24TH ANNUAL MEETING
FRIDAY, OCTOBER 23RD, 2015
SAN DIEGO, CALIFORNIA

INTERNATIONAL SOCIETY FOR ANAESTHETIC PHARMACOLOGY
2015 SYLLABUS

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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.

ACCREDITATION INFORMATION

Target Audience
This program is designed for an international audience of general anesthesiologists, pharmacological anesthesiologists, technology anesthesiologists and specialty physicians.

Learning Objectives:

1. Discuss what's new in anesthetic pharmacology in 2015
2. Discuss new pre-clinical mice models that may result in safer drug development
3. Describe the mechanisms of anesthetic effect
4. Review problematic drug solutions and combinations
5. Identify difficulties that need to be overcome before a new technology or drug is introduced into clinical practice
6. List several reasons why the rejection rate of publication is high and cite the do's and don'ts to improve the chances for acceptance for publication

Practice Gaps:

- Clinicians are often unaware of the ongoing search for new anesthetic drugs, new technology and the progress in knowledge in anesthetic pharmacology.
- Many of these problematic solutions are not well known by clinicians and may be the cause of involuntary harm to the patient.
- Residual anesthetic effect due to pharmacokinetic accumulation of hypnotics
- Although several innovations in drug research have been developed over the last few years, it requires a minimal sense of entrepreneurship to allow a successful introduction of these innovations into clinical anesthesia practice.
- The high rejection rate of submitted scientific papers to major journals raises questions for clinical researchers on how the decision tree for acceptance is organized. If one aims to submit a paper on an anesthetic pharamacology topic, it is not clear how the decision is made to accept or reject the paper for further review and eventually publication.

ACCREDITATION:
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and the International Society for Anaesthetic Pharmacology (ISAP). The IAHB is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT:
The IAHB designates this live activity for maximum of *7.00 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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All people with control of the CME content for this activity (e.g., faculty/speakers, planners, abstract reviewers, moderators, authors, co-authors and administrative staff participating) disclosed their financial relationships to IAHB as shown in the list below, which also indicates the resolution, if applicable.

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ANNUAL MEETING AGENDA • SAN DIEGO, CA

7:00 – 8:00	**Breakfast (Sponsored) -** *Sapphire North Foyer*
8:00 – 8:10	**Welcome:** ISAP President, James Sonner, MD
8:10 – 8:15	**Introduction to the Program:** Program Co-Chairs Peter Nagele, MD, MSc; Hugo Vereecke, PhD
8:15 – 9:45	***Session 1 – Update on Clinical Pharmacology*** *- Sapphire Ballroom M* Moderators: Peter Nagele, MD, MSc; Hugo Vereecke, PhD
8:15 – 8:50	***What's New in the Anesthetic Drug Development Pipeline*:** Ken Johnson, MD
8:50 – 9:30	***Solutions for Problem Solutions:*** Mark Dershwitz, MD, PhD
9:30 – 10:00	**Break**
10:00 – 12:00	***Session 2 – Innovation and Entrepreneurship in Academic Anesthesiology*** *- Sapphire Ballroom M* Moderators: Konrad Meissner, MD; James M. Sonner, MD
10:00 – 10:40	***Annovation BioPharma: Lifecycle of an Anesthesia Start-up*:** Douglas Raines, MD
10:40 – 11:20	***Why Innovation and New Entrepreneurs are Especially Important for Anesthesiology In the 2nd Decade of The 21st Century*:** Theodore Stanley, MD
11:20 – 12:00	***Sedasys: A Story of Drugs and Devices:*** Randy Hickle, MD
12:00 – 13:00	***Lunch & Business Meeting*** *- Sapphire Ballroom I*
13:00 – 14:00	***Moderated Poster Discussion*:** ISAP Board **-** *Sapphire Ballroom E*
14:00 – 15:10	***Session 3 – New Technology and Innovative Ideas*** *- Sapphire Ballroom M* Moderators: Mohamed Naguib, MD; Tom C. Krejcie, MD
14:00 – 14:35	***Human Liver Engineering: From Safer Drugs to Liver Regeneration:*** Gary Peltz, MD, PhD
14:35 – 15:10	***What do we Know about the Mechanism of Anesthesia in 2015*:** Roderic Eckenhoff, MD
15:10 – 15:30	**Break**
15:30 – 16:45	***Session 4 – Anesthesia & Analgesia Panel*** *- Sapphire Ballroom M* Moderators: Peter Nagele, MD, MSc; Hugo Vereecke, PhD
15:30 – 15:50	***Outgoing Editor-in-Chief:*** Steven Shafer, MD
15:50 – 16:10	***Incoming Editor-in-Chief:*** Jean-Francois Pittet, MD
16:10 – 16:45	***A Panel Discussion with the Current and Former Pharmacology Section Editors*** Ken Johnson, MD; Tony Gin, FANZCA, FRCA, MD; Marcel Durieux, MD, PhD
16:45 – 17:30	***Keynote Speaker & Lifetime Achievement Award Winner: Resolving Medicolegal Issues by Means of Pharmacokinetic Pharmacodynamic Simulations:*** Johan Coetzee, MD, PhD Moderator: Talmage Egan, MD
17:30 – 18:30	**Reception** *- Sapphire Terrace*

SAVE THE DATE: 25TH ANNUAL MEETING

FRIDAY, OCTOBER 21, 2016

CHICAGO, IL

ABSTRACT TABLE OF CONTENTS

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Back to
Table of Contents

Examining the Concept of Rescue Reversal by Sugammadex

Authors: Ken B. Johnson*, Mohamed Naguib‡, Lara Brewer*, Cristen LaPierre+, Aaron F. Kopman
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‡Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic
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Background: An unanticipated difficult airway during induction of anesthesia can be a vexing problem. In the setting of can't intubate, can't ventilate (CICV), rapid recovery of spontaneous ventilation is a reasonable goal. The urgency of restoring ventilation is a function of how quickly a patient's hemoglobin oxygen saturation falls *versus* how much time is required for the effects of induction drugs to dissipate, namely the duration of unresponsiveness, ventilatory depression, and neuromuscular blockade. It has been suggested that prompt reversal of rocuronium-induced neuromuscular blockade with sugammadex will allow respiratory activity to recover prior to significant arterial desaturation. Using pharmacologic simulation, we compared the duration of unresponsiveness, ventilatory depression, and neuromuscular blockade in normal, obese, and morbidly obese body sizes in this life threatening CICV scenario. We hypothesized that although neuromuscular function could be rapidly restored with sugammadex, significant arterial desaturation will occur prior to the recovery from unresponsiveness and/or central ventilatory depression in obese and morbidly obese body sizes.

Methods: We used published models to simulate the duration of unresponsiveness and ventilatory depression using common induction techniques with predicted rates of oxygen desaturation in various size patients and explored to what degree rapid reversal of rocuronium-induced neuromuscular blockade with sugammadex might improve the return of spontaneous ventilation in CICV situations.

Results: Our simulations (Figure 1) showed that the duration of neuromuscular blockade was longer with 1.0 mg/kg succinylcholine than with 1.2 mg/kg rocuronium followed 3 minutes later by 16 mg/kg sugammadex (10.0 *versus* 4.5 minutes). Once rocuronium neuromuscular blockade was completely reversed with sugammadex, the duration of hemoglobin oxygen saturation above 90%, loss of responsiveness and intolerable ventilatory depression were dependent on the body habitus, duration of preoxygenation, and induction dosing regimen. There is a high probability of intolerable ventilatory depression that extends well beyond the time when oxygen saturation falls below 90%, especially in obese and morbidly obese patients. If ventilatory rescue is inadequate, oxygen desaturation will persist in later groups, despite full reversal of neuromuscular blockade. Depending on body habitus and the opioid dosed, the duration of intolerable ventilatory depression following sugammadex reversal may be as long as 15 min in 5% of individuals.

Conclusions: The clinical management of CICV should primarily focus on restoration of airway patency, oxygenation, and ventilation consistent with the American Society of Anesthesiologist's Practice guidelines for management of the difficult airway. Pharmacologic intervention cannot be relied upon to rescue patients in a CICV crisis.

Back to
Table of Contents

The Effect of Intra-operative Dexmedetomidine on Postoperative Recovery Profile, Analgesic Consumption, and Sedation in Trans-sphenoidal Resection of Pituitary Adenoma Operations

Presenting Author: Jianbo WU, M.D., Department of Anesthesiology, QiLu Hospital of Shandong University, Jinan, China, 250012

Co--Authors: Ningning FANG, M.D., Tiantian LI, , M.D., Jianchun FEI, , M.D., Dejie LIU, M.D., Department of Anesthesiology, QiLu Hospital of Shandong University, Jinan, China, 250012

BACKGROUND: Smooth recovery from anesthesia is desirable in patients undergoing trans-sphenoidal resection of pituitary adenoma who have severe pain during the postoperative period. Postoperative opioids may result in hypoxemia or airway obstructive symptoms. Dexmedetomidine may be beneficial in these patients owing to its sedative, anxiolytic properties with minimal respiratory depression.We designed a randomized placebo-controlled study to determine the effects of intraoperative dexmedetomidine on postoperative recovery including pain,sedation, and hemodynamics in patients undergoing trans-sphenoidal resection of pituitary adenoma.

METHODS: 123 patients undergoing trans-sphenoidal resection of pituitary adenoma operations were divided into 3 groups randomly in this study: to receive a single intraoperative dose of dexmedetomidine 0.5 μg/kg, dexmedetomidine 1 μg/kg, or physiological saline(placebo) over 15 minutes after anesthesia induction. After surgery the PCA(sufentanil 0.04μg/kg/h,48hrs) was programmed with background of 2 ml/h, bolus dose of 2 ml, lockout of 5 min. Postoperative recovery profile and sufentanil consumption was observed by blinded observers. Postoperative pain(visual analogue scale, VAS), emergence agitation (EA), and discharge readiness from postanesthesia care unit, times of PCA self-press, sedation scores (LOS), comfort scales(bruggrmann comfort scale, BCS), functional activity score (FAS), and adverse effects(bradycardia and hypotension, PONV)was evaluated.

