activity was accompanied by decreased higher frequencies in the gamma and high-gamma bands, and extending beyond 1.0 KHz at LORR. This high frequency activity was not due to multiunit action potential discharge, nor to harmonics from lower frequencies.

Conclusions: Isoflurane depressed high frequency cortical activity well beyond the traditional EEG frequency range of 200 Hz. Future research should investigate brain processes that are associated with this very high frequency brain activity, between 500 to > 1000 Hz.

Key words: Anesthetic, EEG, Cortex, Unconscious, High-gamma, Ultrahigh Frequency.

Pharmacokinetics of Propofol in Severely Obese Surgical Patients

Presenting author: Johan Raeder [1,2]

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Background/Introduction: Existing PK models of propofol include sparse data from very obese patients. The aim of this study was to develop a PK model based on standardized surgical patients spanning from normal weight to a high number of very obese patients.

Methods: Adult patients scheduled for laparoscopic cholecystectomy or bariatric surgery were studied. Anaesthesia was induced with propofol 2 mg/kg adjusted body weight over 2 minutes followed by 6 mg/kg/hr adjusted body weight over 30 minutes. For the remainder of the operation anaesthesia was maintained with sevoflurane. Remifentanil was dosed according to clinical need. 8 arterial samples were drawn in a randomized block sampling regimen over a span of 24 hours. Time-concentration data were analysed by population PK modelling using non-linear mixed-effects modelling.

Results: 474 serum propofol concentrations were collected from 69 patients aged 19-60 years with a BMI 18.5-67.3 kg/m2. Twenty-one patients had a BMI above 50 kg/m2. A 3-compartment PK model was produced wherein three different body weight descriptors (Lean Body Weight; Predicted Normal Weight; Total Body Weight) and sex were included as covariates in the final model. The allometric exponent of 0.75 improved the objective function of all clearances and was added to the model. Accuracy and precision were 1.4% and 21.7% respectively in post-hoc performance evaluation,

Conclusions: We have made a new PK model of propofol for adult normal weight to severely obese patients based on a high number of very obese patients. The new model should be tested in this patient population and compared with present models.

Table 1. Patients´ characteristics. Values are mean, SD (range) (n=69)

Age (years)	40.4 SD 10 (19–60)
Sex (Male/female) (n)	30/39
Weight (kg)	131.5 SD 40.6 (55–241)
Height (cm)	173.3 SD 10.1 (152–195)
BMI (kg/m^2)	43.4 SD 11.7 (21.6–67.3)
Bolus dose propofol (mg)	197 SD 46 (106–323)
Total dose propofol (mg)	475 SD 105 (266–774)

Table 2. Parameter estimates for the final pharmacokinetic model

Theta	Parameter	Typical Value	CV%	Bootstrap mean	Bootstrap 95% CI		Jackknife mean values	Likelihood Profiling 95% CI	
1	CL L/min	1.964*(WGT/129) **0.75	16.6	1.961	1.868	2.071	1.964	1.874	2.061
2	V1 L (M)	3.863*(LBW/65.1) **1	49.7	3.970	2.968	5.191	3.882	2.926	5.297
3	Q2 L/min	1.230*(LBW/65.1) **0.75)	28.2	1.222	1.068	1.381	1.228	1.098	1.376
4	V2 L	65.585*(LBW/65.1)	23.1	66.279	58.330	73.976	65.765	59.299	73.802
5	Q3 L/min	0.611*(WGT/129) **0.75	16.4	0.615	0.561	0.672	0.611	0.565	0.659
6	V3 L	305.111*(PNWT/78.5)+THETA(8)	.-	302.891	3.454	526.531	304.150	56.208	531.702
7	V1 L (F)	6.200*(LBW/65.1) **1	49.7	6.682	4.103	10.267	6.244	4.633	9.239
8	+ V3 L	404.821	.-	429.069	247.470	739.005	408.329		
Intraindividual error %									
Sigma	0.0402291	20.1							

Online Exhaled Propofol Monitoring in Normal-weight and Obese Surgical Patients

Presenting Author: Johan Raeder[1,2]
Co-Authors: Martin Rygh Braathen[1,2], (First Author), Ivan Rimstad[2], Terje Dybvik[2]
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Background/Introduction: Ion Mobility Spectrometry (IMS) allows for online quantification of exhaled propofol concentrations. We aimed to validate a bedside online IMS device, the Edmon®, for predicting plasma concentrations of propofol in normal-weight and obese patients.

