ISAP 30th Annual Meeting

2021 Syllabus

Saturday, October 2nd, 2021

Virtual Meeting

777 N Van Buren St, Unit 2705 • Milwaukee, WI 53202
(p) 414-379-8602 • isaphq@isaponline.org • isaponline.org

INTERNATIONAL SOCIETY FOR ANAESTHETIC PHARMACOLOGY
ISAP

30th 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.

Learner Notification

Program Target Audience

This program is designed for an international audience of general anesthesiologists, and anesthesiologists with a special interest in clinical pharmacology and technology.

Acknowledgement of Financial and/or In-Kind Commercial Support

No financial or in-kind commercial support was received for this educational activity.

Acknowledgement of In-Kind Commercial Support

No in-kind commercial support was received for this educational activity.

Satisfactory Completion

Learners must complete an evaluation form to receive a certificate of completion. 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.

Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and International Society of Anaesthetic. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians (ACCME) Credit Designation

Amedco LLC designates this live activity for a maximum of 3.75 *AMA PRA Category 1 Credits*™. 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. Assess the need for new drugs in their practice and employ them safely where indicated.
2. Manage the impact of COVID-19 in the care of their patients.
3. Describe the effect of anesthetics on brain function and monitoring and apply this in their practice.

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)

All individuals in a position to control the content of CE are listed in the agenda. If their name is not listed below, they disclosed that they had no financial relationships with a commercial interest.

First Name	Last Name	Company
Sorin	Brull	Mayo Clinic:Other,Mayo Clinic/Merck:Research Grant Site Principal Investigator,Senzime AB:Stock Shareholder,The Doctors Company:Scientific/Medical Advisory Board Member,NMD Parma:Scientific/Medical Advisory Board Member,Coala Life Inc.:Scientific/Medical Advisory Board Member,Takeda Pharmaceutical Co, Ltd:Scientific/Medical Advisory Board Member
John	Donovan, MD	Concentric Analgesics:Employee
Joseph	foss	NeuroTherapia:Stock Shareholder
Tong J.	Gan	Edwards:Speakers Bureau,Heron:Consultant,Acacia:Speakers Bureau,Medtronic:Consultant
Jeff	Mandel	Continuous Precision Medicine:Stock Shareholder,Continuous Precision Medicine:Scientific/Medical Advisory Board Member
Harold	Minkowitz	Concentric :Other
Robert	Sneyd	Paion, Germany:Consultant,Altus, Canada:Consultant,Medtronic, UK:Consultant

30th Annual Meeting

How to Get Your Certificate

1. **Go to http://isap.cmecertificateonline.com**
2. **Click on the "ISAP 30th Annual Meeting on Anaesthetic Pharmacology" link.**
3. **Evaluate the meeting.**
4. **Print all pages of your certificate for your records.**

Questions? Email Certificate@AmedcoEmail.com

Participant Notification

We acknowledge the potential presence of limitations on information, including, but not limited to: data that represents ongoing research; interim analysis; preliminary data; unsupported opinion; or approaches to care that, while supported by some research studies, do not represent the only opinion or approach to care supported by research.

Inaugural Mohamed Naguib Lecture and Posthumous Awarding of the Lifetime Achievement Award

Generous support provided by Senzime Corporation

SENZIME

In honor of Dr. Mohamed Naguib's long service to the International Society of Anaesthetic Pharmacology (ISAP), and his distinguished contributions to the field of anesthesiology, he will posthumously receive the ISAP Lifetime Achievement Award during the meeting.

ISAP has established the Mohamed Naguib Lecture to honor his many accomplishments, which will be presented at every ISAP Annual Meeting. The Inaugural Lecture will be 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.

CELEBRATING 30 YEARS

30th Annual Meeting Schedule

0920 - 1430 US Eastern Time Zone

0920 – 0930 **ISAP Announcements** – *Mark Dershwitz, MD, PhD, President*

ISAP Board of Directors Business Meeting/Election of Board

0930 – 1030 **Session 1 – New Drugs / Novel Agents**
Moderator: *Joseph Foss, MD, Cleveland Clinic, Cleveland, Ohio*

0930 – 0950 **Benzodiazepine Sedation & Anesthesia, What Does Remimazolam Offer**
J. Robert Sneyd, MD, FRCA, Emeritus Professor, Faculty of Health: Medicine, Dentistry and Human Sciences, University of Plymouth, United Kingdom

0950 – 1010 **Integrating New Antiemetics into Clinical Practice**
Tong Joo (TJ) Gan, MD, MHS, FRCA, MBA, Professor and Distinguished Endowed Chair, Department of Anesthesiology, Renaissance School of Medicine, Stony Brook University, Stony Brook, New York

1010 – 1030 **Anesthesia Implications of Covid on Peri-op Cognition**
Avindra Nath MD, Chief, Section of Infections of the Nervous System; Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

1030-1045 **Break**

1045 – 1145 **Session 2 – Next Generation EEG Monitoring for Anesthesia**
Moderator: *Hugo Vereecke, MD, PhD, Assistant Professor, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

1045 – 1115 **Towards EEG-based Patient Monitoring with Artificial Intelligence**
Sowmya Ramaswamy, PhD, Researcher, Department of Anesthesiology, UMCG, Netherlands

1115 – 1145 **EEG and Anesthesia: Exactly What Language is the Brain Speaking**
Jamie Sleigh, MD, Professor, Department of Anaesthesia, Waikato Clinical Campus, University of Auckland, New Zealand

1145-1200 **Break**

1200 – 1245 **Keynote Speaker & Lifetime Achievement Awardee**
Mohamed Naguib – His Work and Influence
Sorin Brull, MD, FCARSCI, Emeritus Professor of Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic

1245-1300 **Break**

1300 – 1345 **Moderated Poster Session**

1345 – 1400 **Mohamed Naguib Lecture**
"Reminisces of Mohamed Naguib"
David L. Brown, MD, Principal, Clear Consults, Wisconsin
Pamela Flood, MD, Professor of Anesthesiology, Perioperative and Pain Medicine, (OB) at the Stanford University Medical Center, Stanford, California
Joseph Foss, MD, Cleveland Clinic, Cleveland, Ohio

