New Anesthesia Drugs
Already here or on the Horizon

LTC Peter D. Strube
CRNA MSNA APNP ARNP DNAP(c)

Assistant Professor Rosalind Franklin University

Things are in evolution and only getting faster and faster!
Dedicated to:

Thomas G Healey, RN, CRNA, MA
St Mary’s University
Died January 5, 2014

Navy Corpsman Vietnam
Financial Disclosure

There is no financial conflicts with this presentation.

Lecturing about a topic does not constitute endorsement of any product. Please take the time to research each topic for more information.

Mentioning a product or company does NOT represent endorsement.
PICTORIAL RECORDS OF THE AGONY ENDURED IN OPERATIONS BEFORE THE ADVENT OF ANESTHESIA

A. A surgeon cutting with his big saw.
B. A very painful operation of the seventeenth century.
C. A surgeon torturing his patient.
Life Long Learning = Better Patient Care!

Think outside the BOX—
Think Differently!

Old Drugs, New Ways
New Drugs, Old Battles!

Pharmacogenetics----Micron Technology

Your DNA Affects Your Response to Drugs

Naproxen complex
Pediatric patients don’t learn like we do?

What are the most abused Drugs in Peds?

FDA and Codeine?---- CPY2D6 ultra-rapid metabolizers

Codeine is a prodrug, meaning that it has to be converted into its active form, morphine, for its analgesic effect to be fully realized. Cytochrome P450 isoenzyme-2D6 (CYP2D6) is responsible for its hepatic conversion, and of course this extra biotransformation step increases the chances for alterations in the extent and speed of the enzyme's conversion of codeine to morphine.
Life Long Learning = Better Patient Care!

Think outside the BOX

We can no longer sit by the wayside, we must make ourselves better.
Keep a OPEN Mind!

Multimodal
Synergy
Preemptive
Standard, Policy, Guideline, Suggestion???
Zofran

FDA and Codeine?

FDA Alerts!
these pediatric patients was comparable to the prevention of vomiting in patients 4 years of age and older.

**Postoperative Nausea and Vomiting: Prevention of Postoperative Nausea and Vomiting:**

**Adult Studies:** Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexitol, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curetlar and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving 554 patients. ZOFTRAN Injection (4 mg) I.V. given over 2 to 5 minutes was significantly more effective than placebo. The results of these studies are summarized in Table 8.

### Table 8. Prevention of Postoperative Nausea and Vomiting in Adult Patients

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron 4 mg I.V.</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emetic episodes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>136</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Treatment response over 24-h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postoperative period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Emetic episodes</td>
<td>103 (76%)</td>
<td>64 (46%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 Emetic episode</td>
<td>13 (10%)</td>
<td>17 (12%)</td>
<td></td>
</tr>
<tr>
<td>More than 1 emetic episode</td>
<td>20 (15%)</td>
<td>58 (42%)</td>
<td></td>
</tr>
<tr>
<td>episode/rescued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea assessments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>134</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>No nausea over 24-h postoperative period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emetic episodes:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Life Long Learning = Better Patient Care!

Tablets

Topamax®
(topiramate)

Sprinkles

15 mg
25 mg
400 mg of riboflavin, 65 mg of caffeine and 325 mg Tylenol
Comfort Zone

Most of us practice our art in the comfort zone.

New and different ideas tend to pull people from the comfort zone to the scare zone.

Try new things.
Enhance your patient outcomes.
Wow.....

“You shouldn’t have that much pain?”

“Pain doesn’t raise your blood pressure”

“You should feel this way”

“This won’t be that painful”

“Do you have any pain?

... do you feel?”
Oxytocin is also thought to modulate inflammation by decreasing certain cytokines. Thus, the increased release in oxytocin following positive social interactions has the potential to improve wound healing.

