Table of Contents
August, 2012

Cardiovascular Anesthesiology

氨甲環酸減少不停跳冠狀動脈手術後失血:一個前瞻性、隨機、雙盲、安慰劑對照研究
(唐瑩譯 馬皓琳 李士通校)
Tranexamic Acid Reduces Blood Loss After Off-Pump Coronary Surgery: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study
  o Guyan Wang,
  o Gaoqiang Xie,
  o Tingting Jiang,
  o Yuefu Wang,
  o Weipeng Wang,
  o Hongwen Ji,
  o Mingzheng Liu,
  o Lei Chen,
  o and Lihuan Li

絲氨酸蛋白酶抑制劑 MDCO-2010 對健康人以及心臟手術患者的啟動凝血時間的影響
(陸秉瑋譯 陳傑校)
The Effects of MDCO-2010, a Serine Protease Inhibitor, on Activated Clotting Time in Blood Obtained from Volunteers and Cardiac Surgical Patients
  o Heezoo Kim,
  o Fania Szlam,
  o Kenichi A. Tanaka,
  o Andreas van de Locht,
  o Satoru Ogawa,
  o and Jerrold H. Levy
Anesth Analg August 2012 115:244-252; published ahead of print May 14, 2012
**Ambulatory Anesthesiology**

全身給予利多卡因改善門診腹腔鏡手術術後蘇醒品質
(鄧利兵譯 薛張綱校)

Systemic Lidocaine to Improve Postoperative Quality of Recovery After Ambulatory Laparoscopic Surgery

- Gildasio S. De Oliveira, Jr.,
- Paul Fitzgerald,
- Lauren F. Streicher,
- R-Jay Marcus,
- and Robert J. McCarthy


**Anesthetic Pharmacology**

教會一個舊的 GABA 受體新的技能
(張怡譯 馬皓琳 李士通校)

Special Article: Teaching an Old GABA Receptor New Tricks

- James R. Trudell,
- Edward Bertaccini,
- and M. Bruce MacIver


以安慰劑和咪達唑侖為對照組評價 Remimazolam（CNS 7056）藥物安全性、藥代動力學和藥效學的 I 期單遞增劑量研究: 第一部分: 安全性、有效性和基礎藥代動力學
(俞芳譯 陳傑校)

A Placebo- and Midazolam-Controlled Phase I Single Ascending-Dose Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Remimazolam (CNS 7056): Part I. Safety, Efficacy, and Basic Pharmacokinetics

- Laurie J. Antonik,
- D. Ronald Goldwater,
- Gavin J. Kilpatrick,
- Gary S. Tilbrook,
- and Keith M. Borkett


- Hugh R. Wiltshire,
- Gavin J. Kilpatrick,
- Gary S. Tilbrook,
- and Keith M. Borkett

*Anesth Analg August 2012 115:284-296; published ahead of print January 16, 2012*

In Vivo and In Vitro Pharmacological Studies of Methoxycarbonyl-Carboetomidate

- Ervin Pejo,
- Joseph F. Cotten,
- Elizabeth W. Kelly,
- Ri Le Ge,
- Gregory D. Cuny,
- Joydev K. Laha,
- Jifeng Liu,
- Xiang Jie Lin,
- and Douglas E. Raines

*Anesth Analg August 2012 115:297-304; published ahead of print September 29, 2011*

Brief Report: Pharmacological Studies of Methoxycarbonyl Etomidate's Carboxylic Acid Metabolite

- Ri Le Ge,
- Ervin Pejo,
- Marian Haburcak,
- S. Shaukat Husain,
- Stuart A. Forman,
- and Douglas E. Raines

*Anesth Analg August 2012 115:305-308; published ahead of print November 3, 2011*
Technology, Computing, and Simulation

技術交流：麻醉呼吸內迴圈：學步兒童與新生兒到達設定七氟烷濃度的時間：模擬肺測試
(郭晨躍譯 薛張綱校)
Technical Communication: Inside Anesthesia Breathing Circuits: Time to Reach a Set Sevoflurane Concentration in Toddlers and Newborns: Simulation Using a Test Lung
  o Delphine Kern,
  o Claire Larcher,
  o Bertrand Basset,
  o Xavier Alacoque,
  o Rose Fesseau,
  o Kamran Samii,
  o Vincent Minville,
  o and Olivier Fourcade


麻醉中鎮靜成分在監視器上的延遲：狀態熵和意識指數分析
(許辛譯 馬皓琳 李世通校)
Technical Communication: Time Delay of Monitors of the Hypnotic Component of Anesthesia: Analysis of State Entropy and Index of Consciousness
  o Matthias Kreuizer,
  o Robert Zanner,
  o Stefanie Pilge,
  o Sabine Paprotny,
  o Eberhard F. Kochs,
  o and Gerhard Schneider


Patient Safety

美國 1998 – 2008 間住院關節置換術術後主要併發症發生率和死亡率的趨勢
(龔寅譯 陳傑校)
Critical Care, Trauma, and Resuscitation

比較在正常情況下的綿羊和膿毒血症高代謝狀態下的綿羊中，苯腎對全身和局部血液動力學的影響
(韓旭譯 薛張綱校)
The Systemic and Regional Hemodynamic Effects of Phenylephrine in Sheep Under Normal Conditions and During Early Hyperdynamic Sepsis
  o Hiroshi Morimatsu,
  o Ken Ishikawa,
  o Clive N. May,
  o Michael Bailey,
  o and Rinaldo Bellomo

Obstetric Anesthesiology

既往腰椎間盤切除術不會改變椎管內分娩鎮痛的效果
(崔曉娜 譯 馬皓琳 李士通 校)
Prior Lumbar Discectomy Surgery Does Not Alter the Efficacy of Neuraxial Labor Analgesia
  o Jeanette R. Bauchat,
  o Robert J. McCarthy,
  o Tyler R. Koski,
  o Christopher R. Cambic,
  o Amy I. Lee,
Pediatric Anesthesiology

行雙側鼓膜切開及放置通氣管手術患兒，術中芬太尼滴鼻、肌內或靜脈注射嗎啡對術後鎮痛療效及精神行為的影響
(陳毓雯譯 陳傑校)
Postoperative Analgesic and Behavioral Effects of Intranasal Fentanyl, Intravenous Morphine, and Intramuscular Morphine in Pediatric Patients Undergoing Bilateral Myringotomy and Placement of Ventilating Tubes
  o Helena K. Hippard,
  o Kalyani Govindan,
  o Ellen M. Friedman,
  o Marcelle Sulek,
  o Carla Giannoni,
  o Deidre Larrier,
  o Charles G. Minard,
  o and Mehernoor F. Watcha

評論文章：評論在小兒心臟外科手術中使用未被臨床實驗認可的重組活化Ⅶ因數。
(賀盼譯 薛張綱校)
Review Article: Review of the Off-Label Use of Recombinant Activated Factor VII in Pediatric Cardiac Surgery Patients
  o Nina A. Guzzetta,
  o Isobel A. Russell,
  o and Glyn D. Williams

Neuroscience in Anesthesiology and Perioperative Medicine

晝夜節律鐘基因 HPER3 與非心臟手術後的認知功能障礙沒有關聯
(余亦南譯 馬皓琳 李士通校)
There Is No Association Between the Circadian Clock Gene HPER3 and Cognitive Dysfunction After Noncardiac Surgery

- Melissa Voigt Hansen,
- Lars Simon Rasmussen,
- Cathrine Jespersgaard,
- Jacob Rosenberg,
- and Ismail Gogenur


The Frequency and Magnitude of Cerebrospinal Fluid Pulsations Influence Intrathecal Drug Distribution: Key Factors for Interpatient Variability

- Ying Hsu,
- H. D. Madhawa Hettiarachchi,
- David C. Zhu,
- and Andreas A. Linninger


Analgesia

Pain Medicine

The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis

- Hance Clarke,
- Robert P. Bonin,
- Beverley A. Orser,
- Marina Englesakis,
- Duminda N. Wijeysundera,
- and Joel Katz

Pain and Analgesic Mechanisms

Antihypersensitivity Effects of Tramadol Hydrochloride in a Rat Model of Postoperative Pain

- Masafumi Kimura,
- Hideaki Obata,
- and Shigeru Saito

*Anesth Analg August 2012 115:443-449; published ahead of print May 10, 2012*

Intrathecal Clonidine in the Neonatal Rat: Dose-Dependent Analgesia and Evaluation of Spinal Apoptosis and Toxicity

- Suellen M. Walker,
- Marjorie Grafe,
- and Tony L. Yaksh

*Anesth Analg August 2012 115:450-460; published ahead of print March 30, 2012*

Regional Anesthesia

The Presence of Transverse Cervical and Dorsal Scapular Arteries at Three Ultrasound Probe Positions Commonly Used in Supraclavicular Brachial Plexus Blockade

- Hiroaki Murata,
- Akiko Sakai,
- Admir Hadzic,
- and Koji Sumikawa

*Anesth Analg August 2012 115:470-473; published ahead of print April 20, 2012*

Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery.
BACKGROUND: Perioperative systemic lidocaine has been shown to have beneficial postoperative analgesic effects. The only previous study examining the use of lidocaine in the outpatient setting did not detect an opioid-sparing effect after hospital discharge. More importantly, it is unknown whether systemic lidocaine provides a better postoperative quality of recovery to patients undergoing ambulatory surgery. Our objective in the current study was to examine the effect of systemic lidocaine on postoperative quality of recovery in patients undergoing outpatient laparoscopic surgery.