1400 – 1430 **Virtual Reception**

2021 Board of Directors

President
Mark Dershwitz, MD, PhD

President Elect
Hugo Vereecke, MD, PhD

Vice-President
Stuart Forman, MD, PhD

Secretary & 2021 Annual Meeting Co-Chair
Joseph Foss, MD

Treasurer
Jerry Ingrande, MD, MS

Immediate Past- President
Konrad Meissner, MD

Director 2020-2022 & 2021 Annual Meeting Co-Chair
Klaus H. Hoerauf, MD, PhD

Director 2019-2021
Amanda M. Kleiman, MD

A&A Section Editors
Markus Hollmann, MD, PhD, DEAA
Ken Johnson, MD

Historian
Tom Krejcie, MD

Executive Director
Jane Svinicki, CAE

Planning Committee

Joseph Foss, MD, Co-Chair
Cleveland Clinic, Cleveland, Ohio

Klaus H. Hoerauf, MD, PhD, DBA, Co-Chair
Becton, Dickinson & Co, Franklin Lakes, NJ, USA and Department of Anesthesiology, Medical University of Vienna, Austria

Speakers & Moderators

David L. Brown, MD
Principal, Clear Consults, Wisconsin

Sorin Brull, MD, FCARSCI
Emeritus Professor of Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic

Pamela Flood, MD
Professor of Anesthesiology, Perioperative and Pain Medicine, (OB) at the Stanford University Medical Center, Stanford, California

Tong Joo (TJ) Gan, MD, MHS, FRCA, MBA
Professor and Distinguished Endowed Chair, Department of Anesthesiology, Renaissance School of Medicine, Stony Brook University, Stony Brook, New York

Avindra Nath MD
Chief, Section of Infections of the Nervous System; Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Sowmya Ramaswamy, PhD
Researcher, Department of Anesthesiology, UMCG, Netherlands

Jamie Sleigh, MD
Professor, Department of Anaesthesia, Waikato Clinical Campus, University of Auckland, New Zealand

J. Robert Sneyd, MD, FRCA
Emeritus Professor, Faculty of Health: Medicine, Dentistry and Human Sciences, University of Plymouth, United Kingdom

Hugo E.M. Vereecke, MD, PhD
Assistant Professor, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium

Abstract Table of Contents

Sponsors

Platinum

BD

Advancing the world of health

Silver

abbvie

Dräger

Back to Abstract Table of Contents

A Selective $GABA_A$-Slow Agonist Produces a Unique EEG Profile

Presenting Author: M. Bruce MACIVER[1]
Co-Authors: Sarah L. EAGLEMAN[1], M. Frances DAVIES[2], Hilary S. MCCARREN[3], Dinesh PAL[4], George. A. MASHOUR[4], and Edward J. BERTACCINI[1,2];

[1]Stanford University, CA; [2]Palo Alto VA, Palo Alto, CA; [3]US Army Med. Res. Inst. of Chem. Def, Aberdeen Proving Ground, MD; [4]University of Michigan, MI

Background/Introduction: Anesthetic agents like propofol increase power in slow delta frequencies (1 to 4 Hz), with a general decrease in EEG frequencies above 30 Hz. Propofol is non-selective for $GABA_A$ response subtypes, enhancing all three $GABA_A$-subtypes (slow, fast, and tonic). A new anesthetic, BB, selectively targets $GABA_A$-slow synapses to depress brain responsiveness. We hypothesized that a selective GABAA-slow agonist, BB, would produce a different EEG signature compared to the broad spectrum $GABA_A$ agonist (propofol), and tested this using rat EEG recordings.

Methods: Male rats were used following IACUC approval from the US Army Medical Research Institute of Chemical Defense or the University of Michigan. Rats were anesthetized using isoflurane (3-5% induction, 1-3% maintenance; with oxygen @ 0.5-1.0 L/min. Stainless steel screws were used to capture cortical EEG activity.

Results: Propofol administration generated increased power in slow delta frequencies (1 to 4 Hz) and a general decrease in EEG power above 30 Hz at loss of righting reflex (LORR). By contrast, BB administration increased theta activity markedly (5 - 8 Hz), and slightly increased delta power, but did not depress high frequency responses above 30 Hz. Neither agent produced burst suppression activity at LORR. Both anesthetics produced a characteristic flattening of time-delayed embeddings, similar to volatile and dissociative anesthetics at LORR. Propofol's EEG effects were in agreement with those seen in previous studies across individuals and species. At LORR a generalized slowing in EEG was seen with increased power in frequencies below 4 Hz. BB produced a markedly different EEG pattern, with a selective increase observed in the theta frequency range.

Conclusion: Increased theta frequencies are interesting because $GABA_A$ slow synapses have previously been suggested to underlie theta frequency oscillations, while fast synapses control high, gamma frequency oscillations (30-60 Hz). Tonic $GABA_A$ responses produce a generalized depression of neuronal activity across all frequencies. BB and propofol share the ability to flatten EEG time-delayed embeddings at LORR. Flattened embeddings are also observed in humans and thought to reflect a decrease in EEG information content at LORR. It appears that propofol's effects on fast and/or tonic responses contribute to its respiratory and cardiovascular unwanted side effects, since these were not produced by BB.