Methods: Patients of body mass index (BMI) >20 kg/m2 scheduled for laparoscopic cholecystectomy or bariatric surgery were recruited. Exhaled propofol concentrations (CA), arterial plasma propofol concentrations (CP) and bispectral index (BIS) values were collected during target-controlled infusion anaesthesia. Generalised estimation equation (GEE) was applied to all samples and stable-phase samples at different delays for best fit between CP and CA. BMI was evaluated as covariate. BIS and exhaled propofol were also assessed with GEE.

Results: 29 patients (BMI 20.3–53.7) were included. A maximal R2 of 0.6 was found during stable concentrations and with five minutes lag-time of CA to CP; the intercept a=-0.69 (95% CI -1,7;0,3) and slope b=0.87 (95% CI 0.7,1.1). BMI was found to be a non-significant covariate. The median absolute performance error predicting plasma propofol concentrations was 13.4%. There was a maximal negative correlation of R=-0.44 at two minutes delay from BIS to CA.

Conclusions: Online monitoring of exhaled propofol concentrations is clinically feasible. Modest correlation with plasma concentrations makes the clinical usefulness questionable. The best correlations were found with delays between plasma propofol and exhaled propofol of five min.

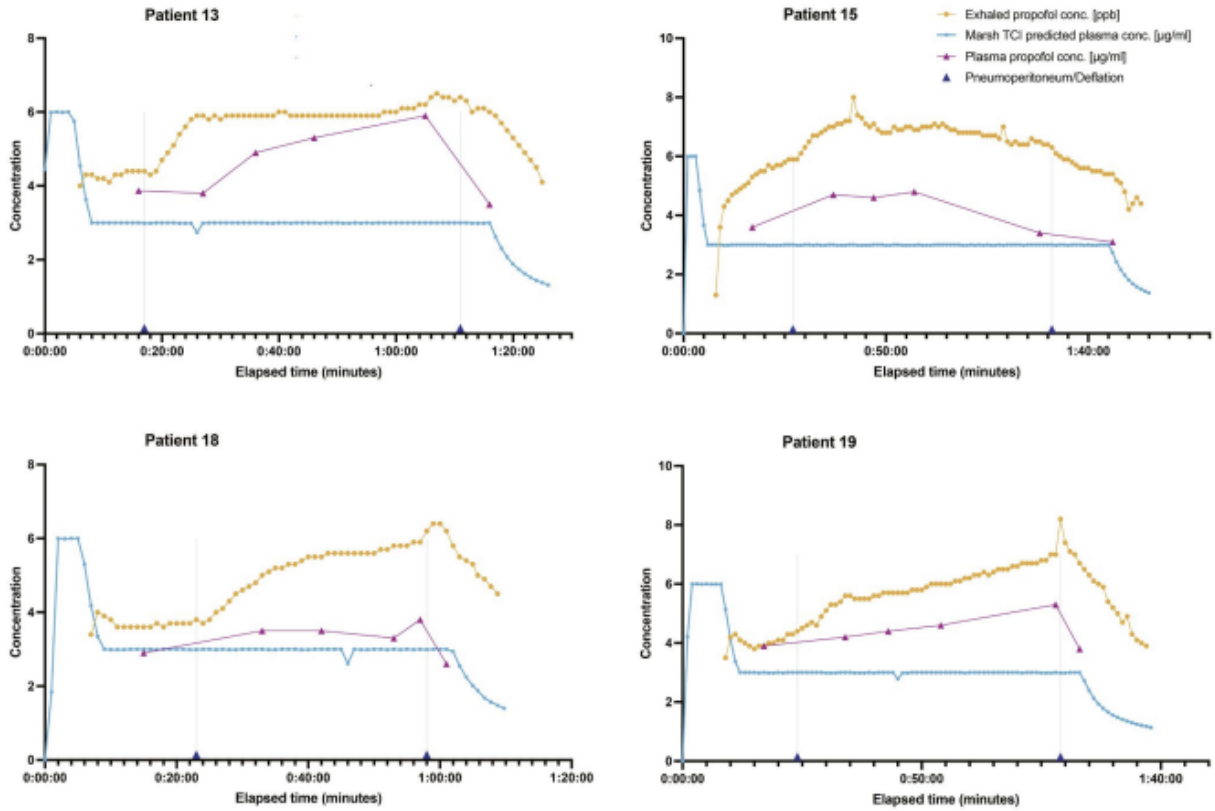

FIGURE 1 Exhaled propofol concentrations, plasma propofol concentrations, Marsh plasma target TCI predicted concentrations and time points of peritoneal inflation and deflation from four study patients

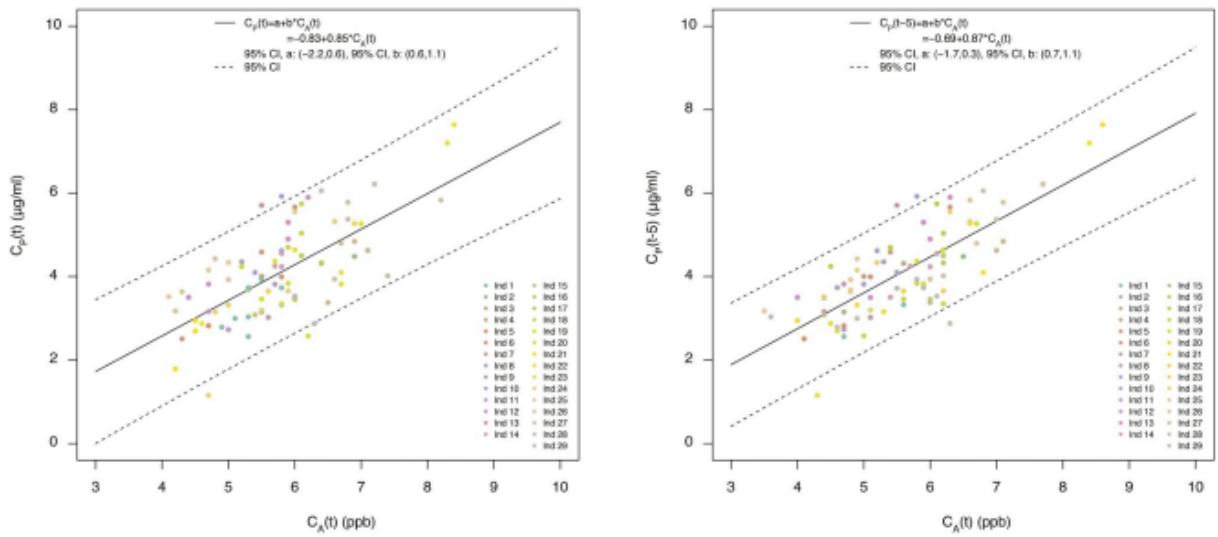

FIGURE 2 (A) Generalized estimating equation (GEE) with propofol concentration in exhaled air (C_A) as dependent variable and propofol concentration in plasma (C_p) as dependent variable. The first two plasma samples from each patient have been omitted. (B) Final GEE model of propofol concentrations in exhaled air and plasma, with first two plasma samples omitted and five minutes delay of (C_A) to (C_p)

Exploring The Predictability Of The Decrement Time When Accounting For Interpatient Variability.

