25th Annual Meeting

Friday, October 21st, 2016

Hyatt Regency Chicago,
151 East Wacker Drive, Chicago, Illinois

International Society For Anaesthetic Pharmacology
2016 Syllabus

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25th Annual Meeting • Chicago, Illinois

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:
The overall purpose of this activity is to enable the learner to:

1. Decide whether he/she needs to adjust anesthetic management to avoid persistent post-operative cognitive decline.
2. Comprehend the potential of new drug modeling technology to improve clinical drug titration.
3. Understand the mechanisms of N2O and ketamine as modulators of depression.
4. Learn about the history of the International Society of Anesthetic Pharmacology (ISAP) and of the implementation of target controlled infusions (TCI) around the world.

Practice Gaps:

- A long term outcome of anesthesia is "persistent post-operative cognitive decline." Anesthesiologists (both clinicians and academics) are in doubt whether they need to adjust their drug titration in view of these outcomes.
- Improving technology for modeling drug-concentration and effect leads to better control of the dose-effect relationship, but is insufficiently known by anesthesiologists.
- The use of nitrous oxide may negatively affect patients that are at risk for depression. Ketamine may play a role in the treatment of depression.

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 Amedco and the International Society of Anaesthetic Pharmacology (ISAP). Amedco is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT:
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25th Annual Meeting Agenda · Chicago, Illinois

7:00 – 8:00 *Grand Ballroom A*	Registration and Continental Breakfast
8:00-8:10 *Grand Ballroom B*	Welcome: ISAP President *Vesna Jevtovic-Todorovic, MD, PhD, MBA*
8:10-8:15 *Grand Ballroom B*	Introduction to the Program *Program Co-Chairs Hugo E.M. Vereecke, MD, PhD and Michael Avram, PhD*
8:15-9:00 *Grand Ballroom B*	**Session 1 – ISAP's 25th Anniversary**
8:15 – 8:35	ISAP: A History of a Significant Society! *Tom C. Krejcie, MD*
8:35 – 9:00	The History (and Future) of Target Controlled Infusion *Michel Struys, MD, PhD, FRCA (Hon)*
9:00 – 9:30 *Grand Ballroom A*	Break w/ Exhibitors
9:30 – 11:30 *Grand Ballroom B*	**Session 2 – Persistent Postoperative Cognitive Dysfunction/Decline (POCD) – Myth or Reality?**
9:30 – 10:00	Assessing Cognitive Function, Postoperative Cognitive Dysfunction, and the Cognitive Trajectory: Lessons from the International Study of Postoperative Cognitive Dysfunction (ISPOCD) *Jacob Steinmetz, MD, PhD*
10:00 – 10:30	Persistent Postoperative Cognitive Dysfunction/Decline (POCD) – A Reality! *Terri Monk, MD, MS*
10:30 – 11:00	Persistent Postoperative Cognitive Dysfunction/Decline (POCD) – A Myth! *Michael S. Avidan, MBBCh*
11:00 – 11:30	Persistent POCD – Panel Discussion on the Presented Evidence *Jacob Steinmetz, MD, PhD; Terri Monk, MD, MS; Michael S. Avidan, MBBCh*
11:30 – 12:30 *Grand Ballroom B*	Lunch, ISAP Business Meeting, Break with Exhibitors
12:30 – 13:30 *Grand Ballroom B*	Moderated Poster Discussion *ISAP Board of Directors*
13:30 – 14:30 *Grand Ballroom B*	**Session 3 – New Concepts for Drug Titration**
13:30 – 14:00	Noxious Stimulation Response Index: The Next Generation of MAC? *Laura Hannivoort, MD*
14:00 – 14:30	Allometric Scaling in PK-PD Modeling *Douglas Eleveld, PhD*
14:30 – 15:00 *Grand Ballroom A*	Break w/ Exhibitors
15:00 – 16:00 *Grand Ballroom B*	**Session 4 – Anesthetics and Depression**
15:00 – 15:30	Ketamine and Its Metabolites and Their Potential Use for the Treatment of Depression *Irving Wainer, PhD, DHC*
15:30 – 16:00	Nitrous Oxide as a Treatment for Major Depression *Peter Nagele, MD, MSc*
16:00 – 16:45	Keynote Speaker & Lifetime Achievement Award Winner: *Talmage Egan, MD*
16:45 – 17:00	Closing Remarks
17:00 – 18:00 *Grand Ballroom A*	President's Reception

Save the Date

26th Annual Meeting
Friday, October 20th, 2017
Boston, MA

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Which Sevoflurane Wash-In Rates Towards 1.0 MAC Ensure Adequate Anesthetic Depth After a Standardized Intravenous Induction Before Surgical Incision?

Authors: Van Thielen Mira[1], Carette Rik[2], De Hert Stefan[3], De Wolf Andre M.[4], Hendrickx Jan F.A.[2]

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

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

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

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

Keywords: pharmacokinetics, inhaled agents, sevoflurane, synergy, anesthetic depth

Effect on ECG Parameters of ABP-700 Infusions in Combination with Opiates Targeting Sedation in Man

Presenting Author: P. Meyer, MD, PhD 1
Co-Authors: S. Sweeney, BS[2]; J. A. Campagna, MD, PhD[2]; John J. Marota MD, PhD[2]; B.I. Valk, BSc[1]; S. Meier, MD[1]; M.M.R.F.Struys, MD, PhD[1]; Borje Darpo, MD, PhD[3]

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Introduction: ABP-700 is a novel, second-generation metabolically labile etomidate analogue in development for procedural sedation and general anesthesia. The goal of this analysis is to investigate the effects of ABP-700 on electrocardiogram (ECG) parameters of conduction and repolarization during co-administration with commonly used opiates, fentanyl (FEN) and remifentanil (REM) during infusions targeting production of hypnosis ranging from light/moderate to deep sedation.

Methods: An open label, phase I study was performed following ethics approval in accordance with the Declaration of Helsinki and in compliance with GCP. Targeted arterial plasma concentrations of ABP-700 were selected based upon results of prior phase I trials. Dual-stage, 30min ABP-700 infusion regimens were designed to produce clinical effect within 5 minutes. Fifty-six subjects were dosed across 8 cohorts of either 4 or 8 subjects. ABP-700 was given either 5 min after FEN bolus (1mcg/kg, iv) as pre-treatment in 5 cohorts (n = 32), or 5 min after initiation of co-infusion with REM (0.125 mcg/kg/min infusion for 3 min, then reduced to 0.05 mcg/kg/min for 32 min) in 3 cohorts (n = 24).

Five ABP-700 fixed infusion paradigms (PAR) were used: PAR-1, 25 mcg/kg/min for 10 min then 20 mcg/kg/min for 20 min; PAR-2, 50 mcg/kg/min for 5 min then 30 mcg/kg/min for 25 min; PAR-3, 4 and 5, 70, 80 or 90 mcg/kg/min for 3 min then 40, 45 or 50 mcg/kg/min for 27 min. A sixth ABP-700 dosing paradigm tested anesthesiologist titration to effect of moderate sedation as 80 mcg/kg/min for 1 to 5 min then 45-60 mcg/kg/min for 27 min; this cohort received concurrent REMI infusion. FEN cohorts received PAR-1 through 5; REM cohorts received PAR-3, 4 and 6.

Hypnotic effect was assessed by MOAA/S and BIS. Arterial plasma ABP-700 concentration was determined in association with sedation assessments. ECG was recorded continuously by 12-lead Holter monitoring starting 1 h prior to dosing to 4 hours post dose. Serial ECGs were extracted post-dosing at the times of arterial sampling to determine effect on PR, QRS, and QTcF intervals. The effect of ABP-700 on QTc was evaluated by exposure response (ER) analysis.

Results: Subjects (48% male) were aged 18-55 years and predominantly white. Arterial mean peak plasma levels ranged from 574 (PAR-1) to 1957 ng/mL (PAR-5); sedation ranged from light to deep.

With both FEN and REM, ABP-700 had no effect on cardiac conduction; PR and QRS intervals were unchanged over the exposure range. There was a shallow linear relationship between ABP-700 plasma concentrations and the QT effect (ΔQTcF) with a slope of 0.005 msec per ng/mL (90% CI: 0.004 to 0.007). This is likely of little clinical significance.

Conclusions: These data indicate that ABP-700 can produce levels of clinical sedation ranging from light/moderate to deep in the presence of fentanyl and remifentanil without either clinically meaningful effect on cardiac conduction or clinically concerning effect on cardiac repolarization (QTc interval) and support further exploration of ABP-700 for use in procedural sedation.

A Phase 1 Dose Optimization Study of ABP-700 with Opiates and/or Midazolam Targeting Induction of General Anesthesia (Preliminary Results)

Presenting Author: S. Meier, MD, PhD[1]

Co-Authors: S. Sweeney, BS[2]; P. Meyer, MD, PhD[1]; A. R. Absalom, MBChB, FRCA, MD[1]; B.I. Valk, BSc[1]; J. A. Campagna, MD, PhD[2]; J.J. Marota, MD, PhD[2,3]; M.M.R.F.Struys, MD, PhD[1]

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[3]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA.

Background and Objective: ABP-700 is a positive allosteric modulator of the $GABA_A$ receptor in development for procedural sedation and induction of general anesthesia. The goal of this dose ranging study was to determine safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ABP-700 given as an infusion either alone, after premedication with an opiate, benzodiazepine or their combination, or during co-administration with an opiate.

Method: An open label, Phase 1 healthy volunteer study was performed with ethics approval in accordance with the Declaration of Helsinki. Doses of ABP-700 were selected based on prior Phase I results demonstrating a safety, efficacy and tolerability profile consistent with clinical utility for induction of general anesthesia and refined with the use of compartmental PK/PD modeling. 120 subjects were enrolled in fifteen cohorts (8 subjects/cohort, 50% male, ages 18 to 54). Thirteen cohorts received a single stage infusion of ABP-700 at 100, 120, 140, or 160 µg/kg/min for 7 min and 2 cohorts received a 3 stage infusion as 140, 100, 90 µg/kg/min for 2, 2, 3 min. ABP-700 was given alone in 4 cohorts and the remaining 11 cohorts were dosed in combination with three premedication regimens: fentanyl (1 µg/kg), midazolam (30 µg/kg), midazolam-fentanyl (15 µg/kg-1 µg/kg) or as co-administration regimen: remifentanil as a 2 ng/ml effective site target controlled infusion. Safety assessments included clinical labs, hemodynamic, respiratory and adverse event (AE) monitoring. Clinical effect was assessed by MOAA/S scoring and BIS monitoring.