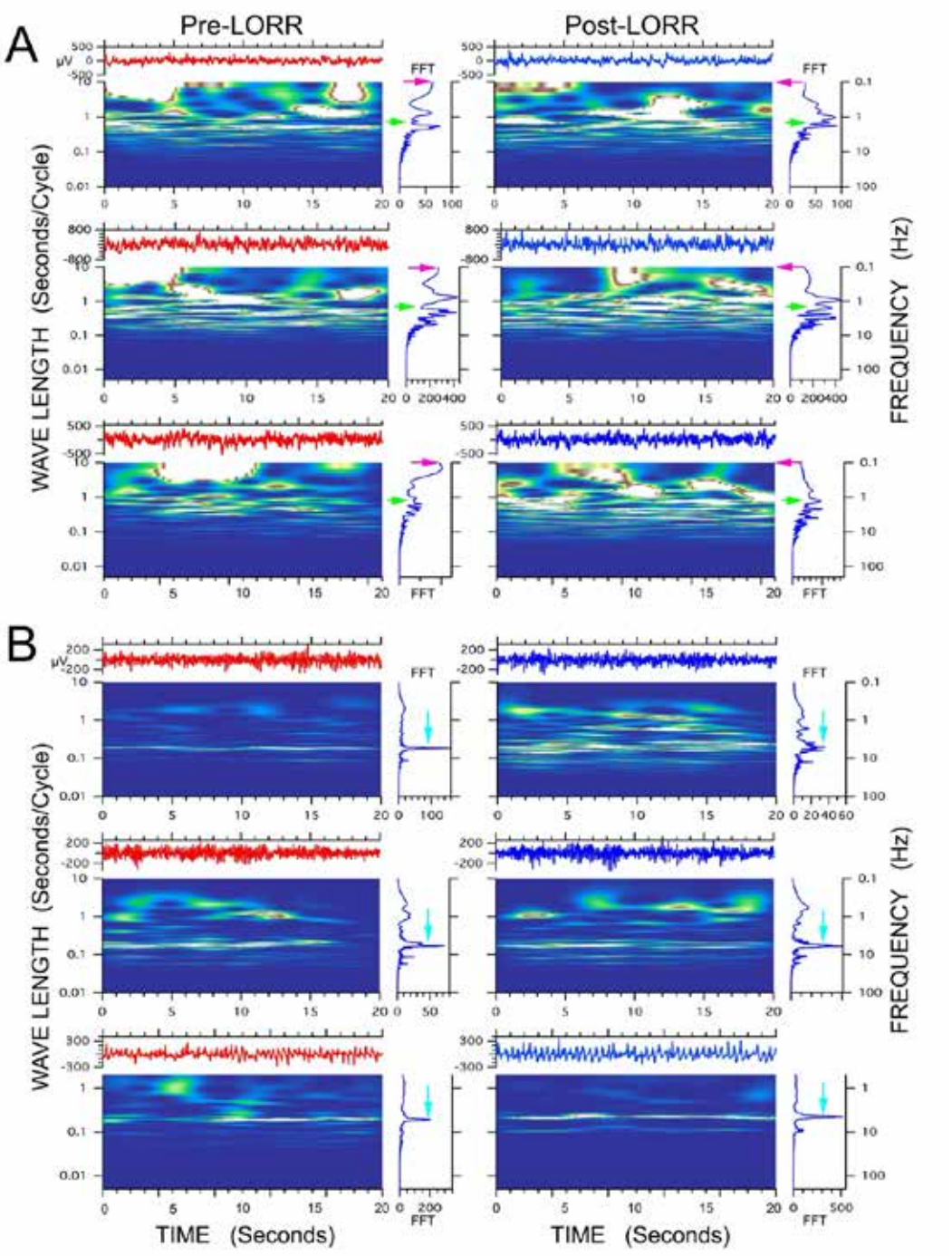


Figure 1. Frequency analysis comparing effects produced by propofol (A) and BB (B) on EEG recordings 20 seconds before loss of righting (LORR) and after. Propofol produced a decrease in slow wave (0.1 Hz – pink arrows in FFT graphs) rhythms together with an increase in delta rhythms (1-3 Hz – green arrows). BB produced a selective increase in theta frequencies (B – blue arrows in FFT), produced by prolonging GABA-slow synaptic inhibition at loss of righting. Each row presents data from individual animals, together with EEG recordings used to create spectrograms and fast-Fourier transforms (FFT).

Urinary Clearance of 11-Nor-9-Carboxy-Δ^9-Tetrahydrocannabinol: A Detailed Pharmacokinetic Analysis

Thomas K. Henthorn[1], Cristina Sempio[1], Jost Klawitter[1], Uwe Christians[1]

[1] Department of Anesthesiology, University of Colorado School of Medicine

Introduction: Urine is a common matrix for screening for cannabis use. Δ^9-Tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, is highly lipophilic, with little THC excreted in urine. Following phase I and phase II metabolism, primarily in the liver, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol-glucuronide (THCCOOH-glucuronide) is excreted as the primary urinary metabolite, accounting for greater than 95% of known urinary THC-derived compounds. The purpose of this report is to examine rigorously the relationship of THCCOOH clearance to creatinine clearance as well as the relationship of urine production (flow) rate to urine creatinine concentration and creatinine clearance as these relationships underlie the common practice of correcting THCCOOH concentrations in urine with creatinine concentrations in the same sample.

Methods: Six healthy male cannabis users were admitted to the secure residential facility at the Intramural Research Program of the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH). Spaced one week apart, cigarettes containing 0, 15.8 mg or 33.8 mg THC were smoked. All urine samples produced were collected for the next 168 h; plasma was collected based on a specific schedule[4], while urine was collected ad libitum[2]. The volume of each urine specimen was recorded as well as the time that it was produced. Urine concentrations of THCCOOH were measured by GC-MS with a limit of detection of 0.5 ng/mL. Population pharmacokinetic modeling was accomplished with Phoenix NMLE 8.3.

Results: There were 506 timed urine collections in which urine volume, creatinine concentration and THCCOOH were measured in the 6 male subjects (mean: 77.6 kg, range: 64.8-93.4 kg and mean: 31.3 years, range: 29-36 years) and included in the pharmacokinetic modeling. Our data and PK modeling indicate that cumulative urinary excretion of THCCOOH had essentially plateaued by the end of one week with less than 0.1% rise from one urine collection to the next during the final day. Our estimate of recovered dose in the urine as THCCOOH was 0.57 ± 0.35% for the low dose and 0.57 ± 0.24% for the high dose. Creatinine clearance was a significant covariate for THCCOOH clearance.

Conclusion: Our model found that only 2.2% of total THCCOOH clearance is via urinary excretion, leaving 97.8% to be accounted for by other routes of elimination. Nevertheless, creatinine clearance is a significant covariate for predicting the urinary excretion of THCCOOH. Finally, urine creatinine concentration is not highly correlated to hydration state as reflected by urine production rate, suggesting that other factors are involved in determining creatinine concentration from an isolated urine sample and that reliance on creatinine concentration or specific gravity to correct urine THCCOOH concentrations may have more limitations than previously appreciated.