METHODS: The study was a prospective, randomized, double-blind, placebo-controlled clinical trial. Healthy female subjects were randomized to receive lidocaine (1.5 mg/kg bolus followed by a 2 mg/kg/h infusion until the end of the surgical procedure) or the same volume of saline. The primary outcome was the Quality of Recovery-40 questionnaire at 24 hours after surgery. A 10-point difference represents a clinically relevant improvement in quality of recovery based on previously reported values on the mean and range of the Quality of Recovery-40 score in patients after anesthesia and surgery. Other data collected included opioid consumption, pain scores, and time to meet hospital discharge. Data were compared using group t tests and the Wilcoxon exact test. The association between opioid consumption and quality of recovery was evaluated using Spearman ρ. P < 0.01 was used to reject the null hypothesis for the primary outcome.

RESULTS: Seventy subjects were recruited and 63 completed the study. There were no baseline differences regarding subject and surgical characteristics between the study groups. Patients in the lidocaine group had better global quality of recovery scores compared with the saline group, median difference of 16 (99% confidence interval [CI], 2–28), P = 0.002. Patients in the lidocaine group met hospital discharge criteria faster than the saline group, mean difference of -26 minutes (95% CI, −6 to −46 minutes) (P = 0.03). After hospital discharge, subjects in the lidocaine group required less oral opioids, median difference of -10 (95% CI, 0 to −30) (oral...
milligrams morphine equivalents), median difference of −10 (95% CI, 0 to −30) than the saline group (P = 0.01). There was an inverse association between postoperative opioid consumption and quality of recovery (p = 0.64, P < 0.001).

**CONCLUSIONS:** Systemic lidocaine improves postoperative quality of recovery in patients undergoing outpatient laparoscopy. Patients who received lidocaine had less opioid consumption, which translated to a better quality of recovery. Lidocaine is a safe, inexpensive, effective strategy to improve quality of recovery after ambulatory surgery.

---

**BACKGROUND:** A new benzodiazepine, remimazolam, which is rapidly metabolized by tissue esterases to an inactive metabolite, has been developed to permit a fast onset, a short, predictable duration of sedative action, and a more rapid recovery profile than currently available drugs. We report on modeling of the data and simulations of dosage regimens for future study.

---


Hugh R. Wiltshire, PhD*, Gavin J. Kilpatrick, PhD†, Gary S. Tilbrook, PhD† and Keith M. Borkett, BSc†

*Independent Consultant, Welwyn, Hertfordshire; and †PAION UK Ltd., Compass House, Vision Park, Histon, Cambridge, United Kingdom.

Anesth Analg August 2012 115:284-296
METHODS: A phase I, single-center, double-blind, placebo and active controlled, randomized, single-dose escalation study was conducted. Fifty-four healthy subjects in 9 groups received a single 1-minute IV infusion of remimazolam (0.01–0.3 mg/kg). There were 18 control subjects taking midazolam and 9 placebos. Population pharmacokinetic and pharmacodynamic modeling of the data was undertaken and the parameters obtained were used for Monte-Carlo simulations of alternative dosing regimens.

RESULTS: A 4-compartment mammillary pharmacokinetic model of midazolam and a physiologically based recirculation model of remimazolam were fitted to the observed plasma levels. The recirculation model of remimazolam explained the observed high venous, compared with arterial, concentrations at later time points. The 2 models were used to simulate the arterial concentrations required for the pharmacodynamic models of sedation (Bispectral Index and Modified Observer's Assessment of Alertness/Sedation [MOAA/S]) and gave population mean pharmacodynamic parameters as follows: Bispectral Index–IC50: 0.26, 0.07 μg/mL; γ: 1.6, 8.6; ke0: 0.14, 0.053 min⁻¹; IMAX: 39, 19, and MOAA/S–IC50: 0.4, 0.08 μg/mL; γ: 1.4, 3.4; ke0: 0.25, 0.050 min⁻¹ for remimazolam and midazolam, respectively. Simulations to obtain >70% of the population with MOAA/S scores of 2 to 4 were developed. This criterion was achieved (95% confidence intervals: 67%–74%) with a 6-mg initial loading dose of remimazolam followed by 3-mg maintenance doses at >2-minute intervals. Recovery to a MOAA/S score of 5 is predicted to be within 16 minutes for 89% (95% confidence intervals: 87%–91%) of the treated population after this loading/maintenance dose regimen.

CONCLUSIONS: Population pharmacokinetic and pharmacodynamic models developed for remimazolam and midazolam fitted the observed data well. Simulations based on these models show that remimazolam delivers extremely rapid sedation, with maximal effect being reached within 3 minutes of the start of treatment. This property will enable maintenance doses to be given more accurately than with slower-acting drugs. No covariate effects considered to be clinically relevant were observed, suggesting that dosing by body weight may offer no advantage over fixed doses in terms of consistency of exposure to remimazolam within the weight range studied (65–90 kg).

技術交流：麻醉呼吸內迴圈:學步兒童與新生兒到達設定七氟烷濃度的時間:模擬肺測試

Technical Communications: Inside Anesthesia Breathing Circuits: Time to Reach a Set Sevoflurane Concentration in Toddlers and Newborns: Simulation Using a Test Lung

Delphine Kern, MD, PhD, Claire Larcher, MD, Bertrand Basset, MD, Xavier Alacoque, MD, Rose Fesseau, MD, Kamran Samii, MD, Vincent Minville, MD, PhD and Olivier Fourcade, MD, PhD

From the Department of Anesthesiology and Intensive Care, University Hospital of Toulouse, Toulouse, France.

Anesth Analg August 2012 115:310-314

我們應用 Primus（Drägerwerk, AG, Lübeck, Germany）麻醉機以及 Avance（GE Datex-Ohmeda, Munich, Germany）麻醉機對於學步兒童和新生兒通氣設定測量了達到預計吸入麻醉濃度所花費的時間。七氟烷濃度從0%至6%的洗入時間和通過1-2倍於分鐘通氣的新鮮氣體流量7氟烷濃度從6%至0%的洗脫時間之和測得七氟烷達到95%目標吸入濃度的時間。在1.5升新鮮氣體流量，潮氣量50ml，呼吸頻率30次/分標準下，Avance麻醉機比 Primus麻醉機快（Avance 65秒[95%可信區間：55-78]，Primus 310秒[95%可信區間：261-359]）。在更高的新鮮氣體流量和更大的分鐘通氣率條件下兩者時間縮短的程度相同。新鮮氣體流量加倍的效果變數大且低於預期。對於 Primus 麻醉機，新生兒比學步兒童達到設定濃度的時間要慢，Avance麻醉機則兩組時間相同。我們的資料證實：呼吸機達到目標吸入麻醉藥物濃度的時間取決於呼吸迴圈容量、新鮮氣體流量以及分鐘通氣量。

（郭憲躍譯 薛張綱校）
We measured the time it takes to reach the desired inspired anesthetic concentration using the Primus (Drägerwerk, AG, Lübeck, Germany) and the Avance (GE Datex-Ohmeda, Munich, Germany) anesthesia machines with toddler and newborn ventilation settings. The time to reach 95% of inspired target sevoflurane concentration was measured during wash-in from 0 to 6 vol% sevoflurane and during wash-out from 6 to 0 vol% with fresh gas flows equal to 1 and 2 times the minute ventilation. The Avance was faster than the Primus (65 seconds [95% confidence interval (CI): 55 to 78] vs 310 seconds [95% CI: 261 to 359]) at 1.5 L/min fresh gas flow, tidal volume of 50 mL, and 30 breaths/min. Times were shorter by the same magnitude at higher fresh gas flows and higher minute ventilation rates. The effect of doubling fresh gas flow was variable and less than expected. The Primus is slower during newborn than toddler ventilation, whereas the Avance's response time was the same for newborn and toddler ventilation. Our data confirm that the time to reach the target-inspired anesthetic concentration depends on breathing circuit volume, fresh gas flow, and minute ventilation.

The systemic and regional hemodynamic effects of phenylephrine in sheep under normal conditions and during early hyperdynamic sepsis.

Hiroshi Morimatsu, MD*, Ken Ishikawa, MD†, Clive N. May, PhD†, Michael Bailey, PhD‡ and Rinaldo Bellomo, MD*

From the *Department of Intensive Care and Department of Medicine, Austin Health, Melbourne, Victoria, Australia; †Howard Florey Institute, University of Melbourne, Parkville, Victoria, Australia; and ‡Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.

Anesth Analg August 2012 115:330-342

BACKGROUND: Phenylephrine treatment of hypotension in sepsis raises concern because it may decrease vital organ bloodflow. Accordingly, we investigated the effects of phenylephrine on systemic and regional bloodflow in normal and septic sheep.