41 G8P3-39 weeks at 31 min ACLS: Given A-OK at 1mg/8mg/30mg
   Survived and left hospital with small neuro deficits

28 G2P1-39 weeks at ?? Min ACLS: Given A-OK at 0.8mg/4mg/30mg
   Survived with no neuro issues

Thromboxane/serotonin

Use this in conjunction to current treatments.
At this time this is a adjunct to get the patient to return to circulation.
Successful Management of Cardiac Arrest From Amniotic Fluid Embolism With Ondansetron, Metoclopramide, Atropine, and Ketorolac: A Case Report

Abstract Number: S 47
Abstract Type: Case Report/Case Series

Phillip L Copper MD1; Maryann P Otto MD2; Barbara L Leighton MD3
Washington University in Saint Louis1; Washington University in Saint Louis2; Washington University in Saint Louis3

Introduction: Amniotic fluid embolism (AFE), a rare obstetric event with high maternal and fetal mortality, consists of cardiac and pulmonary symptoms with consumptive coagulopathy. In animal models of pulmonary embolism, serotonin receptor blockers, cyclooxygenase inhibitors, and vagotomy improve cardiac function and decrease mortality. (1,2) Here we report a successful resuscitation of cardiac arrest from AFE using adult cardiac life support (ACLS) plus ondansetron, metoclopramide, atropine, and ketorolac.

Case: 41 yo G8P3043 woman presented at 39 weeks for labor induction. At complete cervical dilation, the patient complained of shortness of breath. Oxygen saturation decreased to 80% and within 1 minute she developed cardiac arrest. ACLS was initiated and the baby was quickly delivered via forceps. The patient was still pulseless after 40 minutes of ACLS. Atropine 1mg, ondansetron 8mg, metoclopramide 10mg, and ketorolac 30mg were then administered and the patient regained a pulse and stabilized within 2 minutes. A bedside echocardiogram one hour later showed a hyperdynamic left ventricle, a flat intraventricular septum, right ventricle pressure and volume overload, and preserved right ventricular function. Right heart failure improved quickly. The patient then developed consumptive coagulopathy. Profuse uterine bleeding requiring 13u PRBC, 6u FFP, 2u platelets, 30u cryoprecipitate, 2 doses of recombinant Factor VIIa, and an intrauterine Bakri balloon. She required hemodialysis for 5 days due to acute tubular necrosis. The patient developed speech and memory function difficulties which still persist. She was discharged home on day 13.

Discussion: AFE treatment requires prompt resuscitative measures plus fetal delivery, yet maternal mortality is still high. Pulmonary hypertension and right-sided heart failure are seen with echocardiography in AFE cases. (3) Animal models suggest that significant embolism of any material is followed by platelet degranulation, pulmonary hypertension due to serotonin and thromboxane, and systemic hypotension due to vagal stimulation. (1,2) It was not until ondansetron (5-HT3 antagonist), metoclopramide (5-HT3 antagonist), atropine (vagolytic), and ketorolac (cyclooxygenase inhibitor) were given that the patient regained a pulse. It is likely that anti-serotonin, anti-thromboxane, and vagolytic therapy helped restore this patient’s circulation and ultimately helped her survive AFE.

References:

SOAP 2013
Role of Esmolol in Perioperative Analgesia and Anesthesia: A Literature Review

Megan Harless, CRNA, MSN
Caleb Depp, CRNA, MSN
Shawn Collins, CRNA, DNP, PhD
Jon Hewer, CRNA, MSN, MA

Use of opioids to provide adequate perioperative analgesia often leads to respiratory depression, nausea, vomiting, urinary retention, pruritus, and opioid-induced hyperalgesia, with the potential to increase length of stay in the hospital. In an effort to reduce perioperative opioid administration yet provide appropriate pain relief, researchers began to study the use of esmolol beyond its well-known cardiovascular effects. Perioperative esmolol has been shown to reduce anesthetic requirements, decrease perioperative opioid use, decrease the incidence of postoperative nausea and vomiting, lead to an earlier discharge, and increase patient satisfaction. This article provides a review of the literature on the use of esmolol as an adjunct for perioperative analgesia and anesthesia.

Keywords: Esmolol, opioid sparing, perioperative analgesia and anesthesia

Can you do a anesthetic without narcotics?
Blair et al Patient-controlled analgesia for labor using remifentanil: a feasibility study?

Remifentanil PCA with a bolus dose in the range 0.25–0.5 µg kg and a lockout time of 2 min appears a safe and effective drug for use in labor in patient-controlled analgesia systems.
The position of the American College of Nurse-Midwives that women should have access to a variety of measures to assist them in coping with the challenges of labor. Among these should be nitrous oxide, which is commonly used in many other countries.