RESULTS: There were no significant differences among the 3 groups in patient demographics, ASA physical status, extubation time. Compared with physiological saline group,there were less emergence agitation in group dexmedetomidine 1μg/kg ($P < 0.05$), whereas no difference was observed in amount of self-administered sufentanil after resection of pituitary adenoma surgery ($P = 0.07$). The median time to first postoperative PCA press was no significantly difference among groups. Compared with the saline group, the VAS scores at rest at 1, 4, and 8 hours after surgery were significantly lower in dexmedetomidine 1μg/kg group ($P < 0.05$). Patients receiving dexmedetomidine had significantly slower heart rates in the first 30 minutes after surgery compared with those receiving placebo. There was no significant difference in sedation scores among the groups.

CONCLUSIONS: The intra-operative use of dexmedetomidine in trans-sphenoidal resection of pituitary adenoma operations can result in a favorable recovery profile, and improve parturients' satisfaction.

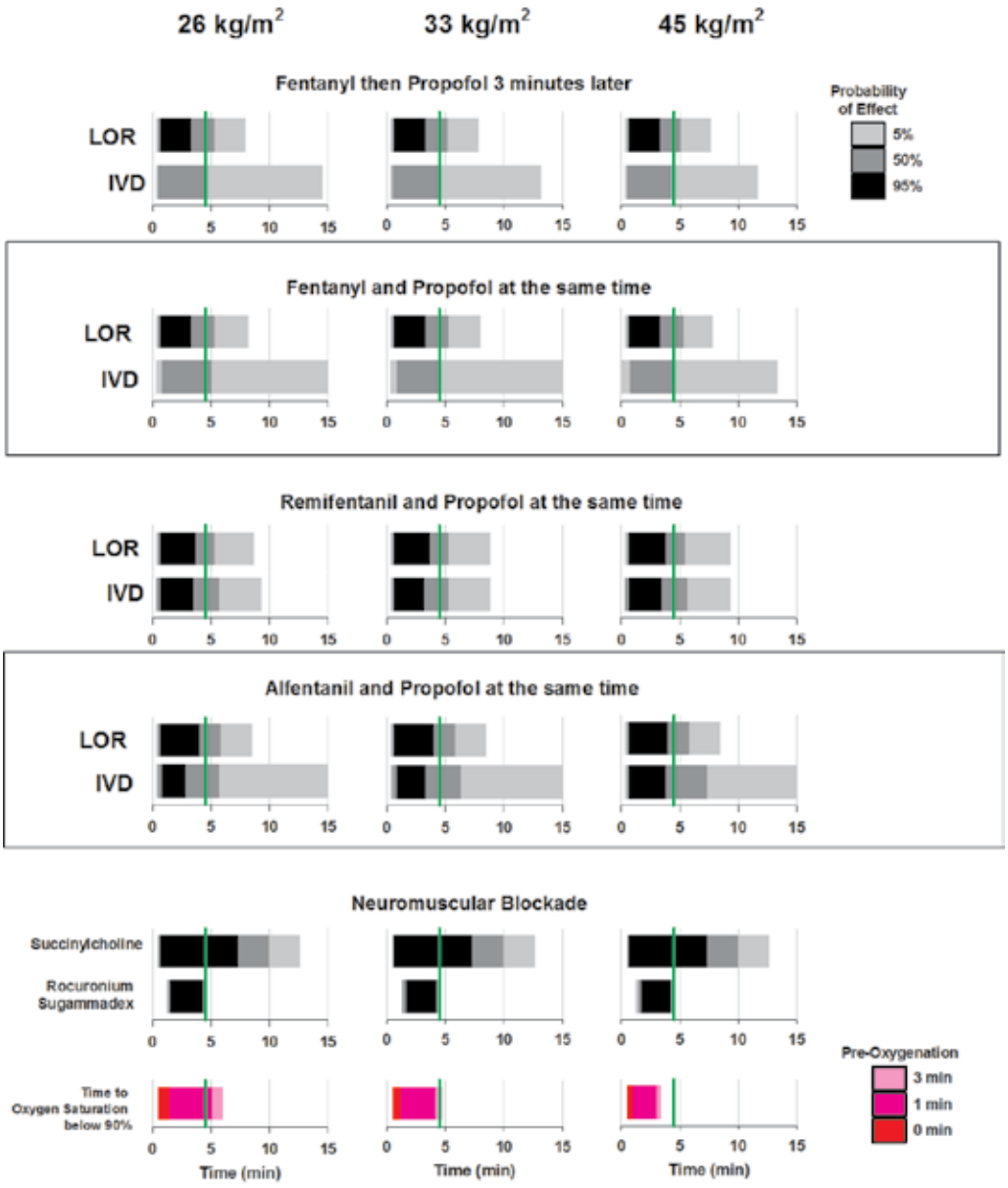

Figure 1. Predicted onset and duration of selected drug effects for various combinations of induction drug sequences administered to people of different sizes. Predicted effects include loss of responsiveness (LOR) defined as a loss of response to verbal and tactile stimuli, intolerable ventilatory depression (IVD) defined as a respiratory rate of 4 breaths or less per minute in an un-stimulated state, neuromuscular blockade is defined as percent of the first twitch depression (T1%) in patients who received succinylcholine or rocuronium/sugammadex paradigm, and duration of oxygen saturation above 90% in the presence of apnea. Induction drug sequences included (1) fentanyl followed 3 minutes later by propofol, (2) fentanyl simultaneously administered with propofol, (3) remifentanil simultaneously administered with propofol, and (4) alfentanil simultaneously administered with propofol followed by either succinylcholine or rocuronium. Rocuronium was reversed 3 minutes later with sugammadex. Doses of each drug are presented in Table 2.

Predictions for each induction sequence were performed for a normal (Body Mass Index, BMI = 26 kg/m^2), obese (BMI = 33 kg/m^2), and morbidly obese (BMI = 45 kg/m^2) individual. The duration of each effect is estimated as a probability greater than 5% (light grey), 50% (dark grey), and 95% (black). The time to oxygen saturation below 90% is presented as a function of the duration of preoxygenation prior to drug induced apnea. Red, dark pink, and light pink represent no preoxygenation, 1 minute of preoxygenation, and 3 minutes of preoxygenation with an FiO_2 of 1.0. The green vertical lines represent the time points at which neuromuscular blockade is completely reversed with sugammadex.

Influence of Menstrual Cycle Phase on Propofol Pharmacokinetics

Presenting Author: Atsuko Tomita, M.D., National Defense Medical College
Co-Authors: Kenichi Masui, M.D., Tomiei Kazama M.D., National Defense Medical College

Background: Several studies[1-4] reported menstrual cycle influenced pharmacodynamics of propofol. Unfortunately, plasma concentration of propofol was not measured in these studies. The aim of the study was to investigate the influence of the phase of menstrual cycle (the follicular and luteal phase) on propofol pharmacokinetics in premenopausal female patients.

Method and Materials: Female patients who were ASA physical status I or II, aged 20-49 years, scheduled to undergo surgery under general anesthesia were enrolled. After oxygenation, the patients received propofol 2 mg/kg for 3 min. Arterial blood samples were taken to measure propofol collected at 15, 30, 45, 60, 75, 90, 105, 120, 140, 160, 180, 195, 210, 225, 240, 260, 280, 300 s, and 5, 5.5, 6, 7, 8, 10, 12, 15, 20, 25, 30, 40, 55, 70, 90, 150, 180, 240 min after the start of the infusion of propofol until the operation was finished. Anesthesia was maintained using sevoflurane and remifentanil.

Pharmacokinetic model was developed. The best model structure was determined using conventional 2 or 3 compartment model with a lag time and transit model. The menstrual cycle phase was assessed as potential covariates for the pharmacokinetic parameters. NONMEM 7.3 (ICON plc, Dublin, Ireland) and PLT tools (PLT Soft, San Francisco, CA) were used for the model development.

Result: Eleven patients in the follicular phase and nine patients in the luteal phase were included. The ranges of age, weight and BMI were 20-45 years, 43-74 kg, and 18-27 kg/m^2. The best model structure was 3 compartment model with a lag time and two transit compartments. The menstrual cycle phase was a significant covariate for the final model.

Conclusion: The pharmacokinetics of propofol was described by a three-compartmental model with a lag time and two transit compartments. Menstrual cycle phase was found not to be a significant covariate.

References

1. Fu, F., et al., Br J Anaesth, 2014. 112(3): p. 506-13.
2. Buchanan,F.F.,et al., Br J Anaesth, 2011. 106(6): p. 832-9.
3. Erden,V., et al, Anesth Analg, 2005. 101(4): p. 1007-11, table of contents.
4. Gan,T.J., Anesthesiology, 1999. 90(5): p. 1283-7.

Closed-loop Anesthesia with Concert-CL® Syringe Pumps Station and Antinociception Titration by Pupillometry

Authors: Philippe Mavoungou, MD, ICO Rene Gauducheau, Nantes, France ; Valerie Bilard, MD, Institut Gustave Roussy, Villejuif, France

Introduction: A closed-loop delivery of anesthetic drugs may help to limit inter and intra individual variability which still remain despite rather good performances of PK/PD population models used in Target Controlled Infusion (TCI) systems (1). Analgesic component is very important for the stability of Bispectral Index of the EEG (BIS®, Covidien™) during balanced anesthesia. Concert-CL® (Veryark™, Nanning, China) is a new, CE-marked, syringe pumps workstation, designed for closed-loop (on the BIS®) delivery of propofol, in order to maintain BIS values between 40 and 60 as recommended for general anesthesia. Remifentanil infusion is not delivered in closed-loop mode with this device, therefore it makes sense to optimize the target effect site concentration of the analgesics when using this device. A pupillometer, for an evaluation of the level of anti-nociception, may be useful in this situation. The performances of the device were studied under these conditions.

Materials and methods: This study received an IRB approval and we bring here preliminary results. It is a prospective, open, non-randomized study, on the records of patients undergoing anesthesia using Concert-CL ® with closed-loop on the BIS ® delivery of propofol and remifentanil TCI. Patients, scheduled for surgical interventions lasting more than 1 hour, gave their informed consent. The data come from anesthesia records and internal memory of the device for each patient : mean value of BIS , the percentage of BIS® value between 40 and 60 (% of BIS40 -60) , the median error absolute performance of the BIS® (MDAPE), the wobble or oscillation of BIS reflecting individual variability within the BIS® , the global score (GS) system defined by the equation : GS = (MDAPE wobble +) /% of BIS®40 -60 and the average concentrations of propofol and remifentanil are provided . The level of antinociception was assessed with a pupilometer (Algiscan® , IdMed™, Marseille France) and a pupillary pain index(PPI) less than 2 was reached for all the patients by adjustment of remifentanil target effect site concentration according to the PPI in response to a calibrated noxious stimulation, performed before the skin incision. This concentration was then maintained during the intervention.