Back to Abstract Table of Contents

Effects of volatile general anesthetics in fly models of mitochondrial disease

Presenting Author: Amanda R. Scharenbrock[1]
Co-Authors: Zachariah P.G. Olufs[1], David A. Wassarman[2], Misha Perouansky[1]

[1]Department of Anesthesiology, University of Wisconsin-Madison, Madison, WI, USA;
[2]Depatment of Medical Genetics, University of Wisconsin-Madison, Madison, WI, USA.

Background/Introduction: Animals harboring mutations in Complex I of the mitochondrial electron transport chain (mETC) display behavioral sensitivity to volatile general anesthetics (VGAs) and may be at increased risk of VGA-induced deleterious collateral effects. We found that mutations in the nuclearly-encoded Complex I gene *ND23* in fruit flies (*Drosophila melanogaster)* also confer behavioral sensitivity to VGAs. The ND23 subunit is the fly ortholog of mammalian NDUFS8. Moreover, we found that exposure of *ND23* mutant flies to isoflurane, but not sevoflurane, caused lethality and that lethality was suppressed by hypoxia (5% O_2) and enhanced by hyperoxia (75% O_2). In the present study, we performed a parallel analysis of the mitochondrially-encoded ND2 subunit of Complex I to determine the extent to which different components of Complex I contribute to deleterious collateral effects of VGAs and to establish a genetically-tractable system to investigate the mechanisms underlying deleterious collateral effects of VGAs.

Methods: Flies of a particular age range were exposed to behaviorally equivalent doses of isoflurane (2%) or sevoflurane (3.5%) in 21% or 75% O_2 for two hours using a custom-made Serial Anesthesia Array (SAA) consisting of agent-specific anesthetic vaporizers, flow meters, and a serial array of anesthetizing positions. Following exposure, flies were incubated under standard culturing conditions and the percent mortality was determined after 24 hours.

Results: As previously observed, isoflurane in normoxia (21% O_2) increased mortality of *ND23* mutant flies relative to unexposed *ND23* mutant flies, but sevoflurane in normoxia did not (unexposed: 5.40 ± 5.01%, isoflurane: 34.45 ± 19.43%, and sevoflurane: 8.04 ± 3.74%). Hyperoxia (75% O_2) further increased mortality from isoflurane exposure to 90.19 ± 11.45%, but hyperoxia did not affect mortality from sevoflurane exposure (3.71 ± 1.89%). Similarly, exposure of *ND2* mutant flies to isoflurane in normoxia increased mortality from 21.89 ± 8.51% to 56.63 ± 12.93 %, and isoflurane in hyperoxia further increased mortality to 99.74 ± 0.64%. In contrast *ND2* mutants deviated from *ND23* mutants in that sevoflurane in hyperoxia increased mortality to 68.21 ± 11.26%, relative to 29.39 ± 8.89% in normoxia.

Conclusions: Mutations in both nuclearly- and mitochondrially-encoded subunits of mETC Complex I increase susceptibility to isoflurane toxicity in flies. However, the mutants differed in their susceptibility to sevoflurane toxicity in hyperoxia. These data indicate that mutations in different Complex I subunits confer VGA-specific susceptibility to toxicity. Using genetic approaches available in flies, we are now in a position to understand the mechanisms underlying vulnerability to VGA-induced toxicity in mitochondrial mutants.

Molecular dynamics simulations reveal how Sugammadex reverses muscle relaxants and interacts with anaesthetic agents

Presenting Author: Amir Irani[1]
Co-Authors: Nicola Whittle[1], Logan Voss[1], Jamie Sleigh[2]

[1]Anaesthesia Department, Waikato District Health Board, Hamilton, New Zealand
[2]Department of Anaesthesia, Waikato Clinical Campus, University of Auckland, Hamilton, New Zealand

Introduction: Sugammadex reverses neuromuscular blockade by rocuronium via a supramolecular mechanism of action. During the design process cyclodextrin host molecules were systematically modified to achieve the highest affinity between the cyclodextrin molecules and rocuronium therefore creating the most stable complex. Through these experiments the size of the hydrophobic binding cavity, electrostatic interactions and Van der Waals forces were found to be important determinants of structure-activity relationships. This was consistent with what is known about cyclodextrin chemistry from previous work (Adam et al., 2002). Our aim for this study was to create a computer model which would allow the dynamic interaction over time of the host and guest molecules to be dynamically visualised in real time and validate this computer simulation by comparison with experimental lab data and previously published data of affinity between various drugs and sugammadex (Zwiers et al., 2011).

Methods: Molecular dynamics (MD) simulations have been performed to understand the interaction of Sugammadex with selected Neuromuscular blocking agents (NMBAs), corticosteroids, anaesthetics and antibacterials using Gromacs2019. Drug molecules were docked into the sugammadex using AutoDock Vina as an initial step for the MD simulations. Change in enthalpy (ΔH) of encapsulated drugs within sugammedex were calculated using Poisson Boltzmann relation via gmx_MMPBSA package. We have verified our simulations with some cortical slice experiments monitoring the change in field potential neuronal population activity.

Results: The affinity of sugammadex with rocuronium and the other drugs modelled by computer simulation correlated with the experimental data previously published. This was measured by the change in enthalpy (ΔH) of the host-guest complex. It was our expectation that the negatively charged side chains would be the first point of binding between the molecules. This was not the case as the rocuronium was first encapsulated by the hydrophobic cavity and then held in place by the negatively charged side chains providing a very stable state. In an interesting finding, the computer simulated model showed some low affinity binding with propofol. This was then verified experimentally by showing that the effects of propofol on in vitro cortical slice model were attenuated by the addition of sugammadex.

Conclusion: Correlation of molecular interactions seen using the computer simulations and data from laboratory experiments as well as previously published data allows validation of the computer simulation model. This has provided some unexpected results around real time molecular interactions between sugammadex and rocuronium and propofol.