METHODS: Responses to phenylephrine or vehicle infusion for 6 hours were determined in conscious normal sheep and sheep with early sepsis induced by administration of live Escherichia coli. Cardiac output and coronary, mesenteric, and renal bloodflow were measured with implanted flow probes.

RESULTS: In normal sheep, phenylephrine decreased cardiac output and heart rate (HR) but increased stroke volume and mean arterial blood pressure (MAP) (84 ± 6 to 108 ± 6 mm Hg, 293 ± 22 vs 347 ± 100 mL/min; average difference 55 [18.8%]; 95% CI 47-65).
magnitude of mean difference [diff.] 19 [22.6%; 95% confidence intervals [CI], 17-21]. There were significant decreases in regional conductance values with a transient decrease in mesenteric bloodflow, no change in coronary bloodflow, and increased renal bloodflow (222 ± 53 to 271 ± 55 mL/min; diff. 31 [13.9%; 95% CI, 26-36]). During hyperdynamic sepsis, vasodilatation and increased bloodflow occurred in all vascular beds. Phenylephrine restored MAP and stroke volume to baseline values, but HR, cardiac output, and total peripheral conductance progressively decreased. Phenylephrine decreased mesenteric and coronary conductance, with no sustained reduction in flows, but renal conductance was significantly decreased and overall renal bloodflow increased (293 ± 22 vs 347 ± 100 mL/min; diff. 55 [18.8%; 95% CI, 47-65]).

CONCLUSIONS: In sheep with early hyperdynamic sepsis, phenylephrine, at a dose that restored MAP, increased stroke volume and renal bloodflow while decreasing HR and coronary bloodflow but not mesenteric bloodflow. Similar responses were seen in normal animals.

Review Article: Review of the Off-Label Use of Recombinant Activated Factor VII in Pediatric Cardiac Surgery Patients.

Nina A. Guzzetta, MD, FAAP*, Isobel A. Russell, MD, PhD, FACC† and Glyn D. Williams, MBChB, FFA‡

From the *Department of Anesthesiology, Emory University School of Medicine, Children’s Healthcare of Atlanta, Atlanta, GA; †Department of Anesthesiology, University of California School of Medicine, San Francisco, Moffitt Long Hospitals, San Francisco, CA; ‡Department of Anesthesiology, Stanford University School of Medicine, Lucile Packard Children’s Hospital, Palo Alto, CA.

Anesth Analg August 2012 115:364-378

Abstract: In recent years the off-label use of recombinant activated factor VII (rFVIIa) has markedly increased, particularly in pediatric cardiac surgery patients, and practitioners differ widely in their usage of the drug. In 2009, the Congenital Cardiac Anesthesia Society (CCAS) assembled a task force to review the literature on rFVIIa administration to pediatric cardiac surgery patients. The goal of the CCAS Task Force was to assess current practices and make recommendations about rFVIIa therapy to enhance quality of care, improve patient outcomes,
reduce costs, and develop future research. In this review we summarized the important topics on current administration of rFVIIa to pediatric cardiac surgery patients including indications for use, efficacy, safety, dosing, and monitoring. All pediatric and pertinent adult literature regarding the administration of rFVIIa to cardiac surgical patients and published since 2000 were selected and studied. Of the 40 pediatric publications reviewed for this report, only 1 was a prospective randomized controlled trial thus making determinations of efficacy difficult. There is no substantive evidence to support the efficacy of rFVIIa as prophylactic or routine therapy during pediatric cardiac surgery. It may prove reasonable as rescue therapy because current observational evidence suggests that potential benefits of rFVIIa for this indication might outweigh the risks. Rescue therapy is appropriate for bleeding that is massive, potentially life-threatening, and refractory to conventional therapy. Nevertheless, extreme caution is advised when considering the administration of rFVIIa to patients who are at risk for thromboembolic complications because rates for clinical and subclinical thrombosis secondary to rFVIIa therapy are unknown at this time. This review is designed to aid practitioners in deciding when and how to administer rFVIIa to pediatric cardiac surgery patients; it is not intended to determine standard-of-care or practice guidelines. There are insufficient data to make evidence-based recommendations. Randomized controlled trials are needed to assess the efficacy of rFVIIa as prophylactic, routine, or rescue therapy and to determine the drug's safety profile particularly with regard to thrombosis. The CCAS rFVIIa Task Force will continue to monitor the literature, gather data, and make updates as more information becomes available.

使用加巴噴丁和普瑞巴林預防術後慢性疼痛：系統回顧與薈萃分析

The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis.

Hance Clarke, MSc, MD, FRCPC*,†‡, Robert P. Bonin, PhD§, Beverley A. Orser, MD, PhD, FRCPCT‡, Marina Englesakis, BA MLIS∥, Duminda N. Wijeysundera, MD, PhD, FRCP*‡¶# and Joel Katz, PhD**

From the *Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Ontario, Canada; †Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; ‡Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada; §Centre de Recherche Université Laval Robert-Giffard, Université Laval, Quebec, Canada; ||Library and Information Services, University Health Network, Toronto, Ontario, Canada; ¶Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada; #Institute of Health Policy Management and Evaluation, University of Toronto; **Department of Psychology and School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada.

Anesth Analg August 2012 115:428-442

背景：許多臨床試驗已經證實了加巴噴丁和普瑞巴林作爲輔助手段在減少術後急性疼痛方面的效果。然而，很少有實驗來研究二者用於減少術後慢性疼痛。我們系統的回顧了一些已發表的關於使用加巴噴丁和普瑞巴林預防術後慢性疼痛（大於術後2個月）文獻，並且依數量大的資料做了薈萃分析。資料檢索相關的英文實驗（Medline, Embase, Cochrane, IPA 和 CINAL）在 2011 年 6 月實行。

方法：進入當前系統回顧所要滿足的標準是：隨機，雙盲評估疼痛和鎮痛藥的使用；利用有效手段鎮痛的報告、鎮痛藥消耗的報告；不應該出現設計的不足，方法的問題或者致使結果模棱兩可的混淆因素。不符合預防性鎮痛定義的和評估不在術後 2 個月的慢性疼痛的實驗被排除在外。

結果：資料庫檢索產生 474 條引文。11 個研究符合納入標準。在這 11 個實驗中，8 個是研究加巴噴丁，其中 4 項發現術期使用加巴噴丁减少了術後 2 月慢性疼痛的發生。3 個關於普瑞巴林的研究闡述了其顯著降低術後慢性疼痛，3 個實驗中的 2 個還發現了其對病
BACKGROUND: Many clinical trials have demonstrated the effectiveness of gabapentin and pregabalin administration in the perioperative period as an adjunct to reduce acute postoperative pain. However, very few clinical trials have examined the use of gabapentin and pregabalin for the prevention of chronic postsurgical pain (CPSP). We (1) systematically reviewed the published literature pertaining to the prevention of CPSP (≥2 months after surgery) after perioperative administration of gabapentin and pregabalin and (2) performed a meta-analysis using studies that report sufficient data. A search of electronic databases (Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, IPA, and CINAHL) for relevant English-language trials to June 2011 was conducted.

METHODS: The following inclusion criteria for identified clinical trials were used for entry into the present systematic review: randomization; double-blind assessments of pain and analgesic use; report of pain using a reliable and valid measure; report of analgesic consumption; and an absence of design flaws, methodological problems or confounders that render interpretation of the results ambiguous. Trials that did not fit the definition of preventive analgesia and did not assess chronic pain at 2 or more months after surgery were excluded.

RESULTS: The database search yielded 474 citations. Eleven studies met the inclusion criteria. Of the 11 trials, 8 studied gabapentin, 4 of which (i.e., 50%) found that perioperative administration of gabapentin decreased the incidence of chronic pain more than 2 months after surgery. The 3 trials that used pregabalin demonstrated a significant reduction in the incidence of CPSP, and 2 of the 3 trials also found an improvement in postsurgical patient function. Eight studies were included in a meta-analysis, 6 of the gabapentin trials demonstrated a moderate-to-large reduction in the development of CPSP (pooled odds ratio [OR] 0.52; 95% confidence interval [CI], 0.27 to 0.98; P = 0.04), and the 2 pregabalin trials found a very large reduction in the development of CPSP (pooled OR 0.09; 95% CI, 0.02 to 0.79; P = 0.007).