Results: Data are presented as mean±SD for the 18 patients included (11 men and 7 females) : age =62±11 years, body mass index = 24±3.2, mean concentration of propofol= 2.4±0.5µg/mL, and remifentanil=3.2±0.7ng/mL. Performances parameters of Concert-CL are presented in table I:

Tableau I

% of BIS® 40-60	Mean BIS®	MDAPE	Wobble	GS
80.5±4.7	44.3±0.9	13.26±2	6.2±1.2	24.4±3.6

P<0,0001

Discussions: In this study,the GS of Concert-CL for closed-loop administration of propofol is similar to the GS of other experimental closed-loop delivery systems of propofol (2). Pupillometry provides a smart way to manage the antinociception in this context.

References : 1 - Anesth Analg. 2013 ; 117 : 1130-8

2 – Anesth Analg. 2011 ; 112 : 546-57

Back to
Table of Contents

Environmental Enrichment Ameliorates the Epigenetic Reduction of BDNF and Memory Deficiency Induced by Neonatal Anesthesia

Authors: Jiang Wu, MD[1], Bihua Bie Md, PhD[1] and Mohamed Naguib, MD, FRCA[1]
[1]Anesthesiology Institute, Cleveland Clinic

Abstract: Although neonatal exposure to commonly used anesthetic drugs has been associated with persisted memory deficiency in rodent models and possibly in pediatric patients, the underlying mechanisms are not known. Brain-derived neurotrophic factor (BDNF) and its cognate receptor tyrosine receptor kinase B (TrkB) play a substantial role in regulating the synthesis of synaptic proteins and in modulating synaptogenesis, synaptic plasticity and memory. Here, we found a substantial reduction of hippocampal BDNF, resulting from the transcriptional factors-mediated epigenetic modification in the promoter region of *Bdnf* exon IV (**Fig. 1a,b**) and decreased histone H3 acetylation in the *Bdnf* exon IV (**Fig. 1c**), but not *Gapdh*, promoter region of rats exposed postnatally (P7) to isoflurane anesthesia (2.5% induction, 1.5% maintenance) for 6h. This BDNF reduction led to the insufficient drive for the synthesis of synaptic protein (**Fig. 1d**) and was associated with significantly decreased synaptic density, dendritic spine number (**Fig. 1e,f**), impaired glutamatergic long-term potentiation (LTP) in the hippocampal CA1 neurons (**Fig.1g**) and extended escape latencies and less time (during the probe trial) spent in the target quadrant (TQ) in the Morris water maze test (**Fig.1h,i**), indicating an impaired synaptic plasticity and cognitive dysfunction induced by neonatal anesthesia in the adult rats (P65). Blocking TrkB receptor activity in naïve rats using TrkB-Fc microinjected into the hippocampal CA1 area resulted in synaptic and cognitive dysfunction (**Fig.1j-l**) similar to that induced by neonatal anesthesia. We also found that exposure to enriched environment (EE) significantly mitigated the epigenetic suppression of BDNF and restored hippocampal synaptic plasticity and cognitive functions (**Fig. 1b,d,e-i**). Our findings elucidated the epigenetic mechanism underlies the memory deficiency induced by neonatal anesthesia and proposed environmental enrichment as a potential therapeutic approach.

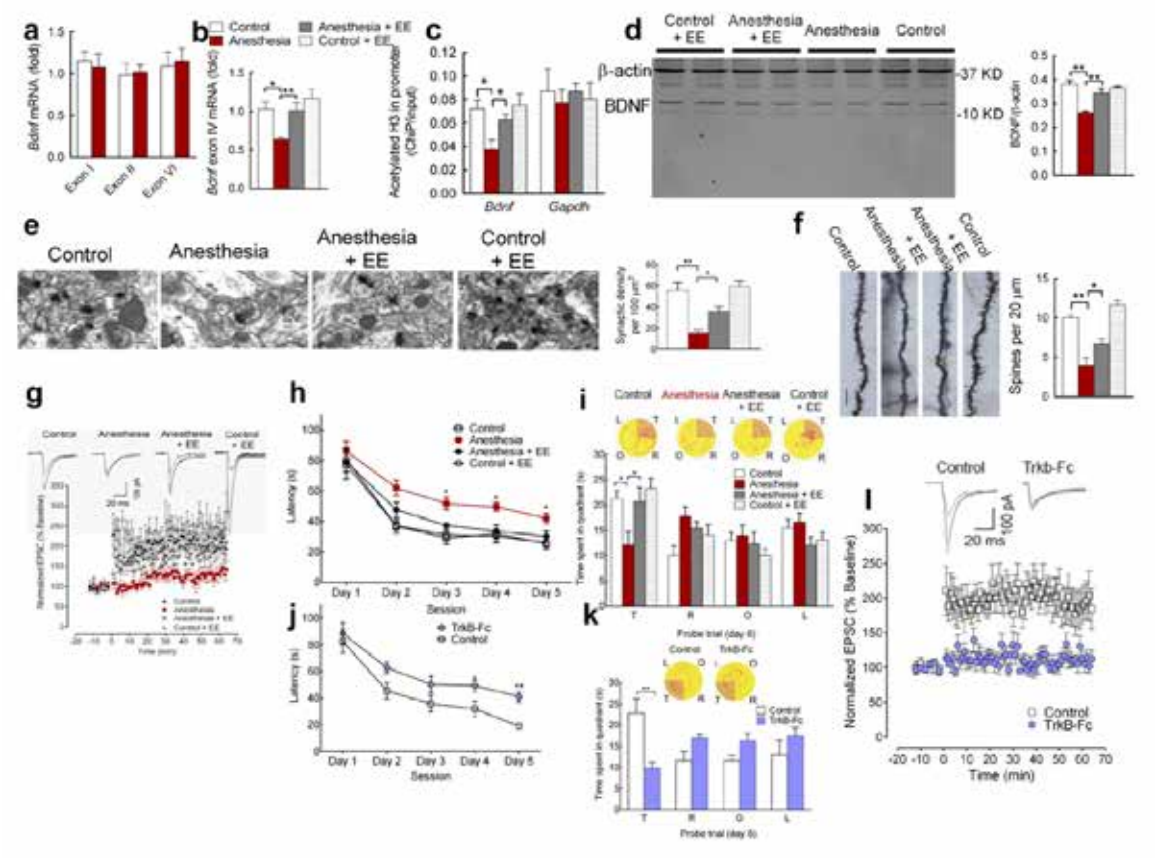

Figure 1. Neonatal (P7) exposure to anesthetics significantly decreased *Bdnf* exon IV mRNA (**a,b**), decreased histone H3 acetylation in the *Bdnf* exon IV, but not *Gapdh*, promoter region (c) and decreased protein expression (d) in the hippocampal CA1 tissue in the adult rats (P65). Hippocampal synaptic density (**e**, scale bar = 0.25 μm), dendritic spine numbers (**f**, scale bar = 10 μm) and HFS-induced LTP (g, n = 9-12 neurons in each group) were significantly reversed by EE in rats with neonatal exposure to anesthetics. Representative path tracings (**i**) in each quadrant during the probe trial of the Morris water Maze test on day 6 (T, target quadrant; R, right quadrant; O, opposite quadrant; L, left quadrant). Bilateral microinjection of Trkb-Fc (2 μg×7 days) into the hippocampal CA1 significantly extended the escape latencies (**j**), and shortened the time spent in the target quadrant (k) in the Morris water maze test and impaired HFS-induced LTP (**l**) in the hippocampal CA1 neurons. *, P<0.05; **, P<0.01. Data represent mean ± s.e.m.

Back to
Table of Contents

Morphine is a Substract of OATP Uptake Transporters in Vitro

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Background: Opioids like morphine are highly potent analgesics but exert a significant interindividual variability in disposition and clinical effects. This results in a considerable risk of both, persisting pain and adverse drug reactions due to genetic variability or drug interactions. Known determinants of morphine pharmacokinetics (i.e. UGT2B7, P-gp, MRP3, OCT1) can only partially explain its effect variability. Furthermore, mechanisms of intestinal and brain uptake of morphine are still unknown. Uptake transporters of the organic anion transporting peptide family (OATPs) mediate the uptake of a broad spectrum of drugs across biological barriers, including the intestine and the blood-brain barrier. Thus, OATPs could possibly be involved in morphine pharmacokinetics and variability. However, evidence for morphine uptake by OATPs is lacking. Therefore, this study investigated the cellular uptake of morphine by OATPs in a cell model.

Methods: Human embryonic kidney cells stably over-expressing OATP1A2, OATP1B1, OATP1B3 or OATP2B1 were incubated with radiolabeled morphine. Cellular morphine uptake was measured by liquid scintillation counting after cell lysis. Enhancement of morphine uptake by OATPs vs. control cells was tested in a preliminary screening. Detailed characterization of morphine transport consisted of time-dependent (10 s – 30 min; 10 nM morphine) and concentration-dependent (0.3 nM – 1 mM morphine; 1 min) uptake assays. Furthermore, inhibition of morphine uptake by the established OATP inhibitors naringin and rifampicin (0 – 1 mM inhibitor; 500 µM morphine) was investigated.

Results: Morphine was a substrate of OATP1A2, OATP1B1 and OATP2B1 but not of OATP1B3. Morphine uptake via OATP1A2, OATP1B1 and OATP2B1 was time- and concentration-dependent, followed typical Michaelis-Menten kinetics (K_m 0.76 – 1.02 mM; V_{max} 5.6 – 6.7 nmol/mg×min), and was inhibitable by naringin and rifampicin (IC_{50} 0.85 – 3.0 µM, maximum inhibition 69 – 93%).

Conclusions: OATPs might play a role in morphine pharmacokinetics and variability. However, further investigations are necessary to establish the clinical relevance of OATPs and their genetic variants in morphine treatments.