Nitrous Oxide During Labor: Less Pain Relief, High Patient Satisfaction

Despite lower reported effectiveness in labor pain, the degree of patient satisfaction in women who received nitrous oxide is similar to that of women who received neuraxial modalities, according to a study described in Anesthesia & Analgesia.²

Although physicians in other countries have used nitrous oxide for decades to alleviate labor pain, this option has only recently been adopted in the United States. Previous research regarding its analgesic effectiveness has been largely inconclusive, and few studies have explored patient satisfaction associated with this modality.³ In the current investigation, researchers at Vanderbilt University Medical Center in Nashville, Tennessee, retrospectively examined data collected since their facility began offering self-administered nitrous oxide as an analgesic option in 2011.


New to Ortho World

A competitive inhibitor of plasminogen, and in high concentrations a non-competitive inhibitor of plasmin.

Less transfusions -- reported 50%

Trauma: Antifibrinolytic agent

Increased trauma survival in prospective analysis

Can’t have blood products, Hextend in same line
Give within 3 hours - 1gm in 100mL NS over 10 mins
Then start infusion of 1gm in 100mL NS over 8 hours
Pump rate 12.5ml/hr
Further doses can be given, though not supported by literature

Joints... dosing all over the place

**Spine surgery, 10 mg/kg up to 1000mg load followed by 1 mg/kg/hr. infusion for duration of case.**
Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blinded, placebo-controlled study.

Anesthesiology, 2015; 15(18)

30 minutes before injecting narcotic spinal or epidural...
New MH Drug? Ryanodex

The drug, an injectable suspension of dantrolene sodium, will be available in 250 mg single-use vials containing the active ingredient in a lyophilized powder.

According to Eagle Pharmaceuticals, Ryanodex can be prepared and administered in less than one minute, compared with 15 to 20 minutes for conventional dantrolene.

The cost for a patient receiving Ryandex treatment for a MH crisis (based off 2.5mg/kg in a 70kg patient) is $1,610 verses $700 with generic dantrolene. This cost does not include additional doses of dantrolene that will be required.

This research and orphan drug status is leading to additional research... for example for heat stroke:
Fospropofol (Lusedra)

Approved by the FDA on 12/12/08, a pro-drug of propofol

Same mechanism of action; except has a slow, smooth and predictable rise in concentration

By; Definition: this is a sedative-hypnotic aqueous agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

NOT FOR GENERAL

This will and has already raised some concern—FDA states that only those trained in delivering anesthesia should use this drug. What about the ago old question??

What about using this in GI clinic
Life Long Learning = Better Patient Care!

Fospropofol (Lusedra)
Magnesium Sulfate Plus Lidocaine Reduces Propofol Injection Pain: A Double-blind, Randomized Study

Jiahan Sun, MD; Riyong Zhou, MD; Wendong Lin, MD; Jiahan Zhou, MD; and Weijan Wang, MD

Department of Anesthesiology, 1st Affiliated Hospital, Wenzhou Medical University, Wenzhou, China

ABSTRACT

Purpose: Propofol injection can cause distressing pain, and no method can inhibit it completely. Neither lidocaine nor magnesium sulfate (MgSO4) was sufficient to prevent pain from the injection of propofol. This prospective, double-blind, placebo-controlled study was designed to investigate the efficacy of the MgSO4 plus lidocaine on suppressing propofol injection pain.

Methods: Three hundred women received 300 mg MgSO4 (Group M), 40 mg lidocaine (Group L), or 300 mg MgSO4 plus 40 mg lidocaine (Group M+L). This was followed by administration of 50 mg propofol. Pain scores, behavior-related responses, and diameter of the vein were recorded following the injection of propofol.

Findings: Patients in Group M+L had lower pain scores. Patients' behavior-related responses in Group M+L were also better compared with the other groups. There were no differences in pain scores priority for improvement. Minimizing propofol injection pain is an important clinical goal because it may influence a patient’s perception of quality and acceptability of anesthesia. Several measures have been used to reduce the occurrence of propofol injection pain, including the addition of lidocaine with tourniquet; cooling or warming the propofol; diluting the propofol solution; injection of propofol into a large vein, or prior injections of meperidine, metoclopramide, magnesium, thiopental, ketamine, methylene blue, or a β-blocker. We have not found a method that suppresses injection pain completely.