CONCLUSIONS: The present review supports the view that perioperative administration of gabapentin and pregabalin are effective in reducing the incidence of CPSP. Better-designed and appropriately powered clinical trials are needed to confirm these early findings.
背景：不停跳冠状动脉旁路移植术（OPCAB）后出血和需要同种异体输血的问题仍然存在。因此，我们评估了抗纤溶药氨甲环酸对实施 OPCAB 手术的患者术后出血和输血需要的影响。

方法：连续 231 名预定择期行 OPCAB 的病人入组参加研究。使用一个双盲方法将病人随机分配到接受氨甲环酸（剖皮前皮下注射 1g，随后以 400mg/h 行术中滴注；n=116）或安慰剂（注射等容积的生理盐水；n=115）。主要观察结果是术后 24 小时胸管引流量。还记录了同种异体输血、大併发症和资源利用。

结果：与安慰剂组相比，接受氨甲环酸的病人在 6 小时时（270± 118 mL vs 416 ± 179 mL，P < 0.001）和 24 小时时（654 ± 224 mL vs 891 ± 295 mL，P < 0.001）的胸管引流量显著减少。同种异体红细胞输注（47 vs 31.9%，P = 0.019）和新鲜冰冻血浆输注（29.6% vs 17.2%，P = 0.027）也显著减少。在死亡率、併发症和资源利用方面两组之间没有差别。

结论：氨甲环酸减少不停跳冠状动脉手术后胸管引流量和同种异体输血的需要。

（唐莹 譯 马皓琳 李士通 校）

BACKGROUND: Bleeding and the need for allogeneic transfusions are still problems after off-pump coronary artery bypass grafting (OPCAB) surgery. We therefore evaluated the effects of an antifibrinolytic, tranexamic acid, on postoperative bleeding and transfusion requirements in patients undergoing OPCAB surgery.

METHODS: Two hundred thirty-one consecutive patients scheduled for elective OPCAB were enrolled in the study. Using a double-blind method, the patients were randomly assigned to receive either tranexamic acid (bolus 1 g before surgical incision followed by an infusion of 400 mg/h during surgery; n = 116) or a placebo (infusion equivalent volume of saline solution; n = 115). The primary outcome was 24-hour postoperative chest tube drainage. Allogeneic transfusion, mortality, major morbidities, and resource utilization were also recorded.

RESULTS: In comparison with the placebo group, the patients receiving tranexamic acid had a significant reduction in chest tube drainage at 6 hours (270 ± 118 mL vs 416 ± 179 mL, P < 0.001) and 24 hours (654 ± 224 mL vs 891 ± 295 mL, P < 0.001). There was also a significant reduction in allogeneic red blood cell transfusions (47 vs 31.9%, P = 0.019) and fresh frozen plasma (29.6% vs 17.2%, P = 0.027) transfusions. There were no differences in mortality, morbidity, and resource utilization between the 2 groups.

CONCLUSIONS: Tranexamic acid reduces postoperative chest tube drainage and the requirement for allogeneic transfusion in off-pump coronary surgery.

教會一個舊的 GABA 受體新的技能

Teaching an Old GABA Receptor New Tricks

James R. Trudell, PhD, Edward Bertaccini, MD and M. Bruce MacIver, PhD

From the Department of Anesthesia, Stanford School of Medicine, Stanford, California.

Anesth Analg August 2012 115:270-273

在這期雜誌發行的特別收錄的伴隨文章中描述了改善依託咪酯和苯二氮卓類的類似藥物藥物分佈動力學和降低副作用的嘗試。兩個類型的藥物在 γ-氨基丁酸 A 受體上都有其主要的作用位點，但是它們的結合位點有很大不同，而且作用機制也不一樣。在這裡，我們綜述了 γ-氨基丁酸 A 受體的結構，並描述了兩個可能的結合位點的部位。此外，我們描述了這些藥是如何在系統某水準上與神經系統相互作用的。我們留給其他的研究者們去探討這些新藥能否提供真正的臨床療效改善。

（張怡 譯 马皓琳 李士通 校）
The accompanying articles in this issue of the journal's special collection describe attempts to improve on the dynamics of distribution and reduce side effects of analogs of etomidate and benzodiazepines. Both classes of drugs have their principal sites of action on γ-aminobutyric acid type A receptors, although at very different binding sites and by different mechanisms of action. Herein, we review the structure of γ-aminobutyric acid type A receptors and describe the location of the 2 likely binding sites. In addition, we describe how these drugs can interact with the nervous system at a systems level. We leave it to other reviewers to discuss whether these new drugs offer true clinical improvements.

In Vivo and In Vitro Pharmacological Studies of Methoxycarbonyl-Carboetomidate

Ervin Pejo, BS*, Joseph F. Cotten, MD, PhD*, Elizabeth W. Kelly, BA*, Ri Le Ge, MD, PhD*, Gregory D. Cuny, PhD†, Joydev K. Laha, PhD†, Jifeng Liu, PhD‡, Xiang Jie Lin, MSc‡ and Douglas E. Raines, MD*

From the *Massachusetts General Hospital, Boston, MA; †Brigham and Women's Hospital, Boston, MA; ‡Aberjona Laboratories, Inc, Beverly, MA.

Anesth Analg August 2012 115:297-304

背景：我們既往曾研發出依託咪酯的兩種同型物：甲酯基-依託咪酯和羧化依託咪酯，這兩種化合物既可保持依託咪酯血流動力學平穩的特性又可縮短其抗腎上腺皮質類作用的持續時間並減輕作用程度。甲酯基（MOC）-依託咪酯代謝迅速，作用時間超短，而(R)-乙基1-(1-苯乙基)-1H-吡咯-2-羧化物（羧化依託咪酯）並不強烈抑制11β-羥化酶。本研究假設MOC-依託咪酯不穩定的酯基可合併到羧化依託咪酯，從而產生一種能同時具備兩種藥劑各自的優點的新藥，我們介紹了羧化依託咪酯的一個軟性類似物——MOC-右旋-乙基1H-吡咯環-2-羧化物（MOC-羧化依託咪酯）的合成及藥理學特性。

方法：層析法測定MOC-羧化依託咪酯的辛醇:水分配係數並與依託咪酯、羧化依託咪酯和MOC-依託咪酯的辛醇:水分配係數進行比較。在蝌蚪及大鼠分別測定MOC-羧化依託咪酯翻正反射消失（LORR）的半數有效藥物濃度（EC50）及半數有效劑量。採用雙微電極電壓膜片鉗電生理技術測定MOC-羧化依託咪酯對GABA_A受體功能的作用，並採集混合大鼠血液標本使用高效液相質譜法評價其代謝穩定性。同時測定MOC-羧化依託咪酯的作用持續時間及對大鼠動脈血壓、腎上腺皮質功能的影響。

結果：MOC-羧化依託咪酯的辛醇:水分配係數為3300 ± 280，而依託咪酯、羧化依託咪酯和MOC-依託咪酯的分別為800 ± 180、15,000 ± 3700和190 ± 25。MOC羧化依託咪酯致蝌蚪LORR的EC50為9 ± 1 μM，致大鼠LORR的EC50為13 ± 5 mg/kg。13 μM的MOC-羧化依託咪酯可提高GABA_A受體電流400% ± 100%。MOC-羧化依託咪酯在混合大鼠血中的代謝半衰期為1.3 分鐘。大鼠LORR持續時間-催眠劑量對數值的曲線斜率，MOC-羧化依託咪酯顯著低於羧化依託咪酯(4 ± 1 vs 15 ± 3; P = 0.0004123)。催眠劑量時，MOC-羧化依託咪酯與單獨的溶劑相比較對動脈血壓和腎上腺皮質功能的影響均無顯著差異。

結論：MOC羧化依託咪酯是一種GABA_A受體的調節劑，催眠作用強，較羧化依託咪酯代謝更為迅速，從腦中清除也較快，維持血流動力學穩定的特性與羧化依託咪酯相似且並不抑制腎上腺皮質功能。

（邱鬱薇 譯 馬皓琳 李士通 校）

BACKGROUND: We previously developed 2 etomidate analogs that retain etomidate's favorable hemodynamic properties but whose adrenocortical effects are reduced in duration or magnitude. Methoxycarbonyl (MOC)-etomidate is rapidly metabolized and ultrashort acting whereas (R)-ethyl 1-(1-phenylethyl)-1H-pyrrole-2-carboxylate (carboetomidate) does not potently inhibit 11β-hydroxylase. We hypothesized that MOC-etomidate's labile ester could be incorporated into carboetomidate to produce a new agent that possesses favorable properties
individually found in each agent. We describe the synthesis and pharmacology of MOC-(R)-ethyl 1-(1-phenylethyl)-1H-pyrrole-2-carboxylate (MOC-carboetomidate), a “soft” analog of carboetomidate.

METHODS: MOC-carboetomidate's octanol:water partition coefficient was determined chromatographically and compared with those of etomidate, carboetomidate, and MOC-etomidate. MOC-carboetomidate's 50% effective concentration (EC50) and 50% effective dose for loss of righting reflexes (LORR) were measured in tadpoles and rats, respectively. Its effect on γ-aminobutyric acid A (GABA_A) receptor function was assessed using 2-microelectrode voltage clamp electrophysiological techniques and its metabolic stability was determined in pooled rat blood using high performance liquid chromatography. Its duration of action and effects on arterial blood pressure and adrenocortical function were assessed in rats.