Back to
Table of Contents

Isoflurane Enhances and Depresses Synaptic Coupling

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Background/Introduction: Anesthetics are known to depress synaptic transmission, and this effect is thought to underlie the uncoupling of brain regions seen with cortical EEG recordings. We tested the hypothesis that anesthetic-induced depression of synapses leads to uncoupling of electrical activity between frontal cortex and hippocampus.

Methods: The present study used electrophysiologically-guided electrode implants to record Schaffer-collateral to CA1 neuron mono-synaptic responses, as well as frontal cortical micro-EEG signals. Rats were allowed to recover from surgery and then isoflurane effects were characterized after several days (>7) to several months (<7) later. Simultaneous recordings of cortical and hippocampal micro-EEG signals, evoked synaptic responses, anesthetic concentration, vital signs and behavior were made.

Results: Loss of consciousness, measured as righting reflex, was consistently associated with increased synchronized delta activity, in hippocampus and cortex, as well as a novel ~15 Hz rhythmic oscillation produced by isoflurane in hippocampal micro-EEG recordings. Surgical anesthesia, measured as loss of tail-clamp reflex, was observed on the transition to burst-suppression activity in both hippocampal and cortical micro-EEG signals. Isoflurane produced a concentration-dependent depression of mono-synaptic responses: at surgical anesthetic depths, excitatory postsynaptic potentials were depressed by 26.6 ± 4.2 % ($n=5$; $p<0.001$) of control amplitudes, but surprisingly, coupling between cortex and hippocampus was further enhanced.

Conclusion: Clearly, our hypothesis was wrong, since increased coupling between brain regions was observed at the same time that mono-synaptic responses were depressed. We demonstrate for the first time that cortical-hippocampal coupling is increased at both low (loss of consciousness) and at high surgical concentrations of isoflurane.

Support: Anesthesia Department at Stanford University, the NIH (R01GM095653 to MBM and R01GM101497 to RAP) and NSERC (A9935 to BHB).

Back to
Table of Contents

Effects of Propofol on Spontaneous Firing Activity of Locus Coeruleus Noradrenergic Neurons

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Background: Previous studies show that propofol activates the ventrolateral preoptic nucleus(VLPO),the main sleep-active nucleus, to exert its sedative effects. However, it is still controversial on the key wake-active nucleus locus coeruleus(LC) are involved in generating the sedative state. In present study, we tested whether lesion of the VLPO neurons would affect the spontaneous firing activity of LC neurons under different concentrations of propofol.

Method: 24 Sprague Dawley rats were divided into two groups, the control group and lesion group. Rats were anesthetized with propofol 10 $mg \cdot kg^{-1}$ IV. Then pump propofol with 30 or 60 $mg \cdot kg^{-1} \cdot h^{-1}$ respectively. Rats were divided into two groups according to the infusion rate， each group was 6 rats. For the lesion group, 0.015ul ibotenic acid(10nmoles/l) were microinjected to bilateral VLPO before recording. Glass microelectrodes filled with 2% Pontamine Sky Blue in 0.5 mol/L sodium acetate were stereotaxically directed to the LC to record extracellular spikes.

Results: The firing rate of LC neurons of low concentration group (30 $mg \cdot kg^{-1} \cdot h^{-1}$) increased significantly compared to high concentration group (60 $mg \cdot kg^{-1} \cdot h^{-1}$) ($p<0.05$).The firing rate of LC neurons of low concentration group (30 $mg \cdot kg^{-1} \cdot h^{-1}$) and high concentration group (60 $mg \cdot kg^{-1} \cdot h^{-1}$) had no significant difference compared to the VLPO lesion group ($p>0.05$).

Conclusion: Propofol may suppress the spontaneous firing activity of LC noradrenergic neurons. Nevertheless, VLPO neurons are not likely involved in the inhibitory effect of propofol on LC spontaneous firing activity.

Back to
Table of Contents

Dexmedetomidine in Patients under Spinal Anesthesia: A Comparison of Clinical Outcomes between Target Controlled Infusion and the Recommended Regimen, Validation of Published Pharmacokinetic Models, and Construction of a New Pharmacokinetic Model

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Background: Little information is available on the usefulness of dexmedetomidine target controlled infusion (TCI) and the predictive performances of published pharmacokinetic (PK) models in patients under spinal anesthesia. We examined the difference in clinical outcomes between the recommended regimen (i.e., the dosing manner recommended by drug manufacturers) and TCI. We also validated published pharmacokinetic models and constructed a new PK model in this population.

Methods: After approval by the institutional ethics committee and written informed consent process, 40 patients were randomly allocated to the recommended regimen group (6 mcg/kg/h in 10 min followed by 0.2–0.7 mcg/kg/h) or TCI group (initial target was 1.5 ng/ml using Dyck model [1] with maximum infusion rate of 6 mg/kg/h). Dexmedetomidine was administered after spinal anesthesia. As clinical outcomes, the time to loss of responsiveness, time to recovery, and incidence of circulatory or respiratory depression were recorded as parameters indicating sedation quality. In selected patients, venous blood samples were collected to measure dexmedetomidine concentrations. The predictive performances of six published models [1-6] were evaluated.[7] Population PK parameters were estimated using a nonlinear mixed effect model. NONMEM 7.2, PLT tools (www.pltsoft.com/), and PKPD tools (www.pkpdtools.com/doku.php) were used for PK analysis and simulations.

Results: There were no differences in background characteristics and clinical outcomes between the two groups ($P > 0.05$). The PK dataset contained 84 venous plasma dexmedetomidine concentrations from 16 patients (1 male, 15 female). The age, weight and Body Mass Index ranges were 25–64 yo, 45–71 kg, and 16.9–27.0 kg/m^2 respectively. PK models reported by Hannivoort et al [6] and Lee et al [2] predicted dexmedetomidine concentrations well, although performances of other models were out of the acceptable range (Fig. 1). PKs of dexmedetomidine were described by a 2-compartmental model, with weight and age as significant covariates. The final PK parameter values were as follows: V1 = 22.6 L, V2 = 41.1 L, CL1 = $1.5 \times Age^{-0.23} \times (Weight / 70\ kg)^{0.75}$ L/min and CL2 = 1.2 L/min. The median performance error of the final model was -2% and the median absolute performance error was 11%.

Conclusion: In patients under spinal anesthesia, the clinical outcomes of dexmedetomidine in the TCI group were not significantly different compared with that in the recommended regimen group. The PK model reported by Hannivoort[6] performed the best. A population PK model was developed in this population.

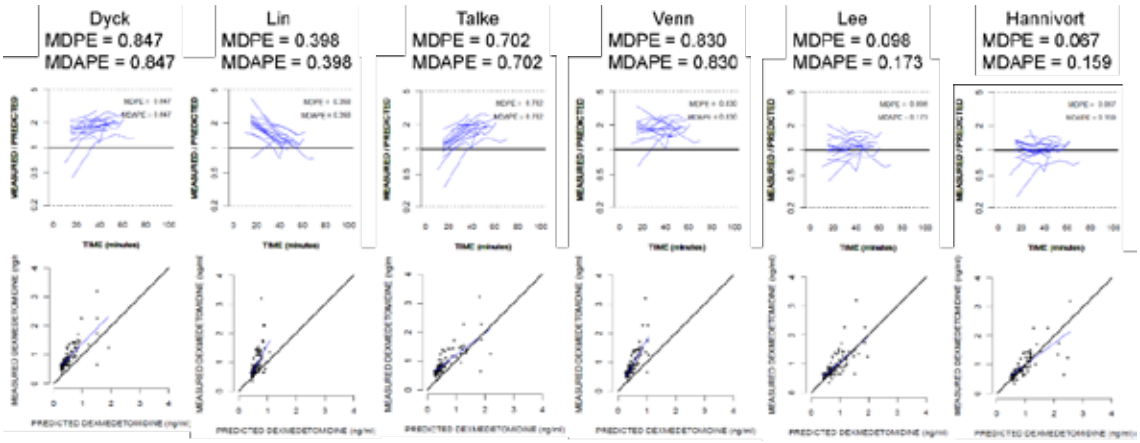

Figure 1. Measured/predicted values vs. time (top panels) and Measured vs. predicted dexmedetomidine concentrations (bottom panels) for six different pharmacokinetic models. MDPE = median performance error, MDAPE = median absolute performance error.

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Back to
Table of Contents

The Distribution of Effect-Site Sevoflurane Concentrations at Wake-up

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Background: There is acceptance of the concept of using real-time calculated effect-site concentrations to guide delivery of *iv* anaesthetic agents. As part of a broader interest in rational use of inhaled anaesthetics we have been investigating use of effect-site concentrations of inhaled anaesthetics. We have previously described our local system which, *inter-alia,* provides real-time estimates of effect-site concentrations and forward predictions of end-tidal and effect-site concentrations of volatile anesthetics. We have recently installed in our ORs a number of GE-Navigator units which provide, along with interaction models, effect-site concentrations for a range of drugs including volatile agents.