Presenting Author: Elie Sarraf

Introduction: Context-Sensitive Half-time (CSHT), the time required to achieve half the blood concentration after a target-controlled infusion (TCI), has become a well-established term in anesthesia education since its introduction in 1992[1].

CSHT has also been used to predict emergence from anesthesia, specifically when to turn off a propofol infusion. The predication occurs despite generally being unable to accurately ascertain the current drug concentration or the drug concentration required for emergence. This abstract seeks to validate the predictability of CSHT, and its more general term, decrement time, with regard to inter-patient variability[2].

Methods: Using MATLAB (R2023a), 2000 patients set to be 50 years of age, 70 kg, 170 cm, and male were simulated using the Eleveld propofol model[3]. The model error from inter-individual variability was created by randomly setting the "η" values to be within [-0.75 to 0.75] of the standard deviation of each parameter (ω). The method described is similar in form to the methods described by Hu et al[4].

A TCI was simulated for an ideal patient to run for 4 hours at a set concentration of 4 mcg/mL. After 4 hours, the infusion was paused, and the decrement time was measured by identifying the time when the blood concentration would be 3, 2, and 1.5 mcg/mL (25%, 50%, and 62.5% decrement time, respectively).

Results: The simulation and corresponding decrement time are plotted in the attached Figure. The decrement times were calculated to have a median value of 1.05, 5.40, and 18.32 minutes for the 25%, 50%, and 62.5% decrement values, respectively. The lower and upper calculated ranges for these values in this patient population were 0.12-6.9, 1.07-28.23, and 2.63-59.2 minutes, respectively.

Conclusions: This simulation study shows that the Decrement time and CSHT cannot accurately reflect patient variability. Rather, the principal conclusion one can leverage is that as one increases the set concentration relative to the patient's emergence concentration, the lengthier and more unpredictable the patient's emergence will become after stopping the TCI pump. The study is limited by the fidelity of early phase pharmacokinetics of the model used, and further empirical studies will need to be performed.

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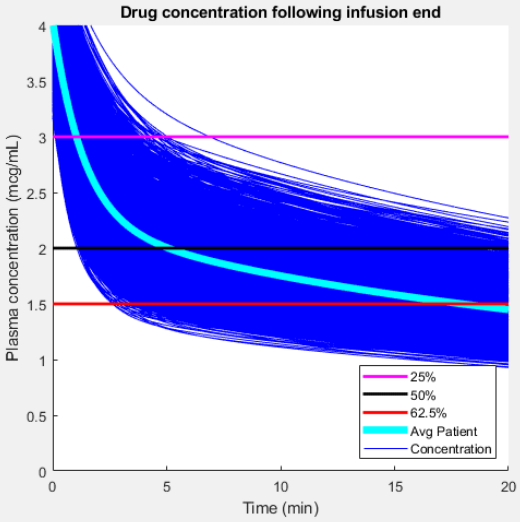
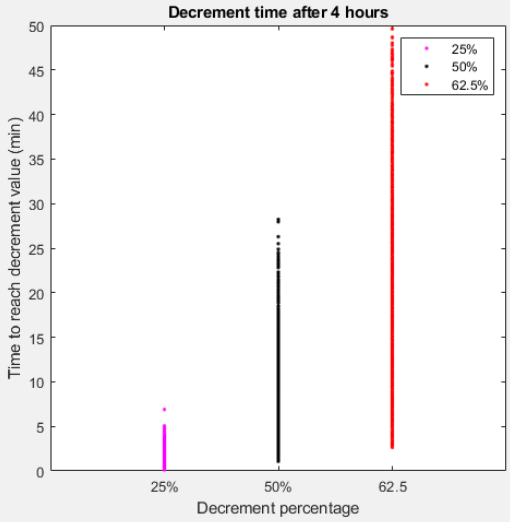

Drug concentration following infusion end
Plasma concentration (mcg/mL)
Time (min)
25%
50%
62.5%
Avg Patient
Concentration


Decrement time after 4 hours
Time to reach decrement value (min)
Decrement percentage
25%
50%
62.5%