Results: ABP-700 produced a dose-dependent increase in the proportion of subjects achieving unconsciousness: within 5 minutes of dose initiation, 12.5%, 62.5% and 100% of subjects achieved a MOAA/S = 0 with 100, 120 or ≥140 µg/kg/min for 7 minutes, respectively. Clinical effect was not substantially affected by any of the pre- or co-medication regimens. Respiration was well preserved with apnea reported in 3 subjects, all of which were co-administered remifentanil.

The most common AEs (>20%) were involuntary muscle movements, sinus tachycardia and systolic hypertension. Premedication improved tolerability and decreased the frequency and extent of hemodynamic excursions and also incidence and intensity of any involuntary muscle movements.

Conclusion: ABP-700 as a 7 min infusion is safe and generally well tolerated. Infusion rates of 100 µg/kg/min and above are associated with drug-induced unconsciousness with good preservation of spontaneous breathing. When dosed with pre- and co- medications, ABP 700 given as a short infusion may be useful as an induction agent.

The Effect of Granisetron on Bupivacaine Induced Sciatic Nerve Block in Rats

Presenting Author: Mehmet Sari, MD[1]

Co -Authors: Fatma Nur Erdogdu, MD[1], Ali Ozgul Saltali, MD[2], Mehmet Sarı, MD[1], Ibrahim Ozkan Onal, MD[1], Jale Bengi Celik, MD[1], Seza Apiliogullari, MD[1]

[1]Department of Anesthesiology, Selcuk University Faculty of Medicine, Konya, Turkey.

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Aim: The effects of the 5-HT_3 receptor antagonists on regional anesthesia are complex and unclear. Saltali et al.(1) show that 800mcg perineural ondansetron decrease the bupivacaine induced motor, sensory and proprioceptive function in the rats sciatic nerve. The primary aim of this study was to determine the effect of perineural granisetron on bupivacaine induced motor block in the rats sciatic nerve.

Methods: The study was approved by Selcuk University Committee for the Use and Care of Animals. Thirty-eight male Wistar Albino rats which received unilateral sciatic nerve blocks were randomly divided into five experimental groups: Group B (control,n=6) received a perineural of 0.3ml of bupivacaine alone; Group BG_{800} (n=8) received perineural 0.3ml of bupivacaine and 800µg of granisetron 10min later; Group BG_{1200} (n=8) received perineural 0.3ml of bupivacaine and 1200µg of granisetron 10min later; Group BG_{1200IP} (n=8) received a perineural 0.3ml of bupivacaine and an intraperitoneal injection of 1200µg of granisetron 10min later; and Group S (n=8) was sham operated. A blinded investigator assessed motor, sensory and proprioceptive function every 10min until the return of normal function.

Results: The time to the return of normal motor, sensory and proprioceptive function was not statistically significantly different between the groups (Table 1). The median time to the return of normal motor function in the Group B, Group BG_{800}, Group BG_{1200}, and Group BG_{1200IP} was 105min, 64min, 85min and 120 min respectively. Motor block did not develop in any of the rats in Group S.

Conclusion: Although local application of perineural 800 µg granisetron causes 39% decrease in the duration of motor block, granisetron did not statistically significantly decrease the duration of bupivacaine induced motor sensory and proprioceptive block in the rats sciatic nerve.

Table 1. The median times to the return of normal motor, sensory and proprioceptive function.

The median times to the return of normal motor, sensory, proprioceptive function (minute)			
Groups	**Motor Function (median, min-max)**	**Sensory Function (median, min-max)**	**Proprioceptive Function (median, min-max)**
Group B	105	80 (30-237)	80 (30-237)

	(30-237)		
Group BG_{800}	64 (43-112)	64 (43-112)	63 (33-105)
Group BG_{1200}	85 (49-124)	84 (54-120)	85 (42-120)
Group G_{1200IP}	120 (77-150)	104 (77-140)	108 (23-140)

Group B: Only bupivacaine group, Group BG_{800}: Bupivacaine + perinöral 800 µg granisetron, Group BG_{1200}: Bupivacaine + perinöral 1200 µg granisetron, Group BG_{1200IP}: Bupivacaine + intraperitoneal 1200 µg granisetron

References:

1. Saltali at al. The reversal effect of ondansetron bupivacaine induced sciatic nerve block in rats. Oral presentation, 7th European Congress of Pharmacology, Istanbul, Turkey.

Anesthetic Technique For Elective Cesarean Section In A Patient With Allergy To Amide Local Anesthetics

Authors: Efrain Riveros-Perez MD[1], Claudia Clavijo MD[2], Joy L. Hawkins MD[3]

Introduction: Neuraxial techniques are integral elements of analgesic and anesthetic management of obstetric patients. Albeit rare, allergic reactions to LA might be clinically significant, and could constitute a contraindication to the use of some regional anesthetic techniques. Here, we present a case of a pregnant patient with allergy to amino-amide LA who underwent cesarean delivery. This case represented a challenge to the anesthesiologists and highlights the importance of anesthetic planning and mastering of different techniques.

Case presentation: A 35 year-old pregnant patient G1P0 at 38 weeks gestation with a fetus in breech presentation, without significant past medical history and pregnancy complicated by gestational diabetes mellitus, presented to the Department of Anesthesiology referred by her obstetrician due to history of allergy to LA. As a teenager the patient experienced an episode of dizziness and syncope during a dental procedure, prompting skin testing for LA, which was positive for both tetracaine, bupivacaine and lidocaine. The patient didn't recall any symptoms on the spectrum from hives to anaphylaxis to suggest an IgE-mediated reaction.

Evaluation by the Allergy and Immunology Department took place, finding significant dermatographism that complicated interpretation of skin allergy tests. The test for tetracaine was negative, tolerating a subcutaneous challenge up to 0,5 mL. With this information, the patient was labeled as allergic to amide LA and the anesthetic plan for labor and delivery was devised.

Cesarean section was scheduled for 39 weeks of gestation; however, because of ongoing labor, she was admitted for the procedure in an urgent fashion 5 days earlier. The patient was prepared for surgery. Standard ASA monitoring was used and the code cart was readily available. An epidural technique with catheter was performed in the sitting position with midline approach at L3-L4 level. Skin was infiltrated with 3 mL of 3% chloroprocaine. The epidural space was identified with loss of resistance to normal saline and a 20 G catheter was advanced without complications. No test dose was utilized and titration of 3% chloroprocaine up to 20 mL with 100 mcg of fentanyl was done. During the procedure, the sensory level achieved was T4 and she maintained hemodynamic stability. Apgar scores were 8 and 9 at one and five minutes respectively. The patient didn't show any signs of skin allergic reaction or bronchospasm during or after the case. Discharge from the hospital was ordered two days later without maternal or neonatal complications.

Discussion: The prevalence of true IgE-mediated allergy to LA has been estimated to be less than 1% (1). In certain instances, side effects related to LA are often attributed to allergic reactions, and some patients are labeled as allergic to LA without further investigation. Neuraxial anesthesia with LA is the technique of choice for cesarean delivery as it may be

associated with a decreased rate of complications (2). Allergic reactions to LA are more common with amino-ester agents, which are derivatives of para-amino benzoic acid (PABA) (3). On the other hand, there are scarce reports of true allergy to amino-amide LA (4,5). In our case, an updated evaluation by the Department of Allergy and additional testing were warranted in order to accurately establish the diagnosis and to determine whether there was negative testing to specific LA. As a result of those investigations, regional anesthesia with ester-type LA was still a possibility for delivery.

When amide-type LA are contraindicated in the surgical patient, an anesthetic plan including different techniques and medications must be devised and discussed with the surgical team. Neuraxial anesthesia in the context of labor and delivery should be devoid of neurotoxic effects, have a favorable pharmacokinetic profile including rapid onset time and be reliable in terms of level and depth of block with fewer side effects. These anesthetic goals can be achieved with LA and non-LA medications. 2-choloroprocaine is an amino-ester LA with anesthetic profile comparable with lidocaine when used for intrathecal and epidural anesthesia/analgesia, and is an excellent alternative when amino-amide LA are contraindicated (7). Meperidine is a phenylpiridine opioid agonist with local anesthetic properties when injected intrathecally (8), and has been used as a sole agent in spinal anesthesia for cesarean section. The dose of meperidine used in this setting is 75 mg with an expected T4 dermatomal level at five minutes. In this case, epidural 3% chloroprocaine was successfully used with predictable onset and offset times as well as adequate block quality. Preparation for general anesthesia must always take place as backup. Finally, should the patient have required labor analgesia, both a narcotic intravenous PCA technique supplemented by nitrous oxide and combined spinal-epidural, with spinal doses of either meperidine or chloroprocaine and epidural infusion of chloroprocaine, would be reasonable options.

Conclusion: a rare situation like allergy to amino-amide LA poses significant challenges to the anesthesiologist. Knowledge of pharmacologic alternatives and mastering of diverse anesthetic techniques are of utmost importance in this scenario.

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Dexmedetomidine Combined With Fentanyl For Monitored Anesthesia Care During Endoscopic Variceal Ligation Surgery

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Objective: To investigate the ideal dosage of dexmedetomidine (DEX) with 1.0 μg/kg fentanyl for monitored anesthesia care (MAC) during endoscopic variceal ligation (EVL).

Methods: A total of 60 patients, of ASA physical status II or III, aged 36–59 yr, with body weight 50–75 kg, scheduled for elective EVL ,were randomly divided into 3 groups (n=20): dexmedetomidine 1.0, 1.5 and 2.0 μg/kg groups (D_1, D_2 and D_3 groups. After fentanyl 1.0 μg/kg was infused intravenously, the loading dosage of DEX 1.0, 1.5, 2.0μg/kg was separately continuous infused in 10 min. When the modified OAA / S scale ≥ 3 point, EVL was carried out. The modified OAA/S score at the time-points of before induction (T_0), before endoscope insertion (T_1) and 5mins later (T_2), end of surgery (T3) were recorded. The operation duration, recovery time, satisfaction of patient and doctor, incidence of nausea, body movement, bradycardia, hypotension, tachycardia, hypertension and hypoxemia was recorded.