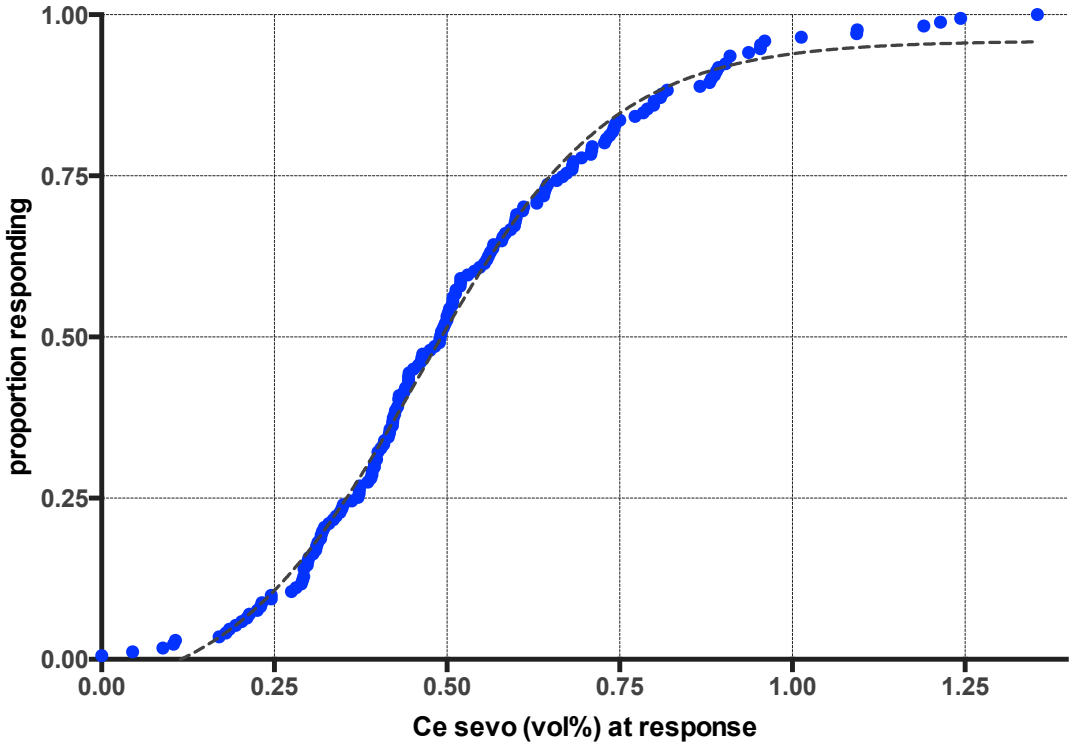
The purpose of this study was to compare the distribution of effect-site sevoflurane concentration (Ce) at the point of first response to command by combining data from two studies.

Methods: Both studies had National Ethics Committee approval. Our previous study (Study A) was designed to explore the influence of different types of surgery on Ce-sevo at awakening and used a locally developed prediction system. In that study we found no difference between groups and all data is pooled for the present analysis. Study B was designed to investigate the point of awakening as predicted by GE-Navigator in a wide variety of clinical settings. In both studies an investigator noted the time at which patients first responded to a command to eye-open. This end-point is based on the definition of "MAC-awake" and corresponds to OASS =4/5. The Ce-sevo at the time of this end-point was retrieved from each system.

Results: The demographics of patients in the two studies were very similar. The 60 subjects in Study A woke at an age-adjusted Ce-sevo of 0.530 (sd 0.227) vol%, very similar to those in Study B (N=112): Ce-sevo of 0.527 (0.254) vol %. (unpaired 2-tailed t-test p = 0.93, 95%CI of difference -0.074 to 0.081). The figure shows the frequency distribution for the pooled data. The interquartile range is 0.37 to 0.75 vol%.

Comments: We found very similar patterns of Ce-sevo at awakening determined using two different technologies suggesting data from studies with these systems are robust. The distribution of Ce-sevo at awakening is wide.

Figure: Cumulative frequency plot of proportion responding against calculated effect-site sevoflurane concentration (Ce sevo). The sigmoid dose-response line of best fit is also shown.



Back to
Table of Contents

The Influence of Covariates on Effect-Site Age-Adjusted MAC Fraction Estimated by GE-Navigator at the Point of First Response After Inhalational Anesthesia

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Background: We are interested in using effect-site levels to guide delivery of a wide range of drugs used in anesthesia. Based on this interest we have installed Navigator™ systems from GE in a number of our operating rooms. Navigator takes inputs from gas analyzers, syringe drivers and direct user input. The "outputs" are displays of the probability of recall and response to noxious stimulation along with calculated effect-site concentrations of a range of drugs. A number of drugs are not modeled in Navigator including morphine, clonidine and ketamine.

The primary aim of this ongoing study is to relate the point of first response to command to the predicted likelihood of response in a wide range of patients undergoing a variety of surgery. In this analysis we explore the effect of various covariates on the point of first response. Our hypothesis is that if the effect site modeling is valid then patient demographics and duration of surgery will have minimal effect on awakening volatile concentration.

Methods: This study was approved by the Regional Ethics Committee. Written consent was not required. The patients are an opportunistic sample of those having anaesthesia in an OR with Navigator at a time the investigator (MM) was available. All drugs were recorded by the investigator and modeled drugs entered into Navigator. The time at which subjects first responded to command was noted. The calculated Ce-sevo at this time was retrieved and adjusted for age and converted to a MAC-fraction. The effect of covariates including age, gender, BMI, ASA-PS, invasiveness of surgery, duration of surgery, Ce-fentanyl and use of non-modeled drugs was explored in univariate and multivariate models.

Results: Data from 146 patients was available. These are summarized in the Table. Patients woke at a mean age-adjusted effect-site MAC fraction of 0.26 (sd 0.14) vol%. There was no difference between sevoflurane and desflurane (95%CI diff -0.116 to 0.007, p=0.0807). The median (IQR) Ce-fentanyl was 0.84 (0.60, 1.12) ng/ml.

There was weak evidence that a one unit increase in ASA-PS, use of non-modeled drugs and being male decreased the MAC fraction at first response. There was also

a suggestion of an effect of the degree of surgical insult. None of these effects reached statistical significance.

There was no evidence of an effect of fentanyl levels, age, duration of surgery or BMI.

Comments: The lack of effect of patient age, BMI or duration of surgery supports the use of calculated effect-site concentration as a measure of volatile dosing. Although opioids are included in interaction models underlying technologies such as Navigator we did not see an effect on awakening. This is consistent with older studies suggesting fentanyl levels greater than 2-4ng/ml are needed to alter MAC-awake. The suggestion of an influence of ASA-PS and invasiveness of surgery is an area for further investigation.

Table: Summary of patient demographics and observed variables

Variable	Number of obs.	Median (IQR)
Age, years	146	54.5 (36.5, 71.8)
Sex	144	
Female		53% (76)
Male		47% (68)
BMI	146	26.7 (24.1, 30.1)
ASA	144	
1		24% (35)
2		42% (60)
3		31% (45)
4		3% (4)
Type of surgery	145	
Minor		17% (24)
Intermediate		57% (83)
Major		26% (38)
Duration, mins	143	88 (66, 128)
Other Drugs (*ketamine, morphine)*	139	
No		48% (67)
Yes		52% (72)
Effect-site concentration at response		
Sevoflurane, age adjusted (vol%)	109	0.475 (0.362, 0.641)
Desflurane, age adjusted (vol%)	25	1.178 (0.865, 1.754)
MAC-fraction, age adjusted	133	0.226 (0.170, 0.321)
Fentanyl	143	0.840 (0.600, 1.120)

Back to
Table of Contents

Performance of Pharmacokinetic Models for Propofol in Early Phase of Target-Controlled Infusion

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Background: Pharmacokinetic models applied to target-controlled infusion (TCI) may have a limitation in the early phase of TCI because the compartmental model assumes that an administered drug is instantaneously mixed in the central compartment. The aim of the study was to investigate the performance of pharmacokinetic models for propofol, developed by Marsh[1] or Schnider[2], in the early phase of TCI.

Patients and Methods: Before the start of the TCI, acetate Ringer's solution 10 ml/kg was infused. All patients were receiving TCI of propofol using either of the Marsh or Schnider pharmacokinetic model. Rugloop II® (Demed Medical BVBA, Belgium) and Pump 22 (Harvard Apparatus, MA) was applied for TCI. Propofol was administered for 30 minutes using TCI at fixed targeted plasma concentration determined using the equation, $1.67 \bullet (2.9 - 0.022 \bullet \text{age})$.[3] Then, the infusion of propofol was terminated. Acetate Ringer's solution was infused simultaneously at 300 ml/h through the same intravenous catheter during the study period.

Arterial blood sample was taken from the radial artery every 10 s for 2 minutes, 140, 160, 180, 210 s, 4, 5, 7, 10, 15, 20, 25, 30, 30.5, 31, 31.5, 32, 33, 35, 37, 40, 45, 50, 60 minutes after the start of TCI. Predictive performance was assessed using prediction error (PE) derivatives: median prediction error (MDPE) and divergence PE. The MDPE was calculated for the first 5 minutes ($MDPE_{0-5}$), from 5 to 30 minutes ($MDPE_{5-30}$), from 30 to 35 minutes ($MDPE_{30-35}$), and from 35 to 60 minutes ($MDPE_{35-60}$). The divergence PE during 5 to 30 minutes was calculated as the slope of the linear regression of PE against time. Data was expressed as median [interquartile range]. The MDPEs between the groups were compared using the Mann-Whitney test. The median of divergence PE was compared to zero using the Wilcoxon signed-rank test. $P < 0.05$ was regarded as significant.

Results: The $MDPE_{0-5}$, $MDPE_{5-30}$, $MDPE_{30-35}$, and $MDPE_{35-60}$ were −6.9% [−17.5 to 3.6],

−22.9% [−31.4 to −13.1], −46.4% [−52.7 to -42.7] and −57.2% [−60.4 to −51.7] for the Marsh model *vs.* −40.5% [−47.9 to −32.1] (P <0.001), −26.4% [−33.1 to −21.6] (P =0.325), −19.2% [−27.8 to −4.3] (P <0.001), −21.4% [−35.3 to −15.4] (P <0.001) for the Schnider model. The divergence PE was −18.8%/h [−26.1 to −3.6] for the Marsh model (P <0.001) or 8.5%/h [3.7 to 21.7] for the Schnider model (P =0.003).

Conclusions: Examined pharmacokinetic models overestimated the propofol Cp in 30-min TCI and subsequent 30-min after the stop of infusion except the first 5-min of plasma TCI using the Marsh model. In the Marsh model, the PE decreased from 5 to 30 minutes after the start of TCI.

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Fall and Rise Times of the qCON and qNOX Indices during Induction and Recovery of Anaesthesia

Authors: Erik Weber Jensen, Pedro L. Gambus, Umberto Melia

The objective of this study was to analyze the performance of qCON and the qNOX indices of hypnotic effect and pain/nociception after drug induction and during recovery of consciousness by measuring their fall and rise times.

Data was recorded from 140 patients scheduled for general anaesthesia with a combination of propofol and remifentanil. The qCON 2000 monitor (Quantium Medical, Barcelona, Spain) was used to calculate the qCON and qNOX. Both indices are derived from the frontal electroencephalogram[1].