Tourniquet causes dilation of veins, and, interestingly, vein size is an important factor in propofol injection pain. A meta analysis suggested that use of a rubber tourniquet and lidocaine application before propofol injection was most effective to prevent injection pain. Dae et al demonstrated that higher doses of lidocaine can achieve more analgesia, but the incidence of pain can be still as high as 36.8% when a
Vein pretreatment with magnesium sulfate to prevent pain on injection of propofol is not justified

[Un prétraitement veineux au sulfate de magnésium n’est pas justifié pour prévenir la douleur causée par l’injection de propofol]

Anil Agarwal MD,* Sanjay Dhiraj MD,* Mehdi Raza MD,* Ravinder Pandey MD,* Chandra Kant Pandey MD,* Prabhat K. Singh MD,* Uttam Singh PhD,* Devendra Gupta MD*
Remimazolam

- Analogue of Midazolam
  - that utilizes the ester design.
  - Broken down by nonspecific ester hydrolysis

- Designed for outpatient procedures as well as EGD/C-Scope area

- Linear Clearance superior to Versed

- Better sedation with less side effects of Versed
  - respiratory and cardiac events

- **6mg loading Dose followed by 3 mg maintenance doses**

- Crazy but initial studies have not change in ventilation or oxygenation with remidmazolam with NO supplemental oxygen applied.........
Life Long Learning = Better Patient Care!

Paion Presents Positive Remimazolam Phase III Colonoscopy Results at the 2016 American College of Gastroenterology Annual Scientific Meeting

Chelsea Pratt • October 19, 2016
Add Comment

PAION AG, a specialty pharma company (ISIN DE000A0B65S3; Frankfurt Stock Exchange Prime Standard: PA8) today announces that data on the clinical results of remimazolam’s U.S. Phase III colonoscopy trial were presented in the Colon/Stomach oral session at the 2016 American College of Gastroenterology (ACG) Annual Scientific Meeting in Las Vegas. Remimazolam is an innovative, ultra-short-acting benzodiazepine anesthetic/sedative for which positive topline data from this trial were published in June 2016.

Douglas Rex, M.D., Indiana University, Indianapolis, IN, U.S., principal investigator of this Phase III trial, presented the results.

The Phase III trial enrolled a total of 461 patients at 13 U.S. sites.

*A Rogers WK, McDowell TS (December 2010). "Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day case surgical and non surgical procedures". *I*Drugs: the Investigational Drugs Journal 13 (12) 929-37. *PMID 21154153.*
Methoxycarbonyl-etomidate (MOC-etomidate), a new compound derived from the anesthetic etomidate, is as fast-acting and provides the same hemodynamic stability as its parent drug, but does not cause dangerous adrenal gland suppression as etomidate can.

In the human liver cells, the researchers found that the MOC-etomidate had an in-vitro half-life of 4.4 minutes versus more than 40 minutes for etomidate, and produced carboxylic acid as its only detectable metabolite.

MOC-etomidate is an etomidate analogue that retains etomidate's important favorable pharmacological properties. However, it is rapidly metabolized, ultra-short acting, and does not produce prolonged adrenocortical suppression following bolus administration.

Carboetomidate

- Analogue of etomidate
- When compared to MOC it has slow onset and difficult to formulate.

- ??? Benefit ???
Phaxan

Water-based clear, colorless solution that is easy to manufacture.

Like propofol, the current standard for intravenous anesthesia, Phaxan™ is a fast onset and offset intravenous anesthetic but, unlike propofol, there is no accumulation with repeat dosing.

Phaxan™ is twice as potent as propofol but it causes less blood pressure fall than propofol with a six times higher safety margin.

A clinical trial involving dose finding and comparison with propofol was commenced in December 2013.