Results: There were no differences in the 3 groups about the general status, operation duration and satisfaction score (P＞0.05). (1) Before endoscope insertion (T_1), the improved OAA / S score in Group D_3 (4.4±0.2) were higher than D_1（3.4±0.5）and D_2 groups（3.8±0.3）（P<0.05), there were no differences between D1 and D2 (P＞0.05). At the time-point of 5mins later (T_2), the score in Group D_3 (4.5±0.3) were higher than D_1 (3.5±0.6) and D_2 groups (3.7±0.4)(P<0.05), there were no differences between D1 and D2 (P＞0.05). At the end of surgery (T3), the score were almost similar (P＞0.05) (2) Compared with group D_1 (3.1±0.9) and D_2 (3.8±0.8), group D_3 (6.6±1.2) had longer recovery time (min) (P<0.05). (3) The satisfaction of endoscope doctor in Group D_1 (8.0±0.8) was lower than group D_2 (9.4±0.6) and D_3 (9.5±0.5) (P<0.05) , there were no differences during the two group (P＞0.05). (4)

Complicatons: There were no incidence of tachycardia, hypertension and hypoxemia, no difference of hypotension incidence in the three groups (P＞0.05). The incidences of nausea (30%) and body movement (15%) in group D1 is significantly higher than group D2 (5%) and D3(0) (P<0.05), there were no differences between D2 and D3 (P＞0.05). The incidences of bradycardia (40%) in group D3 is significantly higher than group D1 (0) and D2 (10%) (P<0.05), there were no differences between D1 and D2 (P＞0.05)

Conclusion: Combined with 1.0μg/kg fentanyl, 1.5 μg/kg DEX is more efficacy and safer for EVL in the status of monitored anesthesia care.

Key words: Endoscopic variceal ligation； Dexmedetomidine； Monitored anesthesia care

EEG Effects Produced By Nitrous Oxide And Remifentanil; BIS Vs Chaos

Presenting Author: David Drover, MD[1]

Authors: Caitlin M Drover, Hendrikus J Lemmens MD, M Bruce MacIver MSc PhD, and David R Drover MSc MD

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Remifentanil and nitrous oxide are commonly used in combination, together with other anesthetics, for routine surgical anesthesia, yet the electroencephalogram (EEG) effects of the two agents are poorly described. The present study examined effects of these two agents on EEG signals recorded from 40 randomly chosen surgical patients using a BIS monitor, following patient consent, under an Stanford University approved protocol. Remifentanil concentrations were varied on a steady background of nitrous oxide and cortical responses to a train of four (TOF) stimulus were compared at these different concentrations. At surgical planes of anesthesia high amplitude slow waves (1 to 2 Hz) dominated the EEG, similar to effects seen with most anesthetics, but these slow waves were interspersed with rhythmic theta activity from 4 to 10 Hz that lasted a few seconds to several minutes before reverting to slow wave activity, that could also last several minutes. Changes in remifentanil concentrations had little effect on background activity, marginally increasing slow waves, and did not change the alternating pattern of delta and theta activity. BIS values remained high (>75) in patients, even though they were surgically anesthetized, but occasionally dipped down to 40 following prolonged runs of lower frequency activity. The BIS was somewhat responsive to increased remifentanil doses, regardless of whether the increased dose was on a background of delta or theta activity. Chaos analysis of the same EEG signals showed a typical flatting of attractors that is seen with thiopental, propofol, ketamine as well as with volatile anesthetics. Attractor flattening was seen for both the delta and theta dominant EEG patterns, with little apparent difference, at surgical planes of nitrous oxide/remifentanil anesthesia. TOF stimulation produced cortical activation, seen as a marked decrease in signal amplitude and increase in higher frequency content, which was diminished by higher concentrations of remifentanil. Chaotic attractors were predictive of whether a TOF response would be seen, or not, with a flatter attractor being associated with loss of response. We conclude that remifentanil/nitrous oxide anesthesia is associated with a unique oscillating pattern of delta/theta frequency activity that the BIS failed to correlate to anesthetic depth. Chaos analysis, in contrast, consistently provided a good measure of anesthetic depth in these patients.

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Prediction Of Electroencephalographic Suppression Pattern In Patients Undergoing Total Intravenous Anesthesia For Ambulatory Surgery

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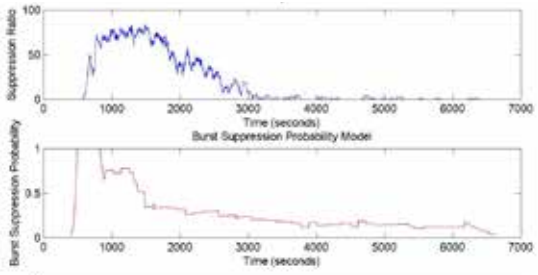
Intro: Electroencephalographic suppression (ES) is defined as the occurrence of isoelectric electroencephalogram during a period of time. ES pattern during general anesthesia is frequently associated with the use of intravenous or inhalation hypnotic drugs. Its presence has been defined as an indicator of too deep hypnotic effect and it has been associated with a poor outcome(1). The present study was designed to characterize factors that could increase the incidence of ES in patients undergoing total intravenous anesthesia.

Methods: Under IRB approval data was collected from patients undergoing general anesthesia for different ambulatory procedures. Patients were routinely monitored and had also EEG monitoring with BISpectral Index. Total intravenous anesthesia was performed via a TCI system administering propofol and remifentanil. Demographics, EEG, hemodynamics and TCI data as well as any relevant event during the procedure were collected online with the software Rugloop. ES was obtained from the BIS monitor data. For the purpose of the study ES was defined as amplitude of electrical activity below 5μV for periods longer than ten seconds. Matlab software was used to implement the logistic regression model of the probability of occurrence of Suppression as a function of different factors. The model validation process was performed using 30 fold cross validation in Matlab.

Results: Data from 600 patients were included. From all the factors studied predicted effect site concentration of propofol and remifentanil as well as mean arterial blood pressure were significantly included in the model. Age was not detected as a significant factor although it is a covariate factor in the PKPD models of the TCI system. The estimated logistic regression model is as follows:

$$BSPred = \frac{1}{1 + e^{B_1 + \mathrm{CeProp} \cdot B_2 + CeRemi \cdot B_3 + MBP \cdot B_4}}$$

Where BSPred stands for the probability of ES, CeProp and CRemi are the effect-site concentrations of Propofol and Remifentanil (in μg/ml and ng/ml, respectively) and MBP is the Mean Blood Pressure (in mmHg). The estimated value of the coefficients were B_1: -0.9221; B_2: 0. 5497; B_3: 0.0102; B_4: -0.0371. The results of the cross validation procedure summarized into a McFadden's pseudo R^2= 0.7962. The following graph shows a typical individual ES observation and the predicted probability as well as predicted propofol (blue trace bottom graph) and remifentanil (green) time course.



Conclusion: Based on real data it has been possible to generate a model to predict the probability of EEG suppression. The prediction ability of this model may be of help in optimal dosing of propofol to avoid overdosing associated with EEG suppression and its associated poor outcome.

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Comparison Of The qCON And Sedline Depth of Anesthesia Monitors To Predict The Hypnotic Effect During Desflurane General Anesthesia

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Objective: The present study aims to compare the performance of two depth of anesthesia monitors, the SEDLINE (Masimo Inc., Irvine CA, USA) [1] and the qCON (Quantium Medical, Barcelona Spain) [2], during general anesthesia with desflurane. Specifically the ability of the processed-EEG index value from each monitor to differentiate between states of clinical consciousness and unconsciousness was assessed by the prediction probability (Pk) [3].

Methods: With IRB approval, 12 patients undergoing elective surgery signed informed consent and were included in the study. The Patient State Index (PSI) and the qCON index were recorded every second during the complete procedure.

In order to assess the performance of both monitors, the prediction probability (Pk) for the qCON and PSI was obtained by averaging one thousand Pk values calculated using one data point per patient in each iteration to ensure statistical independency. The interval considered for the Pk calculation was from 2 minutes before induction until just prior to emergence. The two sets of Pks were tested for Gaussianity (Lilliefors test) to decide the best method to compare average Pk values (t-student for Gaussian samples and Wilcoxon rank test in non-gaussianity scenarios).

Results: Patients enrolled were adults from both genders. The mean (SD) Pk values for the qCON and the PSI were 0.969 (0.029) and 0.814 (0.058) respectively. The sets of computed Pk values did not follow a Gaussian distribution, hence the Wilcoxon rank test was used to show statistical significance. The pk of the qCON was significantly higher than that of the PSI.

Conclusions: The qCON had a significantly higher Pk than the PSI when comparing the awake and the anaesthetized state. The reason for the higher Pk value for the qCON is likely to be due to artifactual increases in the PSI caused by the use of the diathermy or EMG activity as shown in the figure. The PSI appears to be more greatly influenced by high frequency activity than does the qCON.

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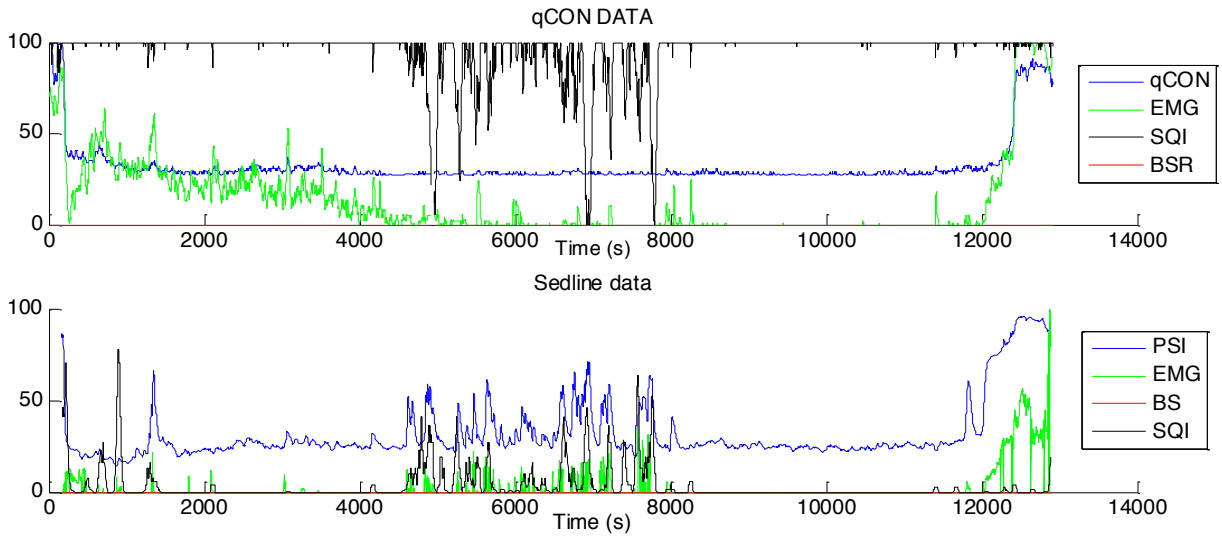

Figure: Examples of qCON and PSI trends

Effect Of Different Remifentanil Effect Side Concentrations On The BIS, Qcon, ANI And Qnox At Constant NSRI

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Part of this work was presented at Euroanesthesia 2016, London, England, May 2016

Introduction: Anesthetic depth is considered to be the probability of hypnosis, immobility and hemodynamic stability, induced by hypnotics and opioids.
NSRI is an index of anesthetic depth, calculated from effect site concentrations of hypnotics and opioids and their interaction. Hypnotic/opioid combinations that attain identical NSRI's (points on the same isobole), attain the same probability of a certain anesthetic depth. Hypnotics can be titrated based on an EEG derived index (BIS, qCON), and opioids can be titrated with an anti-nociception index (ANI, qNOX). We examined whether these indices correlated with different remifentanil effect site concentrations (CeREMI) and with different end-tidal desflurane concentrations ($F_A$des) while keeping the NSRI constant.