Adam, Julia M., et al. "Cyclodextrin-Derived Host Molecules as Reversal Agents for the Neuromuscular Blocker Rocuronium Bromide: Synthesis and Structure− Activity Relationships. " Journal of Medicinal Chemistry 45.9 (2002): 1806-1816.

Zwiers, Alex, et al. "Assessment of the potential for displacement interactions with sugammadex. " Clinical drug investigation 31.2 (2011): 101-111.

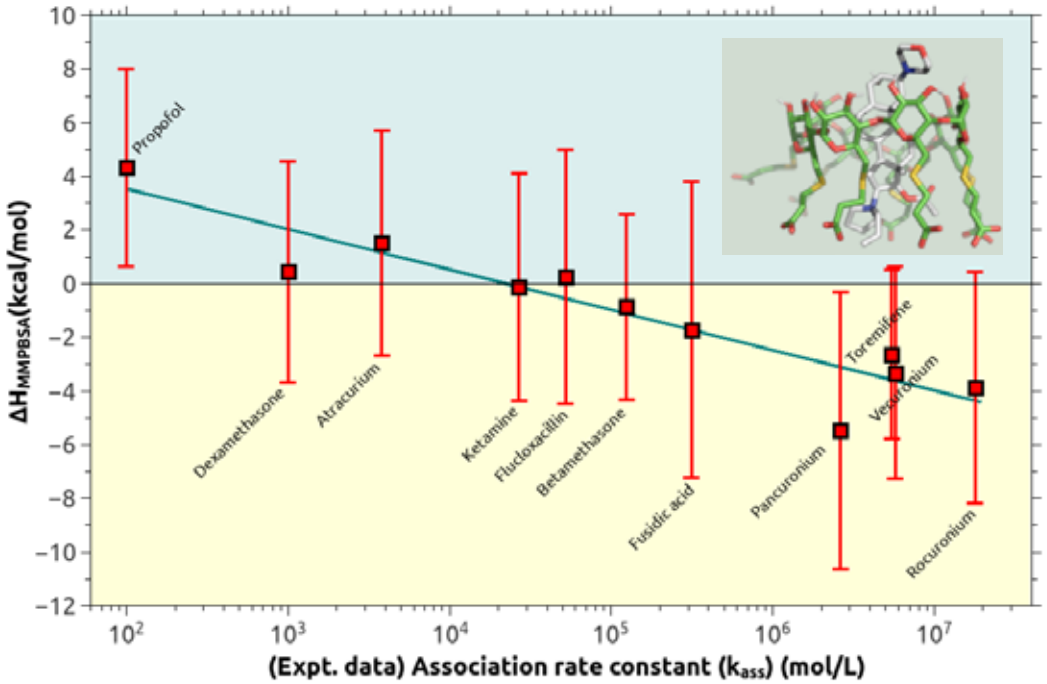


Figure 1. Correlation between change in enthalpy (ΔH) from computational simulations and the experimental data taken from *Zwiers et al., 2011.* The inset shows how sugammadex encapsulates rocuronium.

Leveraging PRC to Guide Remimazolam Dosing for Sedation

Introduction

Remimazolam in a novel short-acting benzodiazepine recently approved in the United States for procedural sedation[1] but has a clinically significant failure rate at achieving adequate sedation (8.7-19.4%)[2-3]. We have previously demonstrated that the use of PRC to identify the dose of propofol required for sedation results in a decrease in the variability in target effect[4], and PRC has been successfully used in DISE procedures[5], as well as endoscopies. Briefly, PRC identifies a target effect site concentration required to achieve a clinical outcome and then determines how to maintain that target. We hypothesize that applying the PRC algorithm would result in more consistent and successful dosing with less significant adverse effects. We tested this hypothesis recognizing the incomplete pharmacokinetic profile of the drug and assuming for a large population heterogeneity.

Methods

Using MATLAB, we performed a Monte Carlo simulation of 20000 patients receiving remimazolam as a single agent in a 60-minute window in order to achieve and then maintain moderate sedation (OAA/S 2-3) while avoiding deep sedation (OAA/S 1). The pharmacokinetic parameters (volumes and clearances) as well as the pharmacodynamic parameters (ke0 and clinical effect) were randomly assigned such that the parameters would fall within the 5th and 95th percentile of their estimated value[6].

Each patient was simulated under three conditions:

1) Following the product monograph: 5 mg bolus initially and then 2.5 mg boluses thereafter at a rate not to exceed once every 2 minutes[1]
2) Using the original PRC algorithm[4] to identify a target effect site concentration followed by a series of infusions so that the effect site concentration remains within 5% of the target value. If the patient became over- or under-sedated the algorithm would adjust the target effect site concentration accordingly.
3) An updated version of the PRC algorithm followed by the same adjustments described above.

Results

Figure 1 demonstrates an example of the simulated effect site concentration over time in the three conditions described previously. Table 1 shows the compiled results of all simulations. Briefly, the bolus technique failed to achieve therapeutic levels in approximately 5% of cases and took more than 10 minutes in over 25 % cases; PRC achieved adequate sedation in all cases within 15 minutes. While the PRC algorithm had more patients achieving deep sedation, this was primarily at the transition from target identification to target maintenance. Of note, the bolus technique yielded deep sedation for a longer of period of time. The second version of PRC resulted in a faster overall target identification time compared to the original PRC algorithm at the cost of more overshoot.

Conclusion

The simulation study demonstrates that PRC can appropriately titrate remimazolam despite an incomplete pharmacokinetic profile. The failure rate identified in this simulation study appears to mimic the clinical failure rate with fentanyl being used to augment sedation in the clinical studies. Clinical evaluation of the PRC algorithm is required for final validation and will allow for further tuning of the algorithm.