RESULTS: MOC-carboetomidate's octanol:water partition coefficient was 3300 ± 280, whereas those for etomidate, carboetomidate, and MOC-etomidate were 800 ± 180, 15,000 ± 3700, and 190 ± 25, respectively. MOC-carboetomidate's EC50 for LORR in tadpoles was 9 ± 1 μM and its EC50 for LORR in rats was 13 ± 5 mg/kg. At 13 μM, MOC-carboetomidate enhanced GABA_A receptor currents by 400% ± 100%. Its metabolic half-life in pooled rat blood was 1.3 min. The slope of a plot of the duration of LORR in rats versus the logarithm of the hypnotic dose was significantly shallower for MOC-carboetomidate than for carboetomidate (4 ± 1 vs 15 ± 3, respectively; P = 0.0004123). At hypnotic doses, the effects of MOC-carboetomidate on arterial blood pressure and adrenocortical function were not significantly different from those of vehicle alone.

CONCLUSIONS: MOC-carboetomidate is a GABA_A receptor modulator with potent hypnotic activity that is more rapidly metabolized and cleared from the brain than carboetomidate, maintains hemodynamic stability similar to carboetomidate, and does not suppress adrenocortical function.

麻醉中鎮靜成分在監視器上的延遲：狀態熵和意識指數分析

Time Delay of Monitors of the Hypnotic Component of Anesthesia: Analysis of State Entropy and Index of Consciousness

Matthias Kreuzer, MSc*, Robert Zanner, MD†, Stefanie Pilge, MD†, Sabine Paprotny, MD*, Eberhard F. Kochs, MD* and Gerhard Schneider, MD†

From the *Department of Anesthesiology, Technische Universität München, Munich, Germany; †Department of Anesthesiology, Witten/Herdecke University, HELIOS Clinic, Wuppertal, Germany.

Anesth Analg August 2012 115:315-319

通過分析腦電圖（EEG）來評估麻醉中鎮靜成分的監護儀可以幫助降低術中知曉及回憶的發生率。為了計算代表麻醉水準的指數，這些監護儀在獲得準確的資料顯示前有不同程度的時間延遲。之前的研究所應用腦電圖信號來確定大腦狀態和麻醉趨勢以及雙頻指數的時間延遲。本研究中著者測定了狀態熵和意識指數的時間延遲。以此，本研究重播了記錄的代表不同麻醉水準的真實和模擬的腦電圖序列來測試監護儀。用類比的和在圍術期真實記錄的“清醒”、“全麻”和“皮層抑制”的穩定狀態的腦電信號以評估時間延遲。在從一個狀態轉換到另一個狀態時測量時間延遲，時間延遲的定義為顯示器達到穩定目標指數需要的時間間隔。使用模擬的和真實的腦電圖序列獲得了類似的結果。時間延遲並不恆定，範圍 18 秒~152 秒。數值增加和減少時時間延遲也不相同。時間延遲取決於起始的和目標指數值。指數計算的時間延遲可能會限制研究的監護儀預防術中知曉及回憶的能力。如果監護儀用於藥效學研究，麻醉水準向深或淺轉換時不同的時間延遲可能是一個問題。

（許辛 譯 馬皓琳 李世通 校）
Monitors evaluating the hypnotic component of anesthesia by analyzing the electroencephalogram (EEG) may help to decrease the incidence of intraoperative awareness with recall. To calculate an index representing the anesthetic level, these monitors have different time delays until the correct index is displayed. In previous studies, intraoperatively recorded real and simulated EEG signals were used to determine time delays of cerebral state and Narcotrend and Bispectral indices. In the present study, we determined time delays of state entropy and index of consciousness. For this purpose, recorded real and simulated EEG sequences representing different anesthetic levels were played back to the tested monitors.

Simulated and real perioperatively recorded EEG signals indicating stable states “awake,” “general anesthesia,” and “cortical suppression” were used to evaluate the time delays. Time delays were measured when switching from one state to another and were defined as the required time span of the monitor to reach the stable target index. Comparable results were obtained using simulated and real EEG sequences. Time delays were not constant and ranged from 18 to 152 seconds. They were also different for increasing and decreasing values. Time delays were dependent on starting and target index values. Time delays of index calculation may limit the investigated monitor’s ability to prevent interoperative awareness with recall. Different time delays for increasing and decreasing transitions could be a problem if the monitors are used for pharmacodynamic studies.

Prior Lumbar Discectomy Surgery Does Not Alter the Efficacy of Neuraxial Labor Analgesia

Jeanette R. Bauchat, MD, Robert J. McCarthy, PharmD, Tyler R. Koski, MD, Christopher R. Cambic, MD, Amy I. Lee, MD and Cynthia A. Wong, MD

From the Department of Anesthesiology, Northwestern University, Chicago, IL.

Anesth Analg August 2012 115:348-353

背景：腰椎間盤切除術是一種常見的神經外科手術。由於手術疤痕和解剖學的改變，椎管內分娩鎮痛的效果可能對有椎間盤切除手術史的產婦較差。在這個前瞻性觀察病例對照研究中，我們通過每小時分娩鎮痛布比卡因的用量，作爲比較曾行椎間盤切除術的婦女和那些未行背部手術的婦女分娩鎮痛效果的間接方法。

方法：對一個較大型的大學的附屬婦產科醫院中所有要求椎管內分娩鎮痛且曾行過椎間盤切除術的婦女進行了研究。對照受試者與麻醉醫師的技術水準相匹配。主要結果是分娩鎮痛每小時布比卡因的用量。記錄硬膜外導管放置的特點，包括椎間隙的嘗試次數、放置的時間和因鎮痛不足重置硬膜外導管次數。使用 Wilcoxon 排名秩和或 Fisher 精確檢驗來分析受試者的特點、分娩結果和鎮痛的效果。採用 Wilcoxon 符號秩、配對資料率或符號檢驗來分析硬膜外導管的放置資料。

結果：對椎間盤切除術組中的 42 名婦女和對照組中 42 名婦女的資料進行了分析。分娩鎮痛每小時布比卡因的用量在兩組之間沒有差別的（中位數 [四分位距，IQR]：椎間盤切除術組 12.7 mg/ h [11.0 至 15.3]和對照組 13.2 mg/ h [11.3 至 15.7]，中位數差異 [95% 置信區間，CI]：-0.55 mg/ h [-1.33 至 1.39]；P = 0.43）。從椎管內鎮痛開始到分娩的時間間隔以及分娩方式在兩組之間沒有差異。放置硬膜外導管的時間中位數在椎間盤切除術和對照組受試者之間的差異（95%CI）是 0 分鐘 (-1 至 2.5)；P = 0.38。椎間盤切除術組和對照組中分別有 17% 和 2% 嘗試穿刺超過一個椎間隙，差異（95%CI）是 15% (2-26)；P = 0.03。硬膜外穿刺技術和估計的導管放置水準沒有差異。此操作過程在椎間盤切除術中有 3 例由高年資的麻醉醫生完成，在對照組中有 2 例（p = 1.0）。這兩組中都沒有硬膜外導管的重置。

結論：進行椎管內鎮痛分娩的曾行椎間盤切除術組產婦和對照組相比，布比卡因每小時用量沒有差異。硬膜外導管放置時間也沒有差異。但是在椎間盤切除術組，穿刺需要嘗試
BACKGROUND: Lumbar discectomy surgery is a common neurosurgical procedure. Neuraxial labor analgesia may be less effective in parturients with a history of discectomy surgery because of postsurgical scarring and anatomical distortion. In this prospective observational case-controlled study, we compared bupivacaine consumption per hour of labor analgesia as an indirect measure of labor analgesic effectiveness between women with prior discectomy surgery and those who did not have back surgery.

METHODS: All women with prior discectomy surgery who requested neuraxial labor analgesia at a high-volume, single university-affiliated women's hospital during the study period were approached. Control subjects were matched for anesthesiologist skill level. The primary outcome was bupivacaine consumption per hour of labor analgesia. Characteristics associated with the epidural catheter placement including the number of interspaces attempted, time to placement, and number of epidural catheters replaced for inadequate analgesia were recorded. Subject characteristics, labor outcomes, and analgesia outcomes were analyzed using the Wilcoxon ranked sum or Fisher exact test. Epidural placement data were analyzed using the Wilcoxon signed rank, McNemar's, or sign test.

RESULTS: Data were analyzed for 42 women in the discectomy group and 42 women in the control group. Bupivacaine consumption per hour of labor analgesia was not different between groups (median [interquartile range, IQR]: discectomy 12.7 mg/h [11.0 to 15.3] and control 13.2 mg/h [11.3 to 15.7]; difference in medians [95% confidence interval, CI]: −0.55 mg/h [−1.33 to 1.39]; P = 0.43). The interval from initiation of neuraxial analgesia and delivery and mode of delivery did not differ between groups. The median difference (95% CI) in the time to place the epidural catheter between the discectomy and control subjects was 0 minute (−1 to 2.5); P = 0.38. More than 1 interspace was attempted in 17% discectomy in comparison with 2% of the control subjects—difference (95% CI) 15% (2–26); P = 0.03. The neuraxial technique and estimated level of catheter placement did not differ. Completion of the procedure by a more senior anesthesiologist occurred in 3 discectomy subjects and 2 control subjects (P = 1.0). No epidural catheters were replaced.