Methods: We measured BIS (Covidien), qCON/qNOX (Quantium Medical) and ANI (MDoloris) in 13 patients undergoing prostatectomy. NSRI, CeREMI and $F_A$des were calculated by the SmartPilotView (Draeger).
CeREMI in each patient was increased from 1 to 3 to 5 ng/mL while $F_A$des was adjusted to keep NSRI at 5.
Once NSRI and $F_A$des had stabilized at the target CeREMI, BIS, qCON, ANI and qNOX values were collected every 5 sec for 20 min.
Effect of different CeREMI on each index (ANOVA on ranks) and the prediction probability (Pk) for ANI and qNOX for CeREMI and the Pk for BIS and qCON for $F_A$des were calculated.

Results: $F_A$des to maintain NSRI at 5 was 6.6±0.4, 4.1±0.2, and 3.0±0.1 % in the CeREMI1, CeREMI3, and CeREMI5 groups, respectively.

	Pk of index versus CeREMI	Pk of index versus $F_A$des
ANI	0.36 (0.08)	
qNOX	0.74 (0.07)	
BIS		0.26 (0.07)
qCON		0.69 (0.07)

Fig. 1. The prediction probability Pk, presented as mean (standard error).

Conclusion: ANI did not reflect opioid effect, qNOX performed better in this regard. In our study, BIS and qCON had poor prediction probability for the hypnotic component of anesthesia ($F_A$des).

Future research could focus on the Pk of BIS/qCON versus calculated drug interaction. Calculated indices that account for interaction like NSRI, might be a better probability prediction for clinical endpoints of anesthetic depth.[1]

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Activation of CB2 Receptor System Reverses Amyloid-Induced Memory Deficiency and Restores SOX2 Activity in a Transgenic Mouse Model of Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory and cognitive function. The brains of patients with AD are characterized by extensive deposits of extracellular aggregation of amyloid-beta peptides. These peptides form senile plaques and intracellular aggregation of hyperphosphorylated tau protein. In addition, amyloid fibrils activate the inflammatory pathway, characterized by the activated microglia and astrocytes seen in the brains of patients with AD.

Cannabinoid type 2 (CB2) agonists are neuroprotective and appear to play modulatory roles in neurodegenerative processes in AD. CB_2 receptors are upregulated in reactive microglial cells in AD. This upregulation of CB_2 receptors tends to attenuate the activation of early pro-inflammatory microglial signaling pathways associated with AD.
Sox2 (sex-determining region Y (SRY)-box 2) is a transcriptional factor that is essential for maintaining self-renewal/proliferation of undifferentiated embryonic stem cells (ESCs) and multipotency of neural stem cells (NSCs). Sox2 behaves as a protective factor during the development of Alzheimer's disease.

We have studied the effect of 1-((3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl) piperidine (MDA7) a novel, blood brain barrier-permeant, and highly selective CB2 agonist that lacks psychoactivity on ameliorating the neuroinflammatory process, synaptic dysfunction, and cognitive impairment in the Tg-APPsw/PSEN1DE9 (APP/PS1) mouse model of AD. APP/PS1 mice are well suited for our investigations because they exhibit high production of Aβ peptides in the brain, accumulation of amyloid plaques, and demonstrate cognitive impairments. Senile plaques can be detected by thioflavin S or 3D6 as early as 4 months of age, and there is an overall increase in plaque burden with age. PAPP/PS1 mice displayed significantly impaired glutamatergic long-term potentiation (LTP) in the hippocampal CA1 neurons, indicating an impaired synaptic plasticity. LTP is an experimental phenomenon that takes place at excitatory glutamatergic synapses and is believed to play a central role in learning and memory.
At 3 mo of age, MDA7 14 mg/kg was administered intraperitoneally (i.p.) every other day for 5 mo. Another cohort of APP/PS1 received i.p. injections of the vehicle at alternate days for 5 mo. In the APP/PS1 transgenic mice, compared to wild type mice, treatment with MDA7 (i) ameliorated the expression of Iba1 (microglia marker), (ii) promoted amyloid-beta clearance in the hippocampal CA1, (iii) restored the expression of SOX2 (stem cell marker) in the hippocampal dentate gyrus, and (iv) restored synaptic plasticity, cognition and memory. Our findings suggest that MDA7 is an innovative therapeutic approach for Alzheimer's disease.

Summary: Activation of CB2 receptor system represents a novel therapeutic target for the treatment of neurodegenerative disorders.

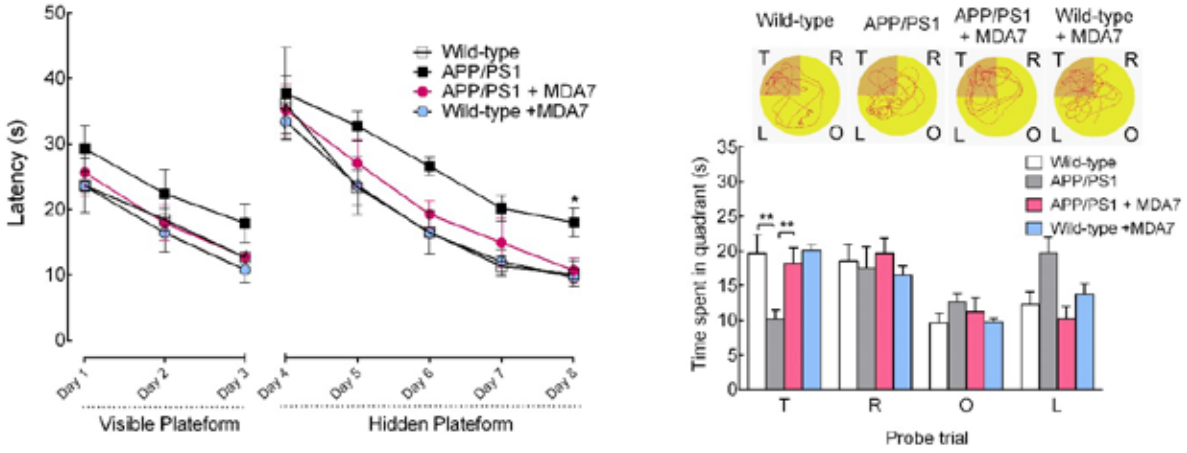

Figure 1. In the APP/PS1 transgenic mice, compared to wild type mice, systemic administration of MDA7 significantly mitigated the memory deficiency.
In APP/PS1 mice, significantly increased escape latency was noted, indicating memory deficiency (a). Treatment of animals at 3 mo of age with MDA7 14 mg/kg i.p. every other day for 5 mo (a) shortened the escape latency (n = 6-7 mice in each group, $P < 0.05$) and (b) increased the time in spent in the target quadrant (n = 6-7 mice in each group, $P < 0.05$) in the APP/PS1 transgenic mice. Representative path tracings in each quadrant during the probe trial on day 8.

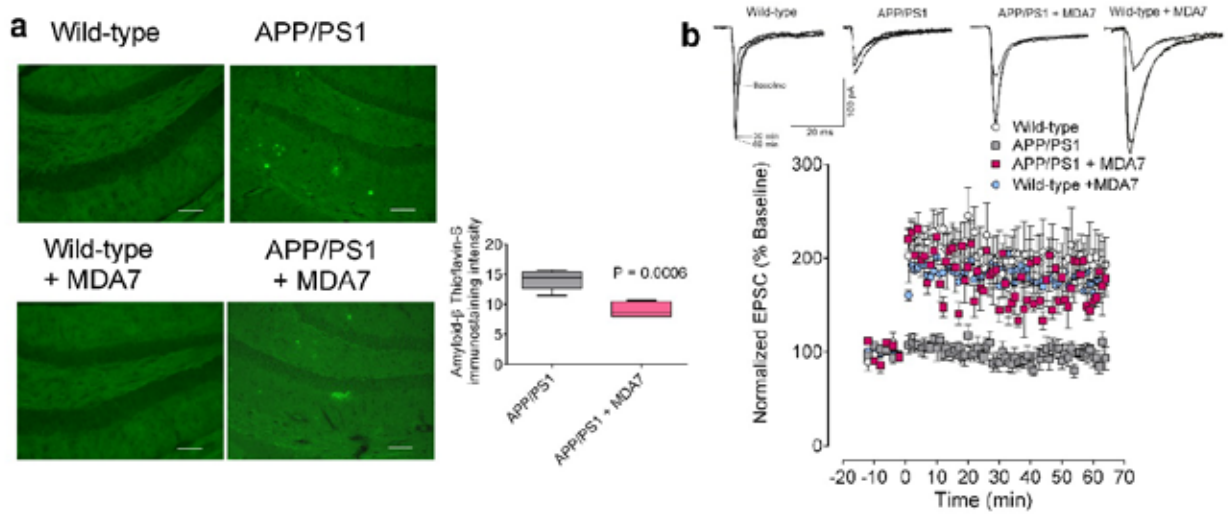

Figure 2 . In the APP/PS1 transgenic mice, compared to wild type mice, systemic administration of MDA7, promoted amyloid -beta (Aβ) plaque clearance in the hippocampal CA1 area and **restored synaptic plasticity in CA1.** (a) Thioflavin-S staining of amyloid plaques in the hippocampus. Treatment of animals at 3 mo of age with MDA7 14

mg/kg i.p. every other day for 5 mo significantly decreased the Aβ burden in the hippocampal CA1 neurons. Scale bar = 50mm. (b) APP/PS1 mice displayed significantly impaired glutamatergic long-term potentiation (LTP) in the hippocampal CA1 neurons, indicating an impaired synaptic plasticity. Treatment of animals at 3 mo of age with MDA7 14 mg/kg i.p. every other day for 5 mo significantly recovered the electric stimuli-induced LTP in the hippocampal CA1 neurons.