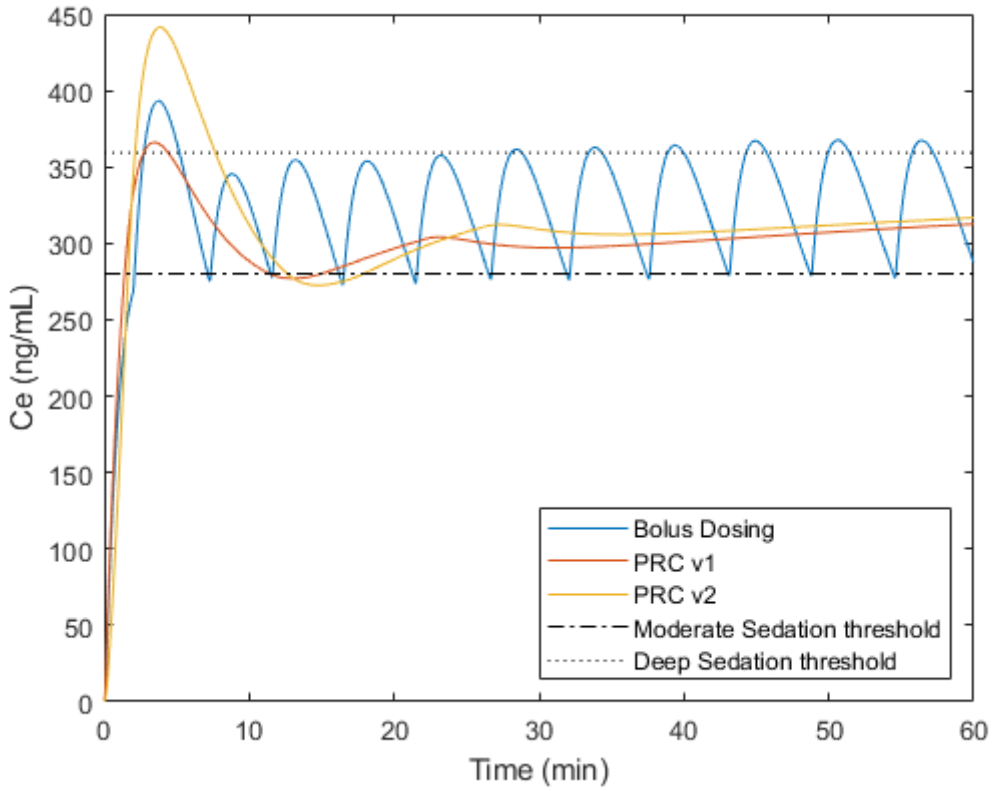


Figure 1: Example of a simulated patient's remimazolam effect site concentration after either Bolus dosing or using the PRC algorithm

N = 20000	Bolus	PRC	PRC v2
Number of patients failed to reach target (%)	951 (4.8%)	0	0
Number who took more than 10 min to reach target (%)	5206 (26 %)	247 (1.2%)	22 (0.1 %)
Average target time (min) (std)	9.16 (9.94)	4.91 (2.83)	2.65 (0.93)
Average time above threshold (min) (std)	48.12(10.53)	50.64 (4.21)	52.51(3.52)
Number of patients over-sedated (%)	5527 (27.6)	10662 (53.3)	13684 (68.2)
If over-sedated, amount of time over-sedated (min) (std)	24.9 (17.72)	6.55 (5.32)	8.02 (5.64)
Median number of doses to achieve a target (50% (25-75, 100))	18 (14-23, 30)	N/A	N/A
Median number of redoses if solution found (50% (25-75, 100))	14 (12-16, 22)	N/A	N/A
Median number of adjustments to titrate PRC once target found (50% (25-75,100))	N/A	3 (0-5, 22)	4 (2-6, 23)

Table 1: Compiled results of Monte Carlo Simulation comparing Bolus dosing with both PRC implementation

References

1. Acacia Pharma I. BYFAVO™ (remimazolam) [package insert]. *US Food and Drug Administration website*. 2020;

2. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest*. Jan 2019;155(1):137-146. doi:10.1016/j.chest.2018.09.015

3. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. Sep 2018;88(3):427-437.e6. doi:10.1016/j.gie.2018.04.2351

4. Mandel JE, Sarraf E. The Variability of Response to Propofol Is Reduced When a Clinical Observation Is Incorporated in the Control: A Simulation Study. *Anesthesia & Analgesia*. 2012;114(6)

5. Atkins JH, Mandel JE, Rosanova G. Safety and efficacy of drug-induced sleep endoscopy using a probability ramp propofol infusion system in patients with severe obstructive sleep apnea. *Anesth Analg*. Oct 2014;119(4):805-10. doi:10.1213/ane.0000000000000229

6. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers. *Anesthesiology*. 2020-04-01 2020;132(4):636-651. doi:10.1097/aln.0000000000003103

TITLE:

Vocacapsaicin reduces pain and opioid consumption for two weeks following a single administration during total knee arthroplasty

AUTHORS:

1. *Sam Teichman, MD*
2. *David Leiman, MD*
3. *Harold Minkowitz, MD*
4. *John Donovan, MD*

BODY:

Introduction:
Multi-day postoperative analgesia following total knee arthroplasty (TKA) remains an important unmet medical need. Vocacapsaicin (formerly CA-008) is a prodrug of capsaicin, a TRPV1-agonist that selectively desensitizes pain-conducting nerve fibers without producing sensory numbness or motor weakness. We previously demonstrated that a single administration of vocacapsaicin produced postsurgical analgesia and reduced opioid consumption (OC) for two weeks following bunionectomy.[1] We sought to replicate these results in a randomized double-blinded multicenter study of patients undergoing TKA.

Methods:
The study was conducted in patients undergoing primary TKA under spinal anesthesia with full standard-of care perioperative analgesia including ropivacaine 200 mg (femoral nerve block, IPACK and periarticular infiltration) and intraoperative acetaminophen and ketorolac (ClinicalTrials.gov: NCT04203537). Eligible subjects were aged 18-80, BMI up to 42 kg/m2. Patients were excluded if opioid tolerant, allergic to capsaicin, or had a concurrent painful condition. Following IRB approval and written informed consent, consenting patients were randomized to placebo, 36 mg, or 60 mg of vocacapsaicin in 120 ml of normal saline. The test article was instilled onto cut bone surfaces, infiltrated into peri-articular tissue, and injected into the closed capsule at the end of the case. Postoperative pain and analgesic consumption were recorded in hospital for 4 days, and after hospital discharge for at least two weeks following surgery. After discharge, all subjects received celecoxib twice daily and acetaminophen or acetaminophen/oxycodone as needed.