CONCLUSIONS: There was no difference in hourly bupivacaine consumption in parturients with prior lumbar discectomy surgery undergoing neuraxial labor analgesia in comparison with controls. Time to placement of the epidural catheter was not different either, but more interspaces were attempted in the discectomy group. Our findings suggest that standard clinical neuraxial analgesic methods are effective in women with discectomy surgery.

芝夜節律鐘基因 HPER3 與非心臟手術後的認知功能障礙沒有關聯
There Is No Association Between the Circadian Clock Gene HPER3 and Cognitive Dysfunction After Noncardiac Surgery
Melissa Voigt Hansen, MD*, Lars Simon Rasmussen, DSc, MD†, Cathrine Jespersgaard, PhD‡, Jacob Rosenberg, DSc, MD* and Ismail Gogenur, DSc, MD*
From the *Department of Gastroenterology, Surgical Section, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; †Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ‡Department of Clinical Biochemistry and Immunology, Statens Serum Institut, Copenhagen, Denmark.
Anesth Analg August 2012 115:379-385
BACKGROUND: The specific clock-gene PERIOD3 is important with regard to circadian rhythmicity, sleep homeostasis, and cognitive function. The allele PER3<sup>5/5</sup> has been associated with worse cognitive performance in response to sleep deprivation. We hypothesized that patients with the PER3<sup>5/5</sup> genotype would have an increased risk of postoperative cognitive dysfunction (POCD) 1 week after noncardiac surgery.

METHODS: Blood samples were analyzed from 93 patients with POCD and 186 patients without POCD from a completed multicenter study. The study population comprised patients ages 40 years and older undergoing noncardiac surgery who were tested preoperatively and 1 week after surgery with a neuropsychological test battery comprising 7 subtests. PER3 genotypes were determined by polymerase chain reaction analysis of DNA from blood samples (Clinicaltrials.gov identifier NCT01088100).

RESULTS: The frequencies of the 3 genotypes were 11.8% (32 patients) PER3<sup>5/5</sup>, 41.7% (113 patients) PER3<sup>4/5</sup>, and 46.5% (126 patients) PER3<sup>4/4</sup>. No significant difference was found in the distribution of the 3 genotypes according to POCD at 1 week (P = 0.68). Twelve percent (6% to 21%) of the patients with POCD and 12% (7% to 17%) of the patients without POCD had the PER3<sup>5/5</sup> genotype. The difference of the incidence of POCD/POCD for the PER3<sup>5/5</sup> genotype was 1% (−7% to 10%). A significantly higher Z score was found in patients having the PER3<sup>4/4</sup> in 1 of the neuropsychological tests (error score of the Concept Shifting Test) (Bonferroni corrected P = 0.042).

CONCLUSION: No significant association was found between the clock-gene PER3<sup>5/5</sup> genotype and POCD at 1 week after noncardiac surgery. If PER3<sup>5/5</sup> does worsen cognitive performance, the incidence is <10% of patients.
BACKGROUND: Tramadol is used to treat a wide range of acute and chronic pain. This drug induces analgesia by 2 mechanisms of action: opioid receptor activation and enhancement of noradrenaline (NA) and serotonin (5-HT) transmission. The effect of tramadol on NA and 5-HT concentrations in the spinal cord, however, have not been assessed. In the present study, we investigated the antihypersensitivity effect of tramadol using a rat model of postoperative pain. We also evaluated the increase in NA and 5-HT levels in the spinal cord after tramadol injection using in vivo microdialysis.

METHODS: We made a hindpaw incision in male Sprague-Dawley rats (postoperative pain model). Tramadol was administered intraperitoneally and intrathecally 24 hours after paw incision. Mechanical hypersensitivity was measured by determining the withdrawal threshold using von Frey filaments. Microdialysis studies from the dorsal horn of the lumbar spinal cord were performed to measure NA and 5-HT levels after intraperitoneal injection of tramadol. We also measured the NA and 5-HT content in the spinal cord in normal rats and rats with paw incision.

RESULTS: Intraperitoneal (10, 20, and 40 mg/kg) and intrathecal (125, 250, and 500 μg) injection of tramadol produced an antihyperalgesic effect in a dose-dependent manner. The antihypersensitivity effect of tramadol was prevented by intrathecal pretreatment with methysergide (30 μg), a serotonin receptor antagonist; idazoxane (30 μg), a noradrenaline receptor antagonist; and naloxone (30 μg), a nonselective opioid receptor antagonist. Microdialysis study revealed that 5-HT and NA concentrations at the spinal dorsal horn were increased, peaking at 30 minutes after intraperitoneal injection of 20 mg/kg tramadol. Furthermore, the NA and 5-HT content in the ipsilateral dorsal half of the lumbar spinal cord was increased 1 day and 3 days after paw incision, respectively.

CONCLUSIONS: These findings indicate that tramadol inhibits postoperative hypersensitivity by increasing NA and 5-HT levels in the spinal cord and activating opioid receptors. Tramadol might be more effective in the early postoperative period when spinal NA and 5-HT levels are increased.
The Presence of Transverse Cervical and Dorsal Scapular Arteries at Three Ultrasound Probe Positions Commonly Used in Supraclavicular Brachial Plexus Blockade

Hiroaki Murata, MD, PhD*, Akiko Sakai, MD*, Admir Hadzic, MD, PhD† and Koji Sumikawa, MD, PhD*

From the *Department of Anesthesiology, Nagasaki University School of Medicine, Nagasaki, Japan; and †Department of Anesthesiology, St. Luke's and Roosevelt Hospitals, College of Physicians and Surgeons, Columbia University, New York, New York.

Anesth Analg August 2012 115:470-473

BACKGROUND: Ultrasound-guided supraclavicular brachial plexus block carries a risk for puncture of vascular structures. In this study, we determined the frequency with which the transverse cervical artery (TCA) and the dorsal scapular artery (DSA) are detected by ultrasound evaluation at 3 probe positions during supraclavicular block.

METHODS: Ultrasound examinations of the supraclavicular region were performed in 53 healthy adult volunteers. Ultrasound images of the supraclavicular region were acquired at 3 probe positions: position A (the brachial plexus and the subclavian artery both lying on the first rib); position B (the brachial plexus on the first rib; the artery on the pleura); and position C (the brachial plexus between the anterior and middle scalene muscles). The primary outcome variables were the frequencies with which TCA and DSA were detected by 2-dimensional and color Doppler imaging at 3 specified probe positions.

RESULTS: One hundred six supraclavicular regions were examined in 53 subjects. The subclavian artery was detected in all subjects. TCA was more often detected than DSA, 94 (88.7%, 95% confidence interval [CI] 80.7%–93.8%) and 36 (34%, 95% CI 25.3%–43.9%) of 106 scans, respectively (McNemar P value <0.001). TCA was detected in 2 (1.9%, 95% CI 0.3%–7.3%), 31 (29.2%, 95% CI 20.9%–38.9%) and 61 (57.5%, 95% CI 47.5%–66.9%) of scans at probe positions A, B, and C, respectively, whereas DSA was detected in 3 (2.8%, 95% CI 0.7%–8.6%), 23 (21.7%, 95% CI 14.5%–30.9%), and 10 (9.4%, 95% CI 4.8%–17.0%) of scans at probe positions A, B, and C, respectively. Thus, the TCA and DSA were less likely to be present with probe position A (all P < 0.001).
CONCLUSION: TCA was more often detected than DSA in the vicinity of the brachial plexus in the supraclavicular region. Both TCA and DSA were least likely to be present in probe position A. Color Doppler, particularly for probe position A, may help to reduce the risk for inadvertent vascular puncture during ultrasound-guided supraclavicular block.

The Effects of MDCO-2010, a Serine Protease Inhibitor, on Activated Clotting Time in Blood Obtained from Volunteers and Cardiac Surgical Patients

Heezoo Kim, MD*, Fania Szlam, MMSc*, Kenichi A. Tanaka, MD, MSc*, Andreas van de Locht, PhD†, Satoru Ogawa, MD* and Jerrold H. Levy, MD, FAHA*

From the *Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; and †The Medicines Company GmbH, Leipzig, Germany.

Heezoo Kim, MD, is currently affiliated with the Department of Anesthesiology, Korea University Guro Hospital, Seoul, Korea.

Anesth Analg August 2012 115:244-252

BACKGROUND: The activated clotting time (ACT) is widely used for monitoring heparin anticoagulation during cardiac surgery. Celite-based ACT values are prolonged when aprotinin is administered. MDCO-2010, a novel serine protease inhibitor, is currently being evaluated as a possible alternative to aprotinin. Therefore, we evaluated the in vitro effects of this novel agent on ACT values using 3 different point-of-care instruments with kaolin or celite as an activator.