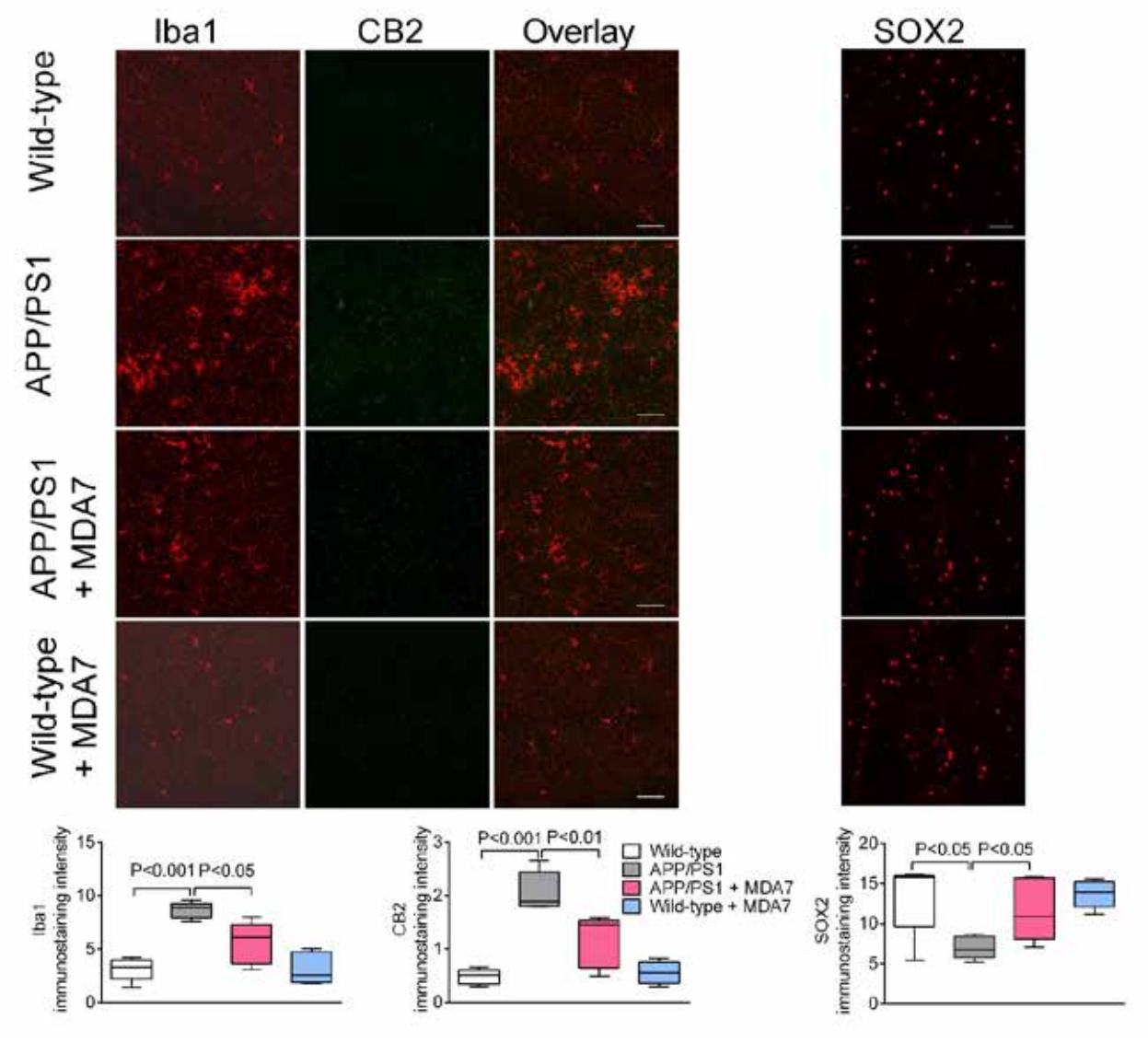

Figure 3. In the APP/PS1 transgenic mice, compared to wild type mice, systemic administration of MDA7 , significantly attenuated the upsurge of CB2 and Iba1expression in the hippocampal CA1 area. APP/PS1 mice displayed significantly increased the expression of Iba1 and CB2; Treatment of animals at 3 mo of age with MDA7 14 mg/kg i.p. every other day for 5 mo significantly attenuated upsurge of CB2 and Iba1

expression in hippocampal CA1 (n = 24 sections from 5 animals in each group). Scale bar = 50 µm.

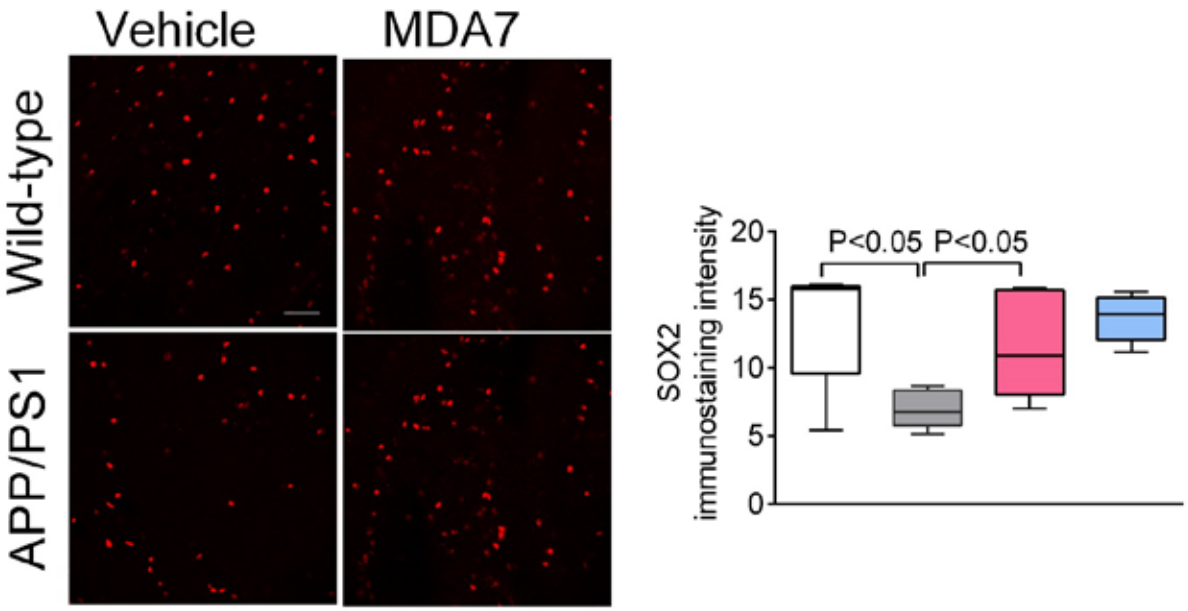

Figure 4. In the APP/PS1 transgenic mice, compared to wild type mice, systemic administration of MDA7, significantly restored SOX expression in the hippocampal CA1 area.
APP/PS1 mice displayed significantly decreased the expression of SOX2; Treatment of animals at 3 mo of age with MDA7 14 mg/kg i.p. every other day for 5 mo significantly restored SOX2 expression in hippocampal CA1 (n = 24 sections from 5 rats in each group). Scale bar = 50 µm.

A High Throughput Selection Strategy in Yeast to Study TASK-3 Potassium Channel Interactions with the Breathing Stimulant Drug PKTHPP

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Background: TASK-3 tandem pore potassium channels provide a constitutive potassium conductance, which regulates neuronal excitability, and that may have an important role in breathing regulation. PKTHPP is a potent inhibitor of TASK potassium channels and is an effective breathing stimulant in rodents (1). The potassium sensitive trk1Δtrk2Δ *S. cerevisae* yeast strain has been developed, previously, as a model system for studying potassium channel function (2). Additionally, growth competition experiments in yeast, combined with next generation DNA sequencing, is a new method for large scale mutational protein analysis (3).

Hypotheses: We hypothesized that PKTHPP binds in the TASK-3 channel pore. Furthermore, we hypothesized that high throughput selection in trk1Δtrk2Δ *S. cerevisae* yeast may identify TASK-3 amino acid residues in the pore essential PKTHPP binding. METHODS: To test our hypotheses, we prepared a library of randomly mutagenized TASK-3 cDNA, targeting the pore amino acid residues 120 to 128 for mutagenesis (180 possible missense mutants). We transformed this library of mutant TASK-3 cDNAs into trk1Δtrk2Δ *S. cerevisae* yeast and cultured them in low potassium media in the presence of PKTHPP (10 microM) or DMSO (vehicle only). The plasmid library cDNA was recovered from the yeast just before and just after growth/selection with DMSO/PKTHPP and TASK-3 sequence was analyzed by next generation sequencing (Illumina MiSeq platform). To quantify selection, we calculated an enrichment ratio for each TASK-3 pore mutant: [(frequency (in %) after PKTHPP growth/ frequency before PKTHPP growth)/(frequency after DMSO growth/ frequency before DMSO growth)]. PKTHPP selected for several mutations particularly at TASK-3 residue-122 with the top selected mutants being L122D, L122Q, L122K, L122E, L122Y, L122A, L122N, L122C and L128H with enrichment ratios of 343, 55, 45, 35, 28, 27, 26, 13 and 11, respectively. There was also a significant selection against specific mutations with the top being M124W, L128F, L128C, M124G, T121D, M124C, S127Y with an enrichment ratio compared to the DMSO treated population of 1/3253, 1/2493, 1/1523, 1/1288, 1/413, 1/226, 1/74 respectively. Our results agreed with our previously published electrophysiological studies (3) in which L122D, L122E and L122K were inhibited with an IC_{50}>10 microM (>1000-fold shifted; n = at least 3) compared to wild type (10 nM; 9–11 (95% confidence), n =6). The newly identified sensitive mutants M124W and L128F were inhibited by PKTHPP with an IC_{50} of 1 nM (0.9 -1.9) and 1 nM (0.5-2.1) (n = 2 and 3, each), respectively, in confirmatory electrophysiology studies. CONCLUSION: Our novel high throughput selection strategy is, as hypothesized, an effective and promising assay for studying TASK-3 pharmacology. Multiple mutations in the TASK-3 pore modify its functional interaction with PKTHPP.

Funding: Massachusetts General Hospital Department of Anesthesia, Critical Care, and Pain Medicine; NIH/HL117871; and Kantonsspital Aarau, Aarau, Switzerland (1410.000.062).