The primary efficacy endpoint was the area under the curve (AUC) of the Numerical Rating Scale at rest from 0 to 96 hours (NRS-R $AUC_{0\text{-}96h}$). Secondary efficacy endpoints included evoked pain with activity (NRS-A $AUC_{0\text{-}96h}$), total opioid consumption ($OC_{0\text{-}96h}$), and the time of discontinuation of opioid use (DO). Exploratory endpoints included measures of recovery during

hospitalization and NRS-R, NRS-A and OC from 96 hours to Day 15. Safety endpoints included vital signs, physical examination, surgical site assessments, neurosensory testing, adverse events, and clinical laboratory evaluations.

Results:
A total of 193 patients (mean age 62.3 years) were enrolled at 4 sites from December 2019 to September 2020. Groups were well-matched at baseline. Over the first 4 days, vocacapsaicin 36 mg met the primary and secondary endpoints for both pain and opioid consumption. The NRS-R $AUC_{0\text{-}96h}$, was reduced by 17% ($p=0.0012$). The NRS-A $AUC_{0\text{-}96h}$ was reduced by 20% ($p=0.0006$). $OC_{0\text{-}96h}$ was reduced by 30% ($p<0.0001$). Vocacapsaicin enabled earlier ambulation during hospitalization and produced a trend towards earlier DO.

Reductions in pain and opioid use continued over the 2 weeks following surgery. Vocacapsaicin 36 mg reduced NRS-R $AUC_{0\text{-}15d}$ by 15% ($p=0.03$) and NRS-A $AUC_{0\text{-}15d}$ by 14% ($p=0.04$). Opioid consumption following discharge, $OC_{96h\text{-}15d}$ was reduced by 52% ($p=0.0063$). Overall opioid consumption, $OC_{0\text{-}15d}$ was reduced by 35% ($p<0.0001$). An analgesic effect was still evident on day 15. Vocacapsaicin 36 mg was more effective than vocacapsaicin 60 mg. Both doses of vocacapsaicin generally appeared safe and well-tolerated. No local or systemic safety concerns were observed.

Discussion:
Vocacapsaicin provided durable and clinically meaningful analgesia following TKA, including reduced pain and opioid consumption at remarkably high levels of statistical significance. Vocacapsaicin also improved functional recovery. The reduction in the amount and duration of opioid use helps address the unmet medical need for effective non-opioid postsurgical analgesia by reducing or potentially eliminating the requirement for opioids following hospital discharge. Further studies will confirm and expand the potential of vocacapsaicin for prolonged postsurgical analgesia.

References:
1. Gottlieb IJ, Beaton A, Solanki D, et al. A randomized, placebo-controlled trial of intraoperative administration of CA-008 for post-operative analgesia after bunionectomy. Presented at ASRA 2019. (https://epostersonline.com/ASRASPRING19/node/1194?view=true)

Vocacapsaicin Reduces Pain and Opioid Consumption for Two Weeks Following a Single Administration During Total Knee Arthroplasty

Sam Teichman, MD[2]; David Leiman, MD[1]; Harold Minkowitz, MD[1]; John Donovan, MD[2]
[1]HD Research, Houston, TX; [2]Concentric Analgesics, Inc., San Francisco, CA

ABSTRACT

Introduction: Vocacapsaicin is a novel, non-opioid therapeutic that provides long-lasting postsurgical pain relief after a single intraoperative administration into the surgical field.

Methods: This was a four-site Phase 2 three-arm, double-blinded, randomized, placebo-controlled trial of vocacapsaicin in patients undergoing total knee arthroplasty (TKA). Patients were randomized to placebo, 36 mg or 60 mg of vocacapsaicin in 120 ml of aqueous solution. All groups received full standard-of-care including administration of long-acting local anesthetic. Postoperative pain and analgesic consumption were recorded in hospital for 4 days and after hospital discharge for at least 2 weeks following surgery.

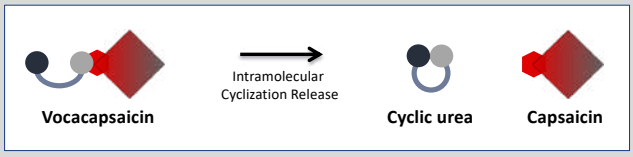
Results: Vocacapsaicin 36 mg produced highly statistically significant and clinically meaningful reductions in pain and opioid consumption vs. placebo for at least 2 weeks following surgery. Vocacapsaicin 36 mg reduced the time to key recovery endpoints.

Conclusion: Vocacapsaicin is the first analgesic to demonstrate sustained analgesia, including decreased opioid use, over 2 weeks following total knee arthroplasty. The safety profile was benign and mostly indistinguishable from placebo.

INTRODUCTION

Multi-day postoperative analgesia following total knee arthroplasty (TKA) remains an important unmet medical need. Vocacapsaicin (formerly CA-008) is a prodrug of capsaicin, a TRPV1-agonist that selectively desensitizes pain-conducting nerve fibers without producing sensory numbness or motor weakness (Figure 1). We previously demonstrated that a single administration of vocacapsaicin produced postsurgical analgesia and reduced opioid consumption (OC) for two weeks following bunionectomy.[1] We sought to replicate these results in a randomized double-blinded multicenter study of patients undergoing TKA.

Figure 1. Vocacapsaicin (CA-008), pH labile, water-soluble prodrug of capsaicin



METHODS

The study was conducted in patients undergoing primary TKA under spinal anesthesia with standard-of-care perioperative analgesia including ropivacaine 200 mg (femoral nerve block, IPACK block, and periarticular infiltration) and intraoperative acetaminophen and ketorolac. Eligible subjects were aged 18-80 years, BMI up to 42 kg/m^2. Patients were randomized to placebo, 36 mg or 60 mg of vocacapsaicin in 120 ml of aqueous solution. The test article was instilled onto cut bone surfaces, infiltrated into peri-articular tissue and injected into the closed capsule at the end of the case. Postoperative pain and analgesic consumption were recorded in hospital for 4 days, and after hospital discharge for at least 2 weeks following surgery. After discharge, all subjects received celecoxib twice daily and acetaminophen or acetaminophen/oxycodone as needed.