Interesting thought... old stuff coming back??
Phaxan™: Intravenous Anaesthetic and Sedative

Phaxan™ is an intravenous general anaesthetic and sedative containing alphaxalone as the active pharmaceutical ingredient. Alphaxalone is a neurosteroid anaesthetic, it is a pregnaneolone with no endocrin hormone activity. This water-insoluble drug was initially formulated using Cremophor EL and marketed as Althesin from 1971 to 1984. It was found to be a safe and versatile intravenous anaesthetic used in clinical practice in anaesthesia and intensive care in many countries until it was withdrawn from clinical practice because of hypersensitivity to the Cremophor EL.

Many subsequent attempts to make an aqueous formulation of neurosteroids suitable for human use have failed. Drawbridge Pharmaceuticals' proprietary and patented formulation, Phaxan™, is a solution of alphaxalone 10mg/ml dissolved in 13% SBECI (7-hydroxy-7-deoxy-β-cyclodextrin) a molecule with a lipophilic cavity that enables drug dispersal in water for human use. The use of SBECI as the excipient preserves all of the advantages and utility of alphaxalone so evident when it was formulated as Althesin® but now avoiding all of the problems caused by the Cremophor EL. The properties of the new anaesthetic preparation:
Life Long Learning = Better Patient Care!

Dexamethasone

- Steroids are useful as adjuvant therapy for pain
- Steroids can directly reduce pain in concert with opioid use and allow for a reduction in dose
- Steroids reduce pain by inhibiting prostaglandin synthesis
- Steroids have been shown to reduce spontaneous discharge in an injured nerve, which reduces neuropathic pain.

**What if we could add it to our Blocks? Increase our Duration!**
Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials

- Doses of 0.1 mg/kg or less are great for PONV but don’t help with pain relief.

- **Doses of about 0.15 mg/kg cover PONV and reduce postoperative pain and opioid demand. 100kg patient should be getting 15 mg**

- Doses above 0.2 mg/kg don’t get you any more pain relief. An exception may be greater pain relief with movement (e.g. early ambulation in total joint patients?).

- Giving dexamethasone *preoperatively* improves pain relief considerably more than giving it after induction. (Optimally 1-2 hours before incision.)

- In general, we need not worry about side effects with 0.15 mg/kg any more than we do with current PONV doses.
Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine

K. C. Cummings III1,2*, D. E. Napierkowski6, I. Parra-Sanchez2, A. Kurz2, J. E. Dalton2,3, J. J. Brems5 and D. I. Sessler2

1 Department of Regional Practice Anesthesiology, Cleveland Clinic, Lakewood Hospital Department of Anesthesiology, 14519 Detroit Avenue, Lakewood, OH 44107, USA
2 Department of Outcomes Research and 3 Department of Quantitative Health Sciences, Cleveland Clinic, 9500 Euclid Avenue—P77, Cleveland, OH 44195, USA
6 Department of Regional Practice Anesthesiology and 5 Department of Orthopaedic Surgery, Cleveland Clinic, Euclid Hospital, 18901 Lake Shore Blvd, Euclid, OH 44119, USA
* Corresponding author: 9500 Euclid Ave, Mailcode E30, Cleveland, OH 44195, USA. E-mail: cummink2@ccf.org

Background. Pain after shoulder surgery is often treated with interscalene nerve blocks. Single-injection blocks are effective, but time-limited. Adjuncts such as dexamethasone may help. We thus tested the hypothesis that adding dexamethasone significantly prolongs the duration of ropivacaine and bupivacaine analgesia and that the magnitude...
Dexamethasone with bupivacaine increases duration of analgesia in ultrasound-guided interscalene brachial plexus blockade

Peter A. Woira, Istvan Pusztai, George C. Tsao, Poomachandran Manikantan, Brunello Keller and Neil Roy Connolly

Background and objectives. Dexamethasone has been shown to prolong the duration of postoperative analgesia when given as an adjunct for peripheral nerve blocks. However, it has not been evaluated when given in conjunction with bupivacaine and clonidine to provide analgesia of the brachial plexus at the interscalene level. The purpose of this investigation was to determine whether the addition of dexamethasone to ultrasound-guided interscalene brachial plexus block would prolong the duration of sensory analgesia in a group of patients undergoing outpatient shoulder arthroscopy.

Methods. This prospective, randomized, double-blind investigation was