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Annexin 2 in Remifentanil-Induced Hyperalgesia

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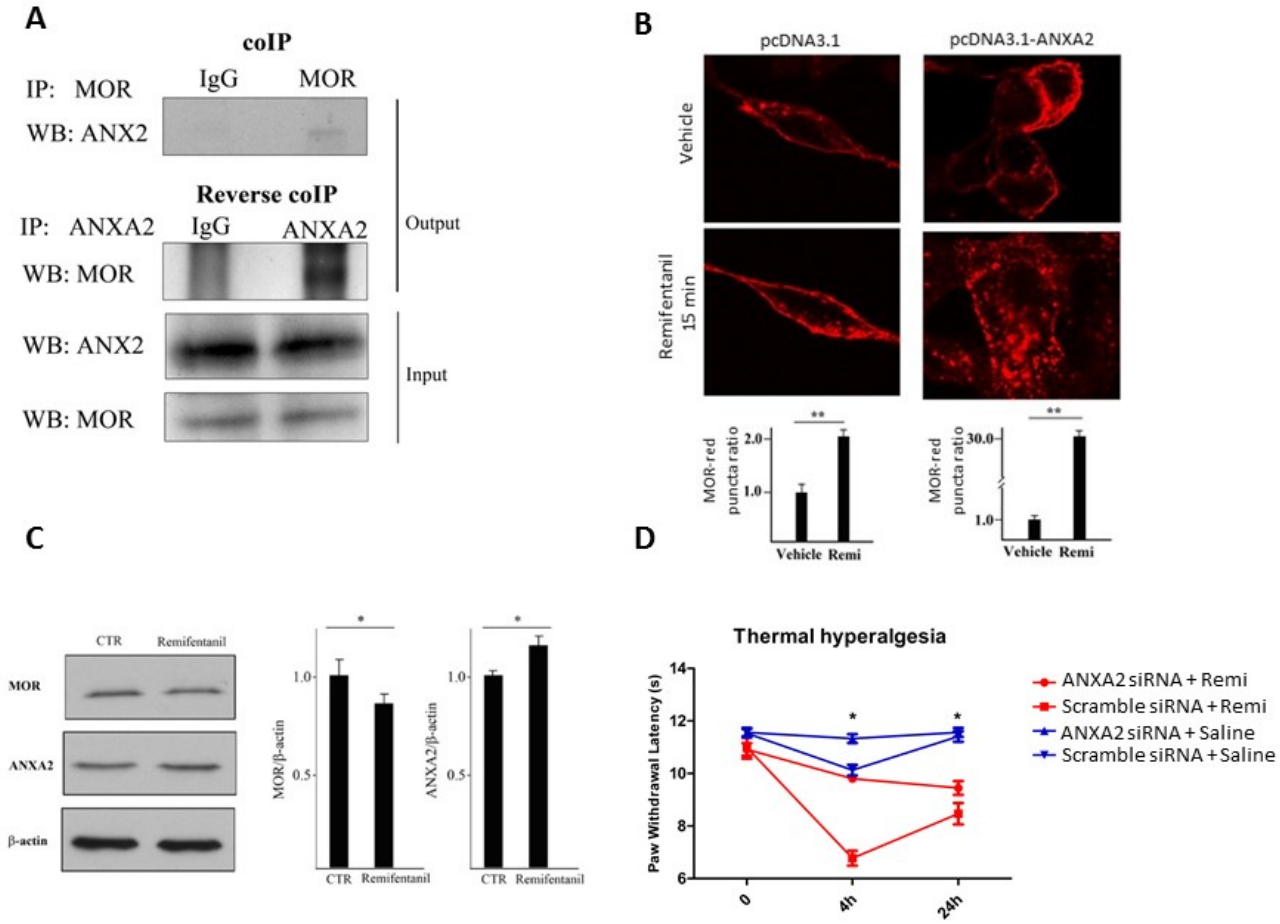
Introduction: Emerging evidence suggests that -opioid receptor interacting protein (MORIP) contribute to the development of remifentanil-induced hyperalgesia. This study aimed to evaluate the role of a novel MORIP – Annexin 2 (ANXA2) in MOR membrane trafficking and to determine whether MORIP knockdown affect the development of remifentanil-induced hyperalgesia in a rat model.

Methods: In a series of cell experiments, we identified MOR signaling complexes using formaldehyde cross-linking immunoprecipitation and high-performance liquid chromatography-mass spectrometer/mass spectrometer. Following extensive bioinformatics analysis, functional annotation and literature reviews, ANXA2 was selected for further study. MOR and ANXA2 interaction was determined using immunoprecipitation. Confocal microscopy was used to reveal the effect of remifentanil and ANXA2 interaction on MOR membrane trafficking. In animal experiments, small interference RNA (siRNA) was injected intrathecally to rats for knockdown of ANXA2 expression. Thermal hyperalgesia was measured. Rats were then euthanized and their lumbar spinal cord and dorsal root ganglia (DRG) were collected for determination of MOR and ANXA2 expression.

Results: ANXA2 co-localized with MOR in the neurons of lumbar spinal cord (Fig A). We further visualized internalization of MOR after 15-minute exposure to remifentanil and that overexpression of ANXA2 facilitated remifentanil-induced internalization of MOR (Fig B). We also observed that the expression of ANXA2 was up-regulated at 24 hours with remifentanil treatment and this was accompanied by a decrease in MOR expression (Fig C). In a rat model of remifentanil-induced hyperalgesia, intrathecal injection of specific siRNA decreased ANXA2 protein level in DRG and was associated with an increase in thermal hyperalgesia (Fig D).

Conclusion: ANXA2 was as a novel MORIP that contributed to remifentanil-induced hyperalgesia. In a rat model, the knockdown of ANXA2 exacerbated hyperalgesia with remifentanil infusion.

Figure A: Validation of MOR-ANXA2 interaction using co-immunoprecipitation (IP) and reverse co-IP in rat lumbar spinal cords. **B:** Effect of ANXA2 on the MOR trafficking. Confocal microscopy of MOR trafficking, with quantitative analysis of red puncta of cells, puncta number was counted and error bars are standard deviation, $^{**}p<0.01$ (unpaired *t*-test). **C:** Western blot and quantitative analysis showing effects on ANXA2 and MOR protein expression with remifentanil-treatment, $^{*}p<0.05$ (unpaired *t*-test). **D:** Thermal hyperalgesia of the rats receiving intrathecal injection of siRNA and tail vein injection of remifentanil.



Isoflurane, 2-Halogenated Ethanols, and Halogenated Methanes Activate TASK-3 Tandem Pore Potassium Channels Likely Through a Similar Mechanism.

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Background: TASK-3 (KCNK9) tandem pore potassium channel proteins mediate a constitutive potassium conductance activated by several clinically relevant volatile anesthetics (e.g., halothane, isoflurane, sevoflurane, and desflurane); knockout mice lacking the TASK-3 potassium channel are resistant to the hypnotic and immoblizing effects of halothane and isoflurane.

Purpose: To better understand the molecular mechanism by which TASK-3 channels are activated by anesthetics, we studied the functional concentration-response of wild-type TASK-3 potassium channels to isoflurane, to ethanol, and to several halogenated ethanols and methanes. We also studied the concentration-response of M159W TASK-3 to 2,2,2-trichloroethanol; the M159W TASK-3 mutant is known to be resistant to isoflurane activation (1). 2,2,2-trichloroethanol, notably, is an active metabolite of the sedative chloral hydrate; and 2,2,2-tribromoethanol is the active ingredient in Avertin, an injectable veterinary anesthetic.

Methods: Wild-type and M159W TASK-3 function were studied by Ussing chamber voltage clamp analysis during transient expression in Fischer rat thyroid cell monolayers.

Results: 2-halogenated ethanols activate wild-type TASK-3 with the following rank order for efficacy: 2,2,2-tribromo > 2,2,2-trichloro > chloral hydrate > 2,2-dichloro > 2-chloro ≈ 2,2,2-trifluoro > ethanol (Table 1). Similarly, carbon tetrabromide (CBr4) and tetrachloride (CCl4) both activate TASK-3 (with CBr4 > CCl4; Table 1).

Conclusions: Increasing halogention of both ethanol and methane promotes TASK-3 activation, and substitution with a larger and more polarizeable bromine atom, relative to chlorine or fluorine, provides for more potent and more effective TASK-3 activation. Since M159W TASK-3 is resistant to activation by either isoflurane or 2,2,2-trichloroethanol, we speculate these agents share commonalities in their mechanism of activation.

Funding: Massachusetts General Hospital Department of Anesthesia, Critical Care & Pain Medicine; NIH/HL117871; and Kantonsspital Aarau, Aarau, Switzerland (1410.000.062).

Refs: (1) Conway & Cotten, Mol Pharm 2012, 81(3):393-400.

Table 1.

	Activation (% ± 95% conf)	EC50 (mM ± 95% conf)	n-

			value
Carbon tetrabromide (CBr4)	191 (146 to 235)	0.017 (0.008 to 0.04)	4
Carbon tetrachloride (CCl4)	79 (63 to 96)	0.3 (0.2 to 0.5)	3
2,2,2-tribromoethanol	166 (135 to 196)	0.3 (0.2 to 0.4)	6
2,2,2-trichloroethanol	114 (89 to 140)	1 (0.6 to 2)	8
M159W: 2,2,2-trichloroethanol	~4 (unable to fit)	N.D.	3
Chloral hydrate	67 (62 to 72)	7 (6 to 8)	5
2,2,2-trifluoroethanol	-13 (-15 to -11)	0.7 (0.3 to 1.2)	3
2,2-dichloroethanol	24 (12 to 36)	9 (5 to 16)	4
2-chloroethanol	-15 (-18 to -11)	1 (0.4 to 3)	3
Ethanol	-25 (-27 to -23)	1.7 (1.4 to 2)	2
Isoflurane	65 (60 to 70)	0.5 (0.4 to 0.6)	4

Methadone in Ambulatory Surgery: Clinical Effectiveness

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Background: More than 50 million Americans undergo outpatient surgery annually. Surveys state that many patients (>80%) report inadequate postop pain relief. Opioids are the primary systemic pharmacotherapy for surgical pain. Clinical research shows that a single intraoperative dose of a long-duration opioid (i.e. methadone) produces better analgesia than repeated doses of short-duration opioids, in inpatient surgery. Nevertheless, in ambulatory surgery, methadone has never been evaluated. Our study tested the innovative hypothesis that in ambulatory surgery, intraoperative use of methadone, compared with conventional short-duration opioids, reduces postoperative pain and opioid consumption, with similar or diminished side effects.

Methods: Patients undergoing short-stay (<24 hr) ambulatory surgical procedures (i.e. laparoscopy) (n=59) , were randomized 2:1 to receive either single-dose methadone (0.1 mg/kg IV N=18 or 0.2 mg/kg IV, N=22 based on ideal body weight, in a dose-escalation cohort design) at anesthesia induction or short-duration opioid (fentanyl, hydromorphone, N=19) throughout the operation per usual practice. Intraoperative and postoperative opioid consumption until discharge was recorded (and converted to morphine equivalents). Patients were assessed for pain intensity at rest, with coughing and with activity at 15, 30, 45 min, 1, 2, 3, 4 h after admission in the PACU, at bedtime and at discharge. Pain relief and level of sedation were assessed at the same times. Opioid side effects assessed included ventilatory depression (respiratory rate, oxygen saturation) and Opioid-Related Symptom Distress Scale (ORSDS). After discharge, patients recorded daily their pain self-assessments, home opioid use, and side effects in a written diary, until 30day postop clinic visit.