The primary efficacy endpoint was the area under the curve of the Numerical Rating Scale at rest from 0 to 96 hours (NRS-R $AUC_{0\text{-}96h}$). Secondary efficacy endpoints included evoked pain with activity (NRS-A $AUC_{0\text{-}96h}$), total opioid consumption ($OC_{0\text{-}96h}$), and the time of discontinuation of opioids. Exploratory endpoints included measures of recovery during hospitalization and NRS-R, NRS-A and OC from to Day 15. Safety endpoints included vital signs, physical examination, surgical site assessments, neurosensory testing, adverse events and clinical laboratory evaluations.

RESULTS

A total of 193 patients (mean age 62.3 years) were enrolled at 4 sites from December 2019 to September 2020. Groups were well-matched at baseline. Over the first 4 days, vocacapsaicin 36 mg met the primary and secondary endpoints for reduction of both pain and OC (Figure 2). The NRS-R $AUC_{0\text{-}96h}$ was reduced by 17% ($p=0.0012$). The NRS-A $AUC_{0\text{-}96h}$ was reduced by 20% ($p=0.0006$). $OC_{0\text{-}96h}$ was reduced by 30% ($p<0.0001$). Vocacapsaicin enabled earlier ambulation during hospitalization and produced a trend towards earlier discontinuation of opioids.

RESULTS (Cont.)

Reductions in pain and opioid reliance continued over the 2 weeks following surgery (Figures 3-5). Vocacapsaicin 36 mg reduced NSR-R $AUC_{0\text{-}15d}$ by 15% (p=0.03) and NRS-A $AUC_{0\text{-}15d}$ by 14% (p=0.04). Opioid consumption following discharge, $OC_{96h\text{-}15d}$, was reduced by 52% (p=0.0063). Overall opioid consumption, $OC_{0\text{-}15d}$ was reduced by 35% (p<0.0001). An analgesic effect was still evident on day 15. Vocacapsaicin 36 mg was more effective than vocacapsaicin 60 mg (figure 2). Both doses of vocacapsaicin were well-tolerated. No local or systemic safety concerns were observed.

Figure 2. Vocacapsaicin 36 mg Produced Clinically Meaningful and Statistically Significant Reductions in Pain and Opioid Consumption Throughout 0-96h

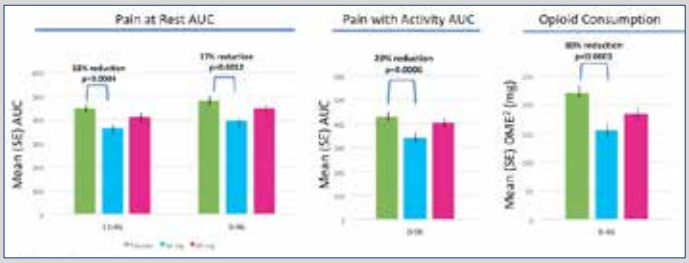


Figure 3. Clinically Meaningful and Statistically Significant Reductions in Pain at Rest, Pain with Activity and Opioid Consumption Over Two Weeks

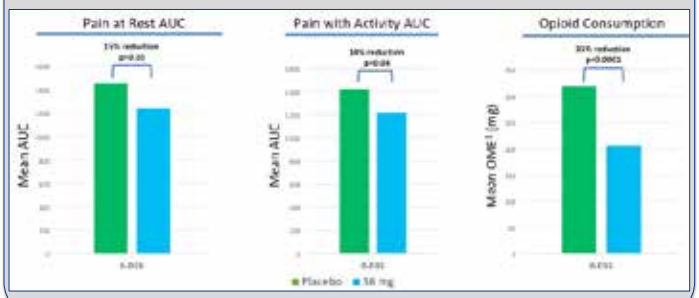


Figure 4. Vocacapsaicin Reduced Opioid Consumption Continuously Throughout 0-D15

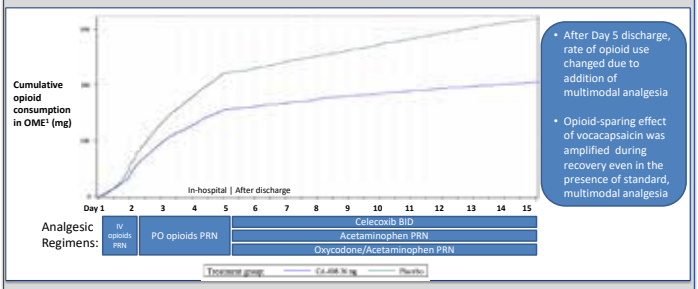
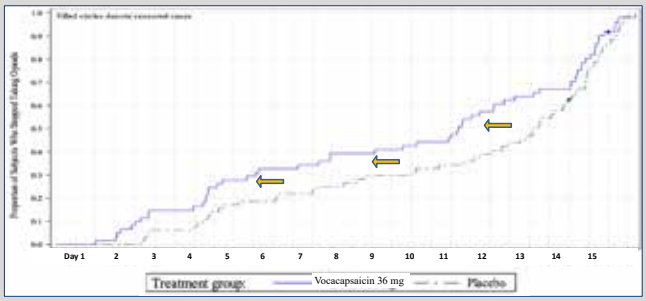


Figure 5. Trend for Earlier Discontinuation of Opioids 0-D15



DISCUSSION

Vocacapsaicin provided durable and clinically meaningful analgesia following TKA, including reduced pain and opioid consumption. Vocacapsaicin improved indices of recovery. These findings suggest vocacapsaicin may address the unmet medical need for effective and sustained non-opioid postsurgical analgesia, reducing or potentially eliminating the requirement for opioids following hospital discharge.

Acknowledgments: Concentric expresses its gratitude to the patients, their referring physicians, the investigators at the sites, HD Research, and Lotus Clinical Research.

Reference: Gottlieb JJ, Beaton A, Solanki D, et al. A randomized, placebo-controlled trial of intraoperative administration of CA-008 for post-operative analgesia after bunionectomy. Presented at ASRA 2019.