In order to analyze the responses of the two indices to the changes of hypnotic and analgesic concentrations, the qCON and qNOX fall and rise times were defined at the beginning and at the end of the surgery. The fall times (Figure 1a) was defined as the difference between the time instants when the effect site concentration of propofol or remifentanil was above zero (T_0) and the time when qCON and qNOX reached a value under 85 ($T_{<85}$) and 65 ($T_{<65}$). The rise times (Figure 1b) were defined as the difference between the time of recovery of consciousness (eye opening) or response to noxious stimuli (T_{RC}) and the times when qCON and qNOX reached a value above 65 ($T_{>65}$) and 85 ($T_{>85}$).

The qCON had a faster decrease than qNOX (p-value<0.05): time to reach 85 and 65 were in median (25^{th}; 75^{th} percentile): 148.5 (67.0; 190.0) s and 198.0 (114.0; 245.0) s after anaesthesia induction. The qNOX fall times were significantly longer (p-value<0.05): 198.0 (114.0; 245.0) s and 249.0 (189.0; 322.0) s. At the end of the surgery, the qNOX started to increase before than qCON: the qNOX raised to 85 at 5.0 (-44.0; 46.0) s after recovery, while the qCON raised to 85 at 96.0 (26.0; 184.0) s after qNOX (p-value<0.05).

Both indices were able to detect differences between the times of actions of hypnotic and analgesic agents. The clinical interpretation is that according to the rate of change of qCON and qNOX loss of consciousness is achieved before adequate analgesia, after anaesthesia induction. During recovery, the probability of response to noxious stimuli (assessed by the qNOX) increases before the patient recovered consciousness as assessed by the qCON. Hence, the qNOX could be interpreted as an arousability index.

Acknowledgement: The qNOX was based on an idea from the Department of Anesthesia Hospital CLINIC de Barcelona (Spain) funded by grant PS09/01209 and has been developed in collaboration with Quantium Medical.

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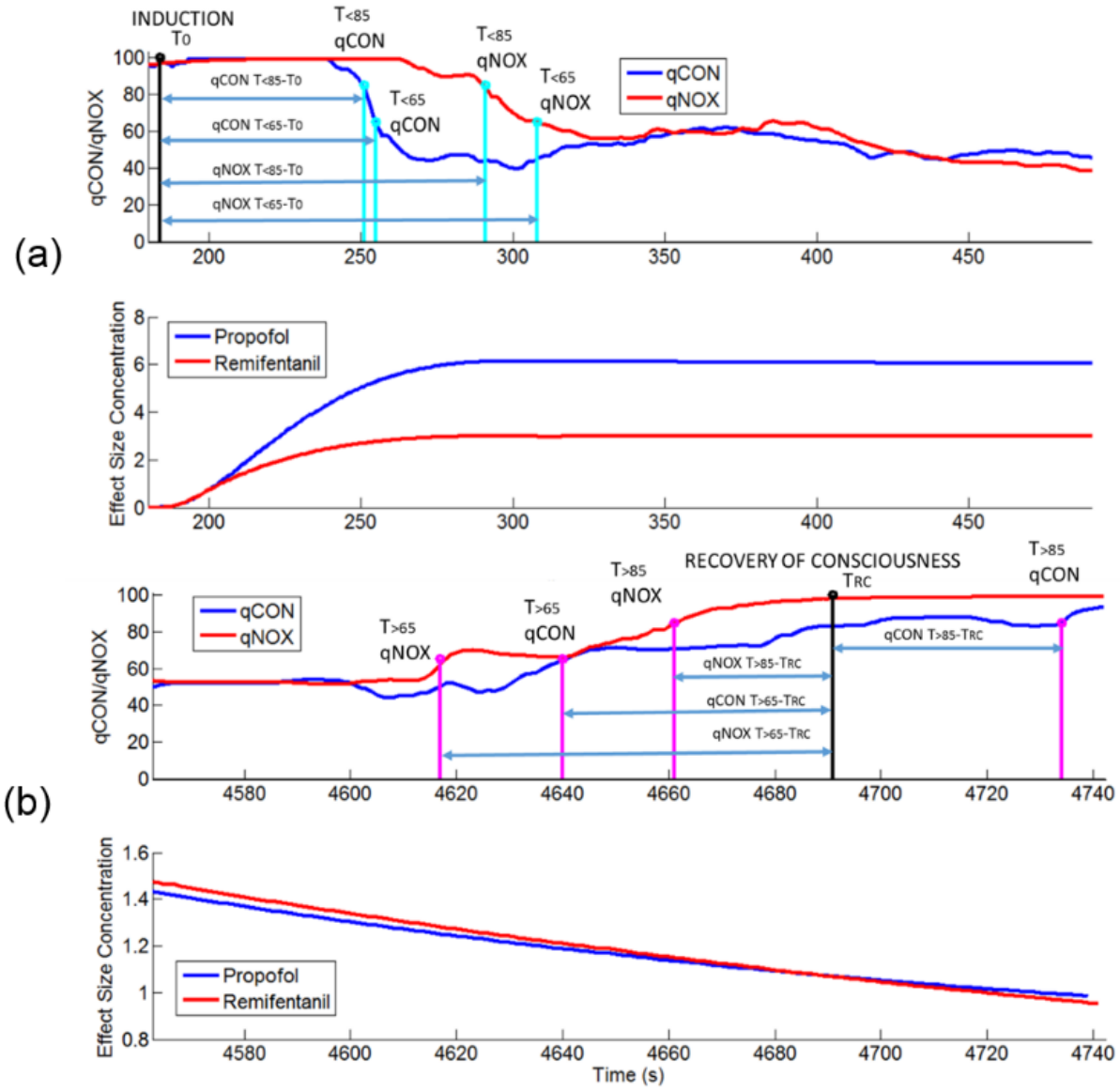

Figure 1 – Example of qCON and qNOX fall and rise times: (a) T_0 is the time instants when the effect site concentration of propofol or remifentanil is above zero; $T_{<85}$ and $T_{<65}$ are the time when qCON and qNOX reached a value under 85 and 65, respectively; (b) T_{RC} is the time of recovery of consciousness (eye opening) or response to noxious stimuli; $T_{>65}$ and $T_{>85}$ are the times when qCON and qNOX reached a value above 65 and 85, respectively.

Back to
Table of Contents

A Comparison of Post-Operative Analgesia Requirements in Patients Following Spinal Anaesthesia with Intra-thecal Morphine vs Fentanyl

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Background and Objectives: Post-operative pain following LSCS can be very severe and require high dose opiates. In order to lower pain scores and reduce the requirement of breakthrough pain relief, a comparison study was done to investigate if any clinically significant difference existed following administration of intra-thecal fentanyl plus morphine vs fentanyl alone.

Methods: All patients who underwent LSCS at Manly Hospital between January and February 2015 were identified. The primary outcome variable was the amount of breakthrough opiate used in the first 72 hours in both groups. Inclusion criteria was set that all patients received a standardized post-operative analgesic regime and any patients put on a PCA were excluded.

Results: 30 patients were identified who met the inclusion criteria. Of those 30 patients 10 received intra-thecal morphine plus fentanyl and 20 received fentanyl alone. Only 20% of those receiving IT morphine required any breakthrough pain relief in the first 72 hours compared with 80% in the fentanyl group. Furthermore the average amount of breakthrough opiate required was just 15mg oxycodone in 72 hours compared to 23.8mg in those who received no IT morphine.

Discussion: The analgesic requirements in patients receiving intra-thecal morphine plus fentanyl was reduced when compared with those who received intra-thecal fentanyl alone. These results support the hypothesis that an optimal analgesic regime for post operative pain following LSCS should include IT morphine during spinal anaesthesia.

Back to
Table of Contents

D1-Like Dopaminergic Receptors May Depress The Propofol Excited Regulation of NA(-) Neurons in Rat Ventrolateral Preoptic Area

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Background: Accumulating evidence shows ventrolateral preoptic area (VLPO), the center of regulating slow-wave sleep, is a critical nucleus of induction and maintenance of sleep. VLPO contains two principal types of neurons, the noradrenalin-inhibited neurons (NA(–) neurons) and the noradrenalin-excited (NA(+) neurons). NA(–) neurons have three major characteristics: triangular and multipolar in shape, low-threshold spike (LTS) and the firings can be inhibited by noradrenalin. Propofol, a systemic intravenous anesthetic, has been reported to excite NA(–) neurons of rat VLPO, which also have nervous pathway projecting to promote wake nucleus, including dopaminergic pathway. However, there is no evidence whether VLPO can be modulated by dopaminergic system, while the neural mechanisms of unconsciousness induced by general anesthesia are not completely understood.

Methods: Firstly, we identified the NA(-) type neurons based on the pharmacological and morphological characteristics. Spikes and firings of VLPO neurons were recorded respectively by the loose-patch cell-attached technique and in whole-cell mode. Then spontaneous excitatory postsynaptic currents (sEPSCs) and spontaneous inhibitory postsynaptic currents (sIPSCs) were recorded from VLPO cells in acute brain slices of rats. In voltage clamp experiments, sIPSCs were examined in whole-cell configuration at a holding potential of 0 mV in the presence of AP5 (50 μM), 6, 7-dinitroquinoxaline-2, 3-dione (DNQX) (20 μM) and strychnine (1 μM) to block glutamate and glycine receptors.
Membrane potential was clamped at -70 mV when sEPSCs were recorded.

Results: Propofol facilitates the firings of NA(–) neurons and increases the frequency, but not the amplitude and decay time of sEPSCs in NA(–) neurons. Meanwhile, propofol may excite VLPO NA(–) neurons by decreasing the frequency and increasing the amplitude, but not the decay time of sIPSCs. However, D1-like dopaminergic receptors antagonist (SCH23390) but not D2-like dopaminergic receptors antagonist (sulpiride) can partly offset the reduced frequency of sIPSCs effection of propofol. At last, both of SCH23390 and sulpiride have no effect on sEPSCs.