Results: Average doses of intraoperative methadone were 6±1mg (0.1 mg/kg cohort) and 11±1mg (0.2 mg/kg cohort). Average intraoperative total nonmethadone morphine equivalents given in short-duration opioid, 0.1mg/kg methadone and 0.2mg/kg methadone group were 30.4±3, 2.0±0.4 and 1.4±0.3 mg respectively. Patients receiving a single 0.2 mg/kg methadone dose required significantly less opioids intraoperatively and postoperatively during their hospital stay, compared to short-duration opioid group (23±3 vs 48±4 mg morphine equivalents; $p<0.05$). Patients receiving intraoperative methadone used less take-home opioid (total 30d opioid averaged 16, 12 and 4 pills in short-duration opioid, 0.1 mg/kg methadone, and 0.2 mg/kg methadone groups), and stopped taking opioids earlier. Methadone did not cause any greater postop sedation or other adverse effects.

Conclusion: A single intraoperative methadone dose (0.2mg/kg ideal body weight) decreases intraoperative and postoperative opioid requirements, decreases post-discharge home opioid use for up to 30days postoperatively, with similar side effects.

Saline Flush Following Rocuronium Bolus Changes Rocuronium Pharmacokinetics

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Background: We previously reported that administering a 20-mL saline flush immediately after infusion of 0.6 mg/kg rocuronium bolus shortened the onset time and prolonged the recovery phase of neuromuscular blockade.[1] It is unlikely that 20-mL saline flush changes rocuronium potency. Therefore, we hypothesized that an infusion of saline flush immediately after rocuronium bolus influences rocuronium pharmacokinetics.

Methods: Patients with an ASA physical status I or II, aged 20 to 80 years, and scheduled for elective surgery were recruited. Patients were randomly allocated to the control or saline flush group. Anesthesia was induced and maintained with propofol and remifentanil, and patients received 0.4, 0.6, or 0.8 mg/kg of rocuronium in 10-mL normal saline through a three-way stopcock which was directly connected to the intravenous catheter. In the saline flush group, 20-mL normal saline was infused immediately after the rocuronium administration. Blood samples were collected through a radial artery catheter before, 15, 30, 45, 60, 75, 90, 105, 120 s and 3, 3.5, 4, 5, 7, 10, 12, 15, 20, 30, 45, 60, 80, 100, 120, 150, 180, 240, 300 and 360 min after rocuronium administration. Plasma rocuronium concentrations were determined using high-performance liquid chromatography. Population pharmacokinetic modeling was performed using NONMEM 7.3. First, we determined a basic model structure among the following models: 2-, 3- or 4-compartment models, 2-, 3- or 4-compartment models with a standard lag time and/or a chain of presystemic compartment. Secondly, when the final basic model had a lag time and/or presystemic compartments, we assessed whether different lag times and/or different transit rate constants (K_{tr}, from a presystemic compartment to a sequential compartment) for each group (control or saline flush group) significantly improved the pharmacokinetic model. Thirdly, we examined possible covariates including total body weight, height, age, sex, heart rate just before rocuronium administration, creatinine clearance for each model parameter. A decrease in objective function value, which is −2 log-likelihood calculated by NONMEM, by 7.88 was considered as a significant improvement of the model. The data was expressed as mean±SD or median [range]. Mann-Whitney's U test was used for the comparison. $P < 0.05$ was considered as significant.

Results: We analyzed the data from seventy-two patients (60.6±10.5 kg, 163.4±9.1 cm, 46.4±19.2 years, male/female 38/34, heart rate 55.5±8.5 beats/min, and creatinine clearance 106.9±32.9 mL/min, mean±SD). The final model was described as a 4 compartment model with a lag time and two presystemic compartments. The lag time and Ktr were different between groups (Table). The total body weight and heart rate were included in the final model as covariates for V1 and lag time of the control group, respectively. The model parameters were shown in Table. The peak predicted concentrations in the control and saline flush group using the final *post-hoc* model were 20.8 [13.6-52.7] and 37.8 [8.1-65.6] (0.4 mg/kg, P =0.046), 23.5 [6.6-70.1] and 62.2 [17.3-146.2] (0.6 mg/kg, P =0.001), 40.0 [19.4–63.8] and 61.4 [37.7–142.8] (0.8 mg/kg, P =0.007).

Conclusion: A 20-mL saline flush immediately after rocuronium bolus changes rocuronium pharmacokinetics.
1) A&A 2016; 122: 706-11

Parameter	value
V_1	0.654 + 0.00463 (body weight – 60)
V_2	1.45
V_3	5.50
V_4	1.67
CL_1	0.300
CL_2	0.338
CL_3	0.133
CL_4	1.68
LAG (control)	0.335 – 0.00921 (heart rate – 50)
LAG (saline flush)	0.224
K_{tr} (control)	10.6
K_{tr} (saline flush)	42.9

Adaptive Neuro Fuzzy Inference System (ANFIS) for Modelling the Effect of Propofol and Remifentanil Combination Using qCON and qNOX Indices During Induction

Authors: Umberto Melia, Mercè Agustí, Joan Fontanet, Erik Weber Jensen, Pedro Gambús

Introduction: The objectives of this study were to describe the relationship between the effect site concentrations of propofol (CeProp) and remifentanil (CeRemi) versus the qCON and qNOX indices of hypnotic effect and pain/nociception by using an adaptive neuro fuzzy inference system (ANFIS) and to estimate their values that correspond to loss of consciousness and no response to nociceptive stimulation during anesthesia induction.

Methods: Data were recorded from 284 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]. The TCI system (Base Primea, FreseniusKabi AG, Bad Homburg, Germany) administered propofol and remifentanil according to the predictions of pharmacokinetic and pharmacodynamic models. The data from the TCI system (CeProp and CeRemi) were recorded with Rugloop (Demed, Belgium). Loss of eye-lash reflex (LER) was assessed during the transition from awake to anesthetized, and used as the indicator that consciousness was lost. Movement as a response to laryngeal mask (LMA) insertion in the period of one minute after applying the stimuli was interpreted as the response to the nociceptive stimuli. The patients were classified as movers or non-movers and the values for the qCON and qNOX over the 1 min period before and after LER and LMA insertion were considered for the analysis.

Firstly, an ordinal logistic regression was performed in order to obtain the qCON and qNOX values and the confidence interval (CI) associated with a 25% and 50% probability of being awake and response to LMA insertion. Then, the qCON and qNOX data were fitted with CeRemi and CeProp by using ANFIS, a fuzzy logic-based modeling approach. ANFIS has the advantage to be a data-driven approach that does not assume an underlying mathematical model governing the relationship between the anesthetic drugs and the response effect. The models were developed on half of the patients and validated on the other half, by calculating the mean absolute error (MAE) and the prediction probability (Pk).

Results: The results of the ordinal logistic regression established that the values of qCON of 85.8 (CI: 85.0; 86.5) and 77.6 (CI: 76.5; 78.5) are associated with a 50 % and 25 % of probability of being awake, while the values of qNOX of 68.1 (CI: 66.5; 69.6) and 51.1 (CI: 52.6; 49.4) are associated with a 50 % and 25 % probability of loss of response to LMA insertion. Figure 1 shows the results of the ordinal logistic regression and the ANFIS models of qCON and qNOX. The results of the validation of the qCON ANFIS model gave MAE=16.01 and Pk=0.791 (standard error: 0.001), while for the qNOX ANFIS were MAE=17.27 and Pk=0.815 (standard error: 0.002).

Discussion and Conclusion: In conclusion, by using an ANFIS modeling approach it was possible to study the relationship between propofol and remifentanil predicted concentrations and hypnotic and analgesic effects during induction, in patients under general anesthesia. A qCON value of 75 corresponds to probability of being awake lower than 25 % while a qNOX of about 50 provided a probability of response to LMA insertion lower than 25 %. The qCON ANFIS surface shows higher slope with respect to CeProp, while the qNOX ANFIS surface shows a decrease with respect to CeRemi at high CeProp values. This suggests that at certain CeProp concentrations, the administration of CeRemi induces a decrease of qNOX.

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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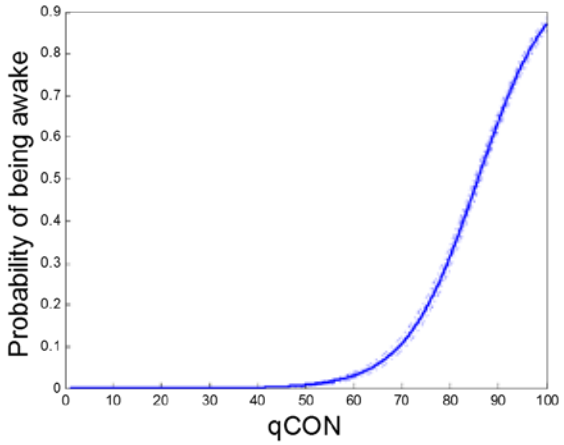
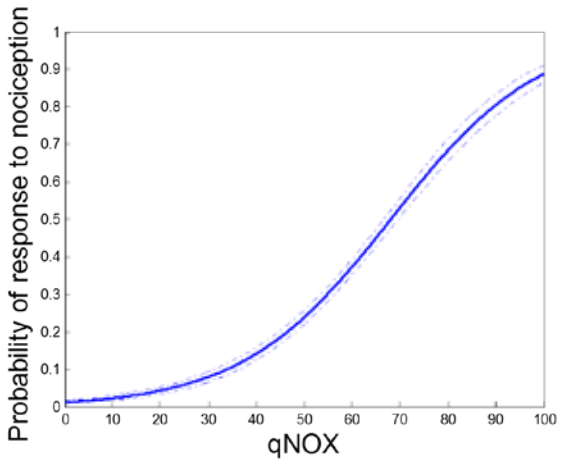
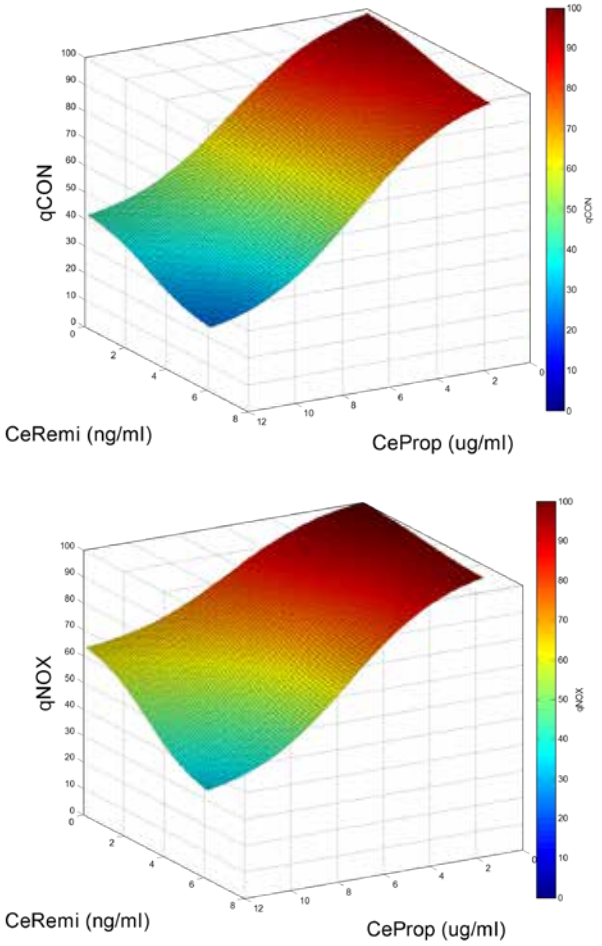