METHODS: The study was performed in 2 parts. In the first part, blood samples were obtained from 15 healthy volunteers. Samples were pipetted into small Eppendorf tubes and 2 concentrations of the MDCO-2010 (100 and 500 nM, final concentration) alone or with heparin (1.2 or 2.4 U/mL) were added. ACTs were measured using Helena (celite), Hemochron (kaolin), and Medtronic (kaolin) devices. In the second part of the study, blood samples were obtained intraoperatively, at 5 time points, from 15 patients undergoing cardiopulmonary bypass. MDCO-2010 at a final concentration of 100 or 500 nM was added and ACT testing was performed as before. Additional coagulation tests included prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin, prothrombin, and anti-Xa levels.
RESULTS: Addition of MDCO-2010 concentration-dependently prolonged ACTs in volunteers' and patients' blood samples regardless of the ACT activator or device used. In volunteer samples (no heparin) and in patient samples (baseline and intensive care unit) percent changes in ACTs due to MDCO-2010 were on average 3.1 ± 1.8 times higher (95% confidence interval 2.6–3.6; P < 0.001) for the celite-based Helena device compared with either Hemochron or Medtronic devices.

CONCLUSION: MDCO-2010 causes less ACT prolongation with kaolin than with celite activation.

以安慰劑和咪達唑侖為對照組評價 Remimazolam (CNS 7056) 藥物安全性、藥代動力學和藥效學的 I 期單遞增劑量研究: 第一部分: 安全性、有效性和檢測藥代動力學

A Placebo- and Midazolam-Controlled Phase I Single Ascending-Dose Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Remimazolam (CNS 7056): Part I. Safety, Efficacy, and Basic Pharmacokinetics

Laurie J. Antonik, MD*, D. Ronald Goldwater, MD†, Gavin J. Kilpatrick, PhD‡, Gary S. Tilbrook, PhD‡ and Keith M. Borkett, BSc‡

From the *Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; †PAREXEL International, Early Phase Clinical Unit, Harbor Hospital, Baltimore, Maryland; ‡PAION UK Ltd., Cambridge, United Kingdom.

Anesth Analg August 2012 115:274-283

BACKGROUND: A new benzodiazepine, remimazolam, metabolized by tissue esterases to an inactive compound, CNS 7054, has been developed to permit a fast onset, a short and more predictable duration of sedative action, and a more rapid recovery profile than with currently available benzodiazepines. We report on the safety and efficacy of the first human study.
METHODS: A phase I, single-center, double-blind, placebo- and active-controlled, randomized, single-dose escalation study was conducted. Up to 10 cohorts of healthy subjects were scheduled to receive a single 1-minute IV infusion of remimazolam, midazolam, or placebo. In the 10 possible cohorts, remimazolam doses were from 0.01 to 0.35 mg/kg. In cohorts 1 to 3, 6 subjects received remimazolam and 1 placebo. From cohort 4 onward, an additional 3 subjects in each cohort received midazolam (0.075 mg/kg). Safety, pharmacokinetics, and pharmacodynamics were measured. A stop criterion of loss of consciousness for >5 minutes in >50% of subjects was predefined.

RESULTS: The stop criterion was reached in cohort 9 (0.30 mg/kg remimazolam) so that 81 subjects were enrolled. Remimazolam was well tolerated in all dose cohorts, and no serious adverse events (AEs) were reported. Three AEs of mild ($\text{SpO}_2$ 85–88%) hemoglobin desaturation (2 in the remimazolam groups and 1 in the midazolam group) resolved spontaneously, and 1 AE of moderate hemoglobin desaturation ($\text{SpO}_2$ 75%) resolved with a chin lift in the highest remimazolam dose group. No supplemental oxygen or manual ventilation was required. Vital signs remained stable throughout, although there was an increase in heart rate 2 minutes postdose for both remimazolam and midazolam. There were no reports of hypotension. The pharmacokinetic behavior of remimazolam was linear and its systemic clearance approximately 3 times that of midazolam. Clearance was essentially independent of body weight. A rapid onset and dose-dependent sedation was observed after administration of remimazolam at 0.05 mg/kg and higher. Remimazolam (0.075 to 0.20 mg/kg) induced peak sedation levels similar to or higher than those achieved with midazolam (0.075 mg/kg). Median recovery times after approximately equieffective doses of remimazolam (0.10 and 0.15 mg/kg) and midazolam (0.075 mg/kg) were 10 and 40 minutes, respectively.

CONCLUSIONS: Remimazolam provided sedation with rapid onset and offset, and was well tolerated. There was no supplemental oxygen or ventilation required. On the basis of these data, further studies on the potential utility of remimazolam for sedation/anesthesia are warranted.

簡報：甲氧羰基依託咪酯的羧酸代謝物的藥理學研究
Brief Report: Pharmacological Studies of Methoxycarbonyl Etomidate's Carboxylic Acid Metabolite

Ri Le Ge, MD, PhD, Ervin Pejo, BS, Marian Haburcak, PhD, S. Shaukat Husain, DPhil, Stuart A. Forman, MD, PhD and Douglas E. Raines, MD
From the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.
Anesth Analg August 2012 115:305-308

背景：甲氧羰基依託咪酯（MOC-依託咪酯）是一個快速代謝和超短效依託咪酯類似物，單次注射後，不會產生長期腎上腺皮質功能抑制。它的代謝產物（MOC-ECA）是一種羧酸，其藥理學尚未研究。作者推測，MOC-ECA 與 MOC-依託咪酯相比，藥理活性顯著降低，單次注射後，催眠作用持續時間非常短暫且不產生長期腎上腺皮質功能抑制。爲了驗證這一假設，作者在3個生物檢測中比較了 MOC-ECA 和 MOC-依託咪酯的效力。

方法：採用蝌蚪的翻正反射消失來評估 MOC-ECA 的催眠效力。通過測定所需直接啟動 $\alpha_1$（L264T）B2y2L GABAA 受體的濃度，界定 MOC-ECA 的 $\gamma$-氨基丁酸 A（GABA A）調節效力並與 MOC-依託咪酯進行比較。通過測定抑制腎上腺皮質細胞外生成皮質醇需要的濃度，比較 MOC-ECA 和 MOC-依託咪酯對腎上腺皮質的抑制能力。

結果：MOC-ECA 使蝌蚪的翻正反射消失的 50%有效濃度為 2.8±0.64 mM，較以前報導的 MOC-依託咪酯的有效濃度（8±2μM）更為精確。MOC-ECA 直接啟動 GABA A 受體的 50%有效濃度為 3.5±0.63 mM 而 MOC-依託咪酯為 10±2.5μM。MOC-ECA 抑制腎上腺皮質細胞在體外的皮質醇最大抑制濃度為 30±7μM，而 MOC-依託咪酯為 0.10±0.02μM。
BACKGROUND: Methoxycarbonyl etomidate (MOC-etomidate) is a rapidly metabolized and ultrashort-acting etomidate analog that does not produce prolonged adrenocortical suppression after bolus administration. Its metabolite (MOC-ECA) is a carboxylic acid whose pharmacology is undefined. We hypothesized that MOC-ECA possesses significantly lower pharmacological activity than MOC-etomidate, accounting for the latter's very brief duration of hypnotic action and inability to produce prolonged adrenocortical suppression after bolus administration. To test this hypothesis, we compared the potencies of MOC-ECA and MOC-etomidate in 3 biological assays.

METHODS: The hypnotic potency of MOC-ECA was assessed in tadpoles using a loss-of-righting reflexes assay. The γ-aminobutyric acid type A (GABA_A) receptor modulatory potencies of MOC-ECA and MOC-etomidate were compared by defining the concentrations of each required to directly activate α_1 β_2 γ_2L GABA_A receptors. The adrenocortical inhibitory potencies of MOC-ECA and MOC-etomidate were compared by defining the concentrations of each required to inhibit in vitro cortisol production by adrenocortical cells.

RESULTS: MOC-ECA's 50% effective concentration for loss-of-righting reflexes in tadpoles was 2.8 ± 0.64 mM as compared with a previously reported value of 8 ± 2 μM for MOC-etomidate. The 50% effective concentrations for direct activation of GABA_A receptors were 3.5 ± 0.63 mM for MOC-ECA versus 10 ± 2.5 μM for MOC-etomidate. The half-maximal inhibitory concentration for inhibiting in vitro cortisol production by adrenocortical cells was 30 ± 7 μM for MOC-ECA versus 0.10 ± 0.02 μM for MOC-etomidate.

CONCLUSIONS: In all 3 biological assays, MOC-ECA's potency was approximately 300-fold lower than that of MOC-etomidate.
BACKGROUND: The use of total joint arthroplasties is increasing worldwide. In this work we aim to elucidate recent trends in demographics and perioperative outcomes of patients undergoing total hip (THA) or total knee arthroplasty (TKA).

METHODS: Data from the US Nationwide Inpatient Sample between 1998 and 2008 were gathered for primary THAs and TKAs. Trends in patient age, comorbidity burden, length of hospitalization, frequency of major perioperative complications, and in-hospital mortality were analyzed. In-hospital outcomes were reported as events per 1000 inpatient days to account for changes in length of hospitalization over time. Deyo index, discharge status, and the interaction effect of time and discharge status were included in the adjusted trend analysis for morbidity.