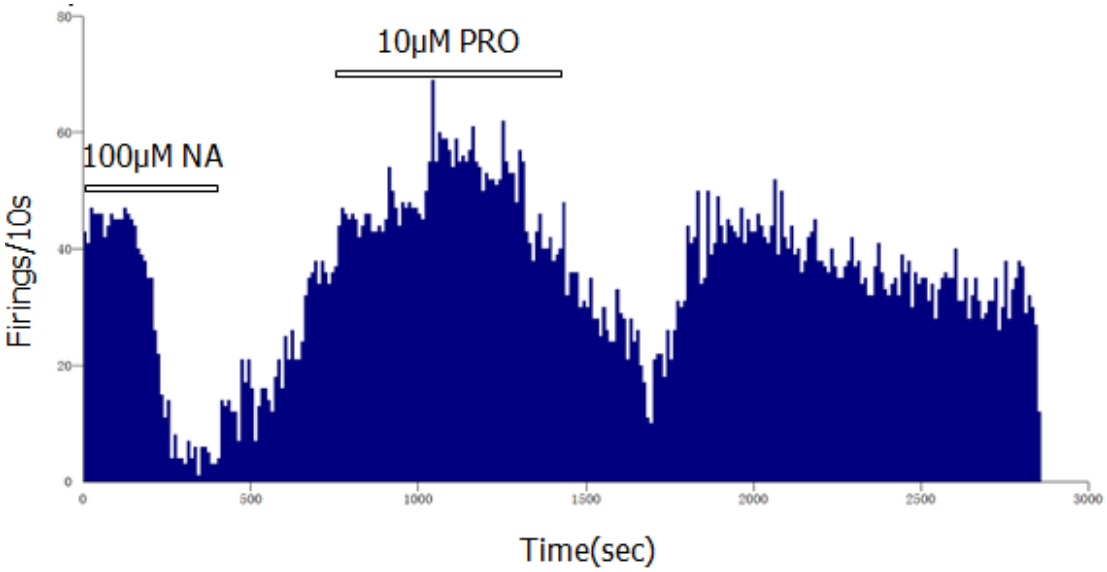

Figure1 The discharges of NA(-) neurons are inhibited by noradrenalin (100 μM). Propofol (10 μM) facilitates the discharges of NA(–) neurons.

Conclusion: Propofol may excite VLPO NA(–) neurons, however, D1-like dopaminergic receptors can depress this effect. Sleep-wake cycle may be involved in the mechanism of unconsciousness induced general anesthesia.

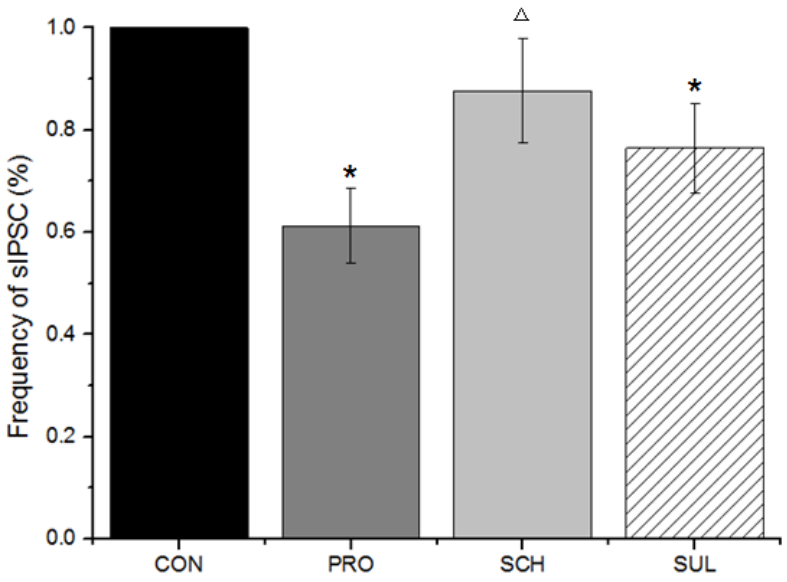

Figure2 Percent changes of sIPSC frequency in NA(–) by different perfusion protocal. (* represents $p<0.05$ compaired with CON group; △ represents $p<0.05$ compaired with PRO group). Perfusion protocal:CON group (ACSF), PRO group (ACSF + 10μM propofol + 100μM dopamine), SCH group (ACSF + 10μM SCH23390 + 100μM dopamine+ 10μM propofol), SUL group (ACSF + 10μM sulpride+ 100μM dopamine + 10μM propofol).

Back to
Table of Contents

Comparison of the Ability of the Quantium Consciousness Index and Bispectral Index to Predict Propofol Effect-Site Concentrations and Probability of Tolerance to Laryngoscopy During Propofol and Remifentanil Induction

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Objective: The present study compares the performance of two electroencephalographic derived depth of anesthesia monitors, the Bispectral Index (BIS) (Covidien, US) and the Quantium Consciousness Index (qCON) (Quantium Medical, Spain). We compared prediction probability (Pk)[1] to detect effect-site concentration of propofol (CePROP) and probability of tolerance to laryngoscopy (PTOL) during effect-site controlled induction of anesthesia with four different combinations of CePROP and effect-site concentrations of remifentanil (CeREMI).

Methods: After IRB approval, 80 patients scheduled for elective surgery were randomized in four groups. Anesthesia was induced using effect-site controlled, target controlled infusion with CePROP set to 8.6, 5.9, 3.6 or 2µg/mL while the corresponding CeREMI was set to 1, 2, 4 and 8 ng/mL respectively. When titrated to steady-state conditions each of these combinations yield a PTOL of 90% according to Bouillon et al. [2,3]. The BIS and qCON, CePROP and CeREMI were recorded every second while the (non-steady state) PTOL and Noxious Stimulation Response Index (NSRI) were computed post hoc using the formula of Luginbühl et al [4,5] NSRI is a derivative of PTOL and is proposed as measure of potency of combined opioids and hypnotics.[5] Data were used from 2.5 minutes before to 11 minutes after starting pumps.

The prediction probability (Pk) [1] for CePROP and NSRI was obtained for each index by averaging ten thousand Pk values that were calculated using one data point per patient in each iteration to guarantee independent inputs. The two sets of Pk's were tested for Gaussianity (Lilliefors test). The sets of Pk values did not follow a Gaussian distribution. Wilcoxon rank test was used to compare the sets of Pk's for respectively CePROP and NSRI.

Results: Patients enrolled were adults from both genders with age 53 ± 13 years, weight 79 ± 14kg and height 174 ± 9cm (mean ± standard deviation). Figure 1 shows the average trend of qCON and BIS in each of the groups. qCON showed an average Pk value of 0.849 ± 0.028 (Pk±SE) for CePROP and 0.885 ± 0.034 for NSRI; Pk values of the BIS were 0.863 ± 0.027 and 0.909 ± 0.031 respectively. No statistical significant difference in Pk's was found between qCON and BIS for predicting CePROP and NSRI, respectively.

Conclusions: BIS and qCON show similar predictive performance for CePROP and NSRI during induction of anesthesia using four different targets of CePROP and CeREMI all yielding a similar PTOL (90%) after 11 minutes of drug administration. The comparability in predictive performance of qCON and BIS is independent of group randomization. The similarity in results for NSRI (or PTOL) are probably related to CePROP that is a part of the NSRI formula.

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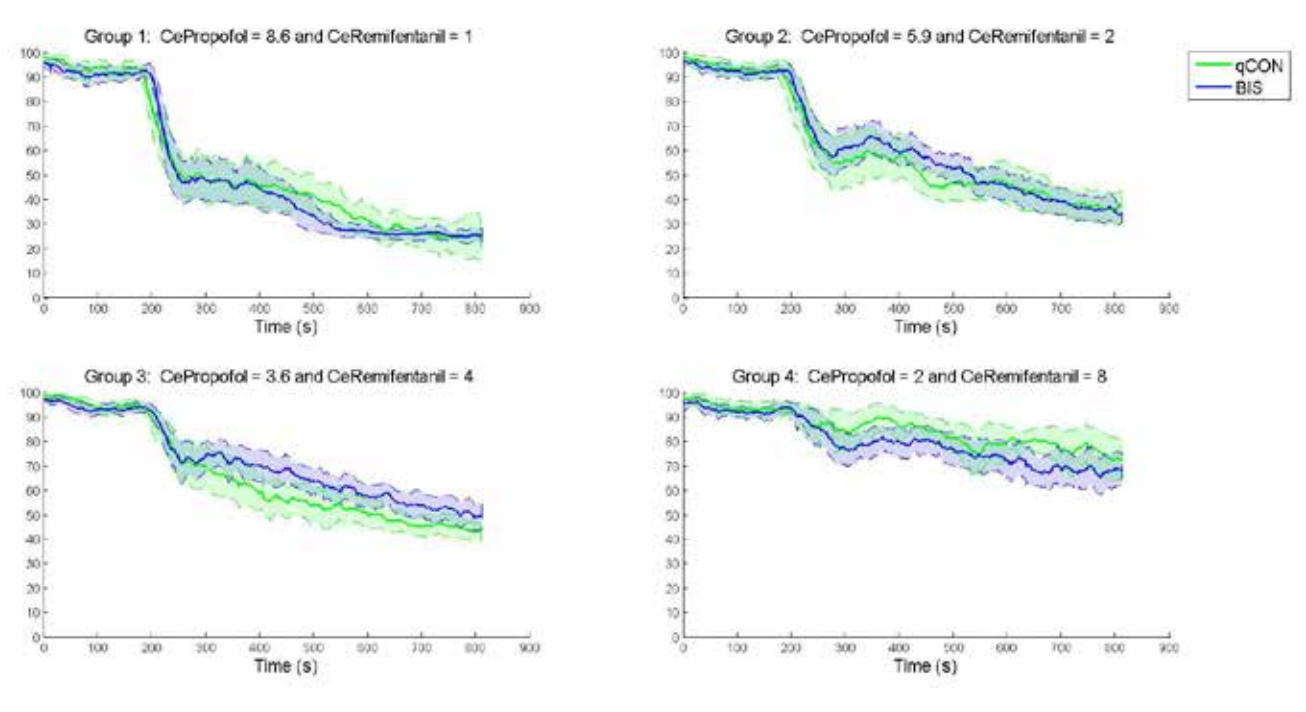

Figure 1: qCON and BIS average values versus time (solid lines) and 95% confidence intervals (dashed lines) during induction for the four combinations of CePROP and CeREMI.