(a) (b)



(c) (d)

Figure 1 – Ordinal logistic regression of (a) qCON vs. loss of consciousness and (b) qNOX vs. response to LMA insertion with the respective confidence intervals (dashed curves); results of the ANFIS models of (c) qCON and (d) qNOX versus CeRemi and CeProp.

Predicted Concentration Against Measured Concentration of Rocuronium by Published Six Pharmacokinetics Models During Continuous Infusion is Lower than that After Single Bolus

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Background: Published population pharmacokinetic models of rocuronium, which are applicable to predict plasma concentration, were developed using samples obtained after bolus without additional doses. The aim of this study was to compare the predictive performance of six published pharmacokinetic models of rocuronium after bolus without additional doses and that during continuous infusion.

Methods: After our institutional review board approval, the registration to a public clinical trial registry, and written informed consent were obtained, we recruited patients undergoing elective surgery. Patients with severe hepatic, renal, or cardiovascular disease, neuromuscular disease, a history of rocuronium allergy, body mass index greater than 30 kg/m^2, and those receiving medications known to influence neuromuscular function were excluded. Anesthesia was induced and maintained with propofol and remifentanil. Patients received 0.6 mg/kg rocuronium at 0.25, 0.5, 0.75, or 1 mg/kg/min, then trachea was intubated. When the train-of four count recovered to 1 or 2, or if necessary, a continuous infusion of rocuronium was started at 4-13 mg/kg/h over 30-240 min. The infusion rates for bolus and continuous infusion was randomly allocated to patients. Blood samples (1 mL each) were drawn via a radial artery as follows: (1) until the start of a continuous infusion of rocuronium; before, at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 150, and just before the start of continuous infusion; (2) during the continuous infusion of rocuronium; 0.5, 1, 2, 4, 8, 15, 30, 45, 60, then every 30 min, and just before the end of the continuous infusion. Plasma rocuronium concentrations were determined using high-performance liquid chromatography with electrochemical detection. Prediction error, defined as ('measured concentration' – 'predicted concentration') / 'predicted concentration' x 100 (%), was calculated for each sample. Individual median prediction error (MDPE) was calculated for the samples collected after the end of bolus before the start of the continuous infusion (MDPE_bolus) and that for the samples collected during the continuous infusion (MDPE_infusion). For each assessed pharmacokinetic models, developed by Wierda, Szenohradszky, Magorian, Cooper,

Alvarez-Gomez, and Kleijn, MDPE_bolus and MDPE_infusion was compared using Welch's t test. A P value <0.05 was regarded as significant. The data was expressed as mean±SD.

Results: Thirty-seven patients (15 males and 20 females; total body weight, 57±9 kg; height, 160±9 cm; age, 58±15 years) were included for the analysis. The MDPE_bolus *vs* MDPE_infusion were −5.5±22.6% *vs* −32.4±24.1% (P <0.001) in the Wierda model, −20.2±17.3% *vs* −50.4±18.8% (P <0.001) in the Szenohradszky model, 7.6±28.6% *vs* −33.3±26.0% (P <0.001) in the Magorian model, 4.1±25.8% *vs* −30.2±24.6% (P <0.001) in the Cooper model, 15.4±27.1% *vs* −17.1±30.0% (P <0.001) in the Alvarez-Gomez model, and −25.0±17.1% *vs* −44.8±20.2% (P <0.001) in the Kleijn model, respectively.

Conclusions: The MDPE_bolus was significantly higher than the MDPE_infusion in all assessed models, which means a measured concentration after bolus without infusion was higher than that during infusion for a predicted concentration on those models. Population pharmacokinetic model of rocuronium, which is developed based on both bolus and infusion dose regimens, is desired.

Menstrual Cycle Phase Influences Propofol Pharmacokinetics

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Background: Previously, we found that menstrual cycle phase determined by questionnaire survey have no significant influence on propofol pharmacokinetics. To determine exact menstrual cycle phase, we used plasma levels of female hormones including luteinizing hormone, estradiol, and progesterone. in the present analysis. The aim of the study was to investigate whether peak plasma concentration of propofol by a bolus dose were different between the follicular and other phases in premenopausal female patients.

Method and Materials: Female patients who were ASA physical status I or II, aged 20-49 years, scheduled to undergo elective surgery under general anesthesia were enrolled. Patients with severe hepatic, renal, or cardiovascular disease, neuromuscular disease, a history of propofol allergy, and body mass index greater than 30 kg/m^2 were excluded. After oxygenation, the patients received propofol 2 mg/kg over 3 min. To measure plasma concentration of propofol, arterial blood samples (1 mL each) were collected before, and 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 min after the start of the infusion of propofol. Additionally, we took 4mL blood sample to measure plasma level of female sex hormones including luteinizing hormone, estradiol, and progesterone.
Plasma propofol concentrations were determined using high-performance liquid chromatography with fluorescence detection. The highest concentration among the measured concentrations in each patient was defined as the peak concentration. A patient with luteinizing hormone level between 5.7 and 64.3 mIU/ml, estradiol level between 6 and 37 pg/ml, and progesterone level ≤0.44 ng/ml was excluded from the analysis as being menopausal. A premenopausal patient with progesterone level ≤0.92 ng/ml and estradiol level ≥22 pg/ml was regarded as the follicular phase.
The data was expressed as mean ± SD. Unpaired Welch's t test was used to compare the peak plasma concentration between the patients in the follicular and other menstrual cycle phases. A P value <0.05 as regarded as significant.

Result: Fourteen patients in the follicular phase and forty-night patients in the others

phases were included for the analysis. Four patients were excluded due to menopause. Age, weight, height were as follows; 31 ± 8 years, 58 ± 9 kg, 162 ± 6 cm for the patients in the follicular phase, 36 ± 8 years, 57 ± 8 kg, 170 ± 5 cm for the patients in the other menstrual cycle phases.
The peak plasma concentration of propofol in follicular phase, 10.1 ± 3.1μg/ml, was significantly higher than that in the other phases, 8.0 ± 2.1g/ml (P =0.025). The level of each sex hormones not correlated with maximum plasma concentrations of propofol.

Conclusion: The peak plasma concentration of propofol was influenced by the menstrual cycle phase. Further pharmacokinetic analysis is desired to examine whether a menstrual cycle phase is a covariate on the pharmacokinetic model.

Amphetamine (Adderall) and venlafaxine (Effexor) Drug Interaction with Dexmedetomidine

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Background: Dexmedetomidine (DEX), a selective α2-adrenoreceptor agonist is commonly used to provide sedation in the ICU. Drug-induced sleep endoscopy (DISE) is an extremely useful tool for assessing the dynamic airway in an asleep patient with obstructive sleep apnea (OSA). DEX provides an optimal agent for sleep endoscopies in this patient population given its reliability as a sedative agent most closely mimicking REM sleep with negligible respiratory depression. Most common adverse effects of dexmedetomidine infusions are bradycardia and hypotension.

Case presentation: We present an intriguing case of a 68-year-old male with a history of OSA status-post right-sided hypoglossal nerve stimulator, chronic neck pain, headaches, depression and adult-ADHD who underwent two DISEs requiring DEX at rates as high as 3 mcg/kg/hr along with 10mg incremental boluses of propofol to successfully induce sleep. Once the patient was finally asleep he was noted to be hypotensive and bradycardic unresponsive to ephedrine requiring a combination of fluids, glycopyrrolate and phenylephrine to support his blood pressure. His home medications included dextroamphetamine/amphetamine (Aderall) 20mg thrice daily, venlafaxine (effexor) 150mg twice daily, and buprenorphine (subutex) 4-8mg SL thrice weekly as needed.

Discussion: The patient had complex neuropharmacology at play. Amphetamines increase the activity of dopamine and norepinephrine in the brain but may also affect serotonin, histamine and other neuropeptides. Venlafaxine is a commonly used antidepressant that is a selective serotonin-norepinephrine reuptake inhibitor, which at high doses may also inhibit dopamine uptake and can potentially increase the activity of Adderall.

On review of the literature, there are no reports of drug interactions between psychopharmacologic drugs (including SNRIs and therapeutic amphetamines) with dexmedetomidine. We theorize that the patient's chronically altered neurobiology may help explain the patient's apparent resistance to dexmedetomidine. In terms of drug safety, atipamezole, a reversal agent for both the sedative and sympatholytic properties of dexmedetomidine, is currently only approved for use in veterinary medicine.

Drug-drug interaction between amphetamines and DEX have not been previously reported. Plausible methods of amphetamine interaction with DEX could involve interaction at the alpha-2 receptor. Amphetamines may modulate the re-uptake of norepinephrine and thus decrease the effect of DEX as reported in a rat model (1). The interaction between amphetamines and clonidine has been reported to be caused by inhibition of binding of clonidine to the alpha-2 receptor (2). It may be likely that inhibition of DEX by amphetamines occurs at the membrane level.

Furthermore, a less known fact about dexmedetomidine is its interaction with the cytochrome P450 enzymes, including inhibition of CYP2D6 which is involved in the metabolism of amphetamines. While this may not play a role in brief procedural sedation as in our patient, it merits further investigation in the intensive care unit population where prolonged infusions of dexmedetomidine are common.

Conclusion: Dexmedetomidine is increasingly used in the operating room, out-of-OR environments, and intensive care units but its interactions with other neurotransmitter altering therapeutics remain unknown.

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