RESULTS: Between 1998 and 2008, the average age of patients undergoing TKA and THA decreased by 2 to 3 years (P < 0.001). The average length of stay decreased by approximately 1 day over the time interval studied (P < 0.001). The percentage of patients being discharged home declined from 29.7% to 25.4% after TKA and from 29.3% to 24.2% after THA, in favor of dispositions to long- and short-term care facilities (P < 0.0001). Comorbidity burden as measured by the Deyo comorbidity index increased by 35% and 30% for TKA and THA patients, respectively (P < 0.0001). After TKA, there was an increase in the incidence of the following major complications: pulmonary embolism (coefficient estimate [CE] 0.069; 95% confidence interval [CI], 0.059 – 0.079; P < 0.0001), sepsis (CE 0.034; 95% CI, 0.014 – 0.054; P = 0.001), nonmyocardial infarction cardiac complications (CE 0.038; 95% CI, 0.035 – 0.041; P < 0.0001), and pneumonia (CE 0.039; 95% CI, 0.031 – 0.047; P < 0.0001). After THA, there was an increase in the incidence of the following major complications: pulmonary embolism (CE 0.031; 95% CI, 0.012 – 0.049; P = 0.001), sepsis (CE 0.060; 95% CI, 0.039 – 0.081; P < 0.0001), nonmyocardial infarction cardiac complications (CE 0.040; 95% CI, 0.036 – 0.043; P < 0.0001), and pneumonia (CE 0.039; 95% CI, 0.029 – 0.048). In-hospital mortality declined after both TKA (CE −0.059; 95% CI, −0.077 to −0.040; P < 0.0001) and THA (CE −0.068; 95% CI, −0.086 to −0.051; P < 0.0001).

CONCLUSION: Between 1998 and 2008, trends show increases in several major in-hospital complications after THA and TKA, including pulmonary embolism, sepsis, nonmyocardial infarction cardiac complications, and pneumonia. Despite the increase in complications, declining in-hospital mortality was noted over this period.
BACKGROUND: Bilateral myringotomy and placement of ventilating tubes (BMT) is one of the most common pediatric surgical procedures in the United States. Many children who undergo BMT develop behavioral changes in the postanesthesia care unit (PACU) and require rescue pain medication. The incidence of these changes is lower in children receiving intraoperative opioids by the nasal, IM, or IV route compared with placebo. However, there are no data to indicate which route of administration is better. Our study was designed to compare the immediate postoperative analgesic and behavioral effects of 3 frequently used intraoperative techniques of postoperative pain control for patients undergoing BMT under general anesthesia.

METHODS: One hundred seventy-one ASA physical status I and II children scheduled for BMT were randomized into 1 of 3 groups: group 1—nasal fentanyl 2 μg/kg with IV and IM saline placebo; group 2—IV morphine 0.1 mg/kg with nasal and IM placebo; or group 3—IM morphine 0.1 mg/kg with nasal and IV placebo. All subjects received a standardized general anesthetic with sevoflurane, N2O, and O2 and similar postoperative care. The primary end point of the study was the pain scores measured by the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale in the PACU.

RESULTS: There were no significant differences in peak FLACC pain among the 3 groups (mean [95% CI] 2.0 [1.2–2.8] for intranasal fentanyl, 2.7 [1.7–3.6] for IV morphine, and 2.9 [2.1–3.7] for IM morphine, respectively). There were no differences in the scores on the Pediatric Anesthesia Emergence Delirium (PAED) scale, incidence of postoperative emergence delirium (PAED score ≥12), emesis, perioperative hypoxemia, or need for airway intervention, and postoperative rescue analgesia. There were also no differences in the duration of PACU stay or parental satisfaction among the groups.
**CONCLUSION:** In this double-blind, double-dummy study, there was no difference in the efficacy of intranasal fentanyl, IM and IV morphine in controlling postoperative pain and emergence delirium in children undergoing BMT placement. The IM route is the simplest and avoids the potential for delays to establish vascular access for IV therapy and the risks of laryngospasm if intranasal drugs pass through the posterior nasopharynx and irritate the vocal cords.

**The Frequency and Magnitude of Cerebrospinal Fluid Pulsations Influence Intrathecal Drug Distribution: Key Factors for Interpatient Variability**

Ying Hsu, BS*, H. D. Madhawa Hettiarachchi, PhD*, David C. Zhu, PhD†‡§ and Andreas A. Linninger, PhD*

From the *Department of Bioengineering, University of Illinois at Chicago, Chicago, Illinois; and Departments of †Psychology, ‡Radiology, and §Electrical and Computer Engineering, Michigan State University, East Lansing, Michigan.

Anesth Analg August 2012 115:386-394

**BACKGROUND:** Intrathecal drug delivery is an efficient method to administer therapeutic molecules to the central nervous system. However, even with identical drug dosage and administration mode, the extent of drug distribution in vivo is highly variable and difficult to control. Different cerebrospinal fluid (CSF) pulsatility from patient to patient may lead to different drug distribution. Medical image–based computational fluid dynamics (miCFD) is used to construct a patient-specific model to quantify drug transport as a function of a spectrum of physiological CSF pulsations.

**METHODS:** Magnetic resonance imaging (MRI) and CINE MRI were performed to capture the patient's central nervous system anatomy and CSF pulsatile flow velocities. An miCFD model was reconstructed from these MRIs and the patient's CSF flow velocities were computed. The effect of CSF pulsatility (frequency and stroke volume) was investigated for a bolus injection of...
a model drug at the L2 vertebral level. Drug distribution profiles along the entire spine were computed for different heart rates: 43, 60, and 120 bpm, and varied CSF stroke volumes: 1, 2, and 3 mL. To assess toxicity risk for patients with different physiological variables, therapeutic and toxic concentration thresholds for a common anesthetic were derived from experimental studies. Toxicity risk analysis was performed for an injection of a spinal anesthetic for patients with different heart rates and CSF stroke volumes.

RESULTS: Both heart rate and CSF stroke volume of the patient strongly influence drug distribution administered intrathecally. Doubling the heart rate (from 60 to 120 bpm) caused a 26.4% decrease in peak concentration in CSF after injection. Doubling the CSF stroke volume diminished the peak concentration after injection by 38.1%. Computations show that potentially toxic peak concentrations due to injection can be avoided by changing the infusion rate. Using slower infusion rates could avoid high peak concentrations in CSF while maintaining drug concentrations above the therapeutic threshold.

CONCLUSIONS: Our computations identify key variables for patient to patient variability in drug distribution in the spine observed clinically. The speed of drug transport is strongly affected by the frequency and magnitude of CSF pulsations. Toxicity risks associated with an injection can be reduced for a particular patient by adjusting the infusion variables with our rigorous miCFD model.

新生鼠鞘內注射可樂定: 剤量依賴鎮痛以及脊髓凋亡和毒性的評估

Intrathecal Clonidine in the Neonatal Rat: Dose-Dependent Analgesia and Evaluation of Spinal Apoptosis and Toxicity

Suellen M. Walker, MBBS, PhD, FANZCA, FFPMANZCA*, Marjorie Grafe, MD, PhD† and Tony L. Yaksh, PhD‡

From the *Portex Unit: Pain Research, UCL Institute of Child Health and Great Ormond Street Hospital NHS Trust, London, United Kingdom; †Department of Pathology, Oregon Health and Science University, Portland, Oregon; and ‡Department of Anesthesiology, University of California San Diego, La Jolla, California.

Anesth Analg August 2012 115:450-460

BACKGROUND: Neuraxial clonidine is used for perioperative analgesia in children of all ages. Preclinical studies in the postnatal rat allow comparison of the relative toxicity and safety of spinal analgesics throughout postnatal development.
METHODS: Rat pups aged 3, 7, or 21 postnatal (P) days were briefly anesthetized for intrathecal injections of saline or clonidine. At each age, the maximum tolerated, antinociceptive (increased hindlimb mechanical withdrawal threshold) and antihyperalgesic (hindpaw carrageenan inflammation) doses were determined. Lumbar spinal cord sections were assessed for apoptosis and cell death (histology, activated caspase-3 immunohistochemistry, Fluoro-Jade C staining), histopathology (hematoxylin and eosin staining), and increased glial reactivity (microglial and astrocytic markers). P3 intrathecal ketamine sections served as positive controls. In additional groups, thermal latency and mechanical withdrawal threshold were measured at P35.

RESULTS: Intrathecal clonidine produces age- and dose-dependent analgesia in rat pups. Maximal doses of clonidine did not alter the degree or distribution of apoptosis or increase glial reactivity in the neonatal spinal cord. No spinal histopathology was seen 1 or 7 days after injection at any age. Intrathecal clonidine did not produce persistent changes in reflex sensitivity to mechanical or thermal stimuli at P35.

CONCLUSIONS: Intrathecal clonidine in the postnatal rat did not produce signs of spinal cord toxicity, even at doses much larger than required for analgesia. The therapeutic ratio (maximum tolerated dose/antihyperalgesic dose) was >300 at P3, >30 at P7, and >10 at P21. These data provide additional information to inform the clinical choice of spinal analgesic drug in early life.