Effect of Methylnaltrexone on Overall Survival in Advanced Illness Patients With Cancer

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Background: Methylnaltrexone (MNTX), a peripherally acting μ opioid receptor antagonist (MOR), is FDA-approved for treatment of opioid-induced constipation (OIC) in patients with advanced illness (AI) or chronic pain. MNTX has restricted passage through the blood brain barrier, and is given to cancer patients receiving opioids without affecting analgesia. Recent cellular, molecular, animal, and human data suggest that the MOR may be a target for potential chemotherapeutic agents. Additionally, a polymorphism in MOR which confers opioid resistance shows improved survival for human breast and esophageal cancer. Further, opiate use has been associated with survival in patients with advanced prostate cancer and with recurrence rates in patients undergoing surgery for lung cancer. It was therefore hypothesized that MNTX may improve overall survival (OS) in cancer patients. We assessed pooled data from two Phase 3/4 randomized, placebo-controlled trials (RPCT) to identify whether MNTX given for OIC could influence the survival in AI patients with cancer.

Methods: OS was recorded in two Phase 3/4 trials of MNTX for OIC in patients with advanced illness. Both RPCT studies (2 weeks followed by a 2-week follow-up period), enrolled AI-OIC patients receiving stable doses of laxatives and opioids. In Study 1, patients received MNTX 0.15 Sq mg/kg or placebo (PBO) every other day. In Study 2 patients received MNTX (12 mg based on body weight 38 to < 62 kg or ≥ 62 kg, Sq, respectively) or placebo administered every other day. MNTX responders were those laxating within 4hr after ≥ 2 of the first 4 doses. A modified Royal Marsden Score (RMH) based on albumin (>/= 3.5) was calculated for all patients.

Results: Of 370 patients in the 2 studies, 229 (62%) had a cancer, of whom 116 and 114 were randomized to MNTX and PBO, respectively. Distribution of cancers and RMH was similar between groups. MNTX patients had longer OS than placebo (79 vs. 59 days, $p = 0.019$). 66 patients receiving MNTX responded with laxation while 50 did not. MNTX responders had longer OS than non-responders and placebo (121 vs. 58 days, $p < 0.001$). Multivariate analysis of MNTX response and albumin showed that MNTX (HR = 0.43, $p < 0.001$) and albumin (HR = 0.48, $p < 0.001$) were independent prognostic factors for OS. In non-cancer AI patients, mostly CHF, COPD, and neurologic, response to MNTX was not associated with a significant change in OS.

Conclusion: While limited by the post-hoc nature of the results, our data demonstrate a potential role for MNTX in treatment of patients with advanced cancer. These are the first placebo-controlled human data suggesting that MNTX can influence OS in cancer patients with AI and are consistent with our preclinical observations. Our observations suggest that the MOR may be an important therapeutic target.

Back to
Table of Contents

Adrenocortical effects of ABP-700 in Dogs and Humans

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Objective: The objective is to present the adrenocortical effects of ABP-700, a second-generation metabolically labile etomidate analogue, when administered to dogs and humans.

Background: ABP-700 induces anesthesia by acting as a positive allosteric modulator of the γ-aminobutyric acid type A ($GABA_A$) receptor. It contains an ester bond that is precisely designed to undergo rapid hydrolysis by nonspecific blood and tissue esterases resulting in a short terminal t½ ranging from approximately 13-19 minutes in dogs and 11-19 minutes in humans. Although it was specifically designed to overcome the liabilities of other IV anesthetics including adverse adrenal effects, ABP-700 is a phenylethyl-imidazole-containing agent with the potential to induce adrenal suppression by the inhibition of 11β-hydroxylase, the enzyme responsible for the production of adrenal cortisol through the conversion of deoxycortisol to cortisol. However, the 'soft-pharmacology' of the engineered ester linker in this agent was predicted to remove any adrenal effects. Studies were performed to investigate the effect of ABP-700 on adrenal function in dogs and humans.

Methods: The effects of ABP-700 were characterized in beagle dogs (n=4). To decrease animal variability in resting levels of cortisol in dogs, the hypothalamo-hypophyseal axis was suppressed with dexamethasone (0.01 mg/kg IV) two hours before the induction of anesthesia. Each dog was administered ABP-700 (3 mg/kg IV bolus and 0.5 mg/kg/min IV infusion), etomidate (2 mg/kg IV bolus and 0.15 mg/kg/min IV infusion), propofol (5 mg/kg IV bolus and 0.4 mg/kg/min IV infusion) or vehicle for 120 minutes. Following infusion of the test article, synthetic ACTH (Synacthen, 250 µg IV) was administered. Blood samples were taken every 30-60 minutes to measure plasma cortisol concentrations and the concentrations of administered anesthetic agent. Plasma levels of cortisol and excursions from baseline were compared and analyzed based on published reports in healthy dogs (Pessina et al., Acta Vet Scand 2009).

Human volunteers were screened to ensure normal morning cortisol levels while at rest. Sixty (60) subjects were randomized to either ABP-700 or vehicle at a 5:1 ratio. Reference cortisol levels were obtained the morning of dosing. Bolus IV injections of ABP-700 (0.03 mg/kg to 1

mg/kg) or vehicle were given followed by a synthetic ACTH (Cosyntropin, 250 µg IV) challenge 60 minutes later. Blood samples were obtained 60 and 120 minutes following the ACTH challenge to measure plasma cortisol concentrations along with the concentrations of the anesthetic agent. Normal response (no evidence of adrenal suppression) was defined as an increase above from the reference plasma cortisol level of at least 200 nM/L at 60 and 120 minutes (Dorin et al., JCEM, 2012).

Results: In all treated dogs, within 1.5-3 hours after the end of infusion with either ABP-700 or propofol adrenal responsiveness was normal and indistinguishable between the agents. Etomidate, however, produced a profound and durable adrenal suppression. The following day, 24 hours post-initial anesthetic administration, all treatment groups showed a similar, normal, response to ACTH.

In humans, adrenal suppression was not observed after ABP-700 administration. All volunteers tested met the definition of normal response at both the 60 and 120 minute time points following ABP-700 IV bolus doses of 0.03 to 1.0 mg/kg or vehicle.

Conclusions: ABP-700 administration showed no adrenal suppression at pharmacologically active doses in both preclinical and clinical testing. These data support the continued evaluation of this novel agent as a broadly applicable anesthetic in humans.

Back to Table of Contents

Safety, Pharmacokinetics, and Pharmacodynamics of ABP-700: a Novel Intravenous Anesthetic

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Objective: The objective of this Phase 1 study is to determine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a single bolus dose of ABP-700, a second-generation metabolically labile etomidate analogue.

Background: ABP-700 is a novel, potent, positive allosteric modulator of the $GABA_A$ receptor currently being developed for monitored anesthesia care (MAC) and/or general anesthesia. ABP-700 contains an ester bond that is precisely designed to undergo rapid hydrolysis in the body by nonspecific tissue esterases in order to produce an inactive carboxylic acid metabolite. The pre-clinical pharmacology of ABP-700 has been previously published and it shows the desirable properties of etomidate including minimal hemodynamic and respiratory depression, but augmented by faster emergence from anesthesia and no adrenocortical suppression.

Methods: A Phase 1, first-in-human, double-blind, randomized, placebo-controlled trial was performed in 60 healthy volunteers. Eight (8) cohorts of 6 subjects (5:1 active to placebo) received a single bolus dose of either placebo, or 0.03, 0.10, 0.175, 0.25, 0.35, 0.50, 0.75 or 1.00 mg/kg ABP-700. Two (2) cohorts of 6 subjects (5:1 active to placebo) received 1 µg/kg fentanyl as a pre-medication followed by 0.25 or 0.35 mg/kg ABP-700. Safety assessments included clinical laboratory evaluations, hemodynamic and respiratory stability and adverse event monitoring. Adrenocortical function was assessed using the ACTH stimulation test. PD effect was measured using the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) and the BIS monitor (Aspect Medical Systems, Inc.)

Results: ABP-700 was safe and well tolerated. For the study overall, 105 of 112 (94%) of adverse events were reported as mild. Adverse events of moderate intensity were reported by 1 of 5 subjects (20%) and 2 of 5 subjects (40%) in the 0.75 and 1.00 mg/kg dose groups and in none of the other groups. PK was linear; peak venous serum concentration (T_{max}) ranged from 1.6-3.6 minutes, and the venous terminal elimination half-life ($T_{1/2}$) ranged from 10.5-18.7 minutes. PD effects as measured by MOAA/S and BIS were dose dependent and rapidly reversible. There was no effect on adrenal function at any of the doses tested.

Conclusions: ABP-700 was safe and well-tolerated following single bolus injections of up to a maximum dose of 1.0 mg/kg. The dose dependent differences in both type and frequency of adverse events are consistent with the mechanism of action of ABP-700 and its structurally related analog, etomidate. Consistent with pre-clinical observation, the PD effect of ABP-700 appears to be highly dose dependent with no adrenal suppression and context-insensitive rapid reversibility at all doses tested. The exposure and other PK parameters are also linear and dose-proportional. Based on these data, further exploration of ABP-700 as a potential anesthetic is warranted.

Back to
Table of Contents

Novel Local Anesthetics Demonstrate Isomer-dependent Analgesia in Mice

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Clinically there is a need for local anesthetics with a greater specificity of action and longer duration. We have synthesized a series of local anesthetic derivatives called boronicaines in which the aromatic, phenyl ring of lidocaine was replaced with an isomeric, polyhedral carborane cluster. A carborane cluster is an icosahedral cage comprised of ten boron and two carbon atoms (C2B10H12), and is more hydrophobic than a benzene ring. The boronicaine derivatives were tested for their analgesic activity and compared to lidocaine using a standard hot plate tests in mice following plantar injections. The use of mice in these studies was approved by the University of Missouri Animal Care and Use Committee. Results showed that the compounds differed in their analgesic activity in the following order: ortho-carborane = C, C′-dimethyl meta-carborane > para-carborane > lidocaine > meta-carborane derivative. Both ortho-boronicaine and C, C′-dimethyl meta-boronicaine had longer durations of analgesia than lidocaine. No analgesia was seen when the phenyl ring of lidocaine was replaced by either an adamantane or cyclohexane group. Differences in analgesic activity are rationalized by variations in chemical structure and protein binding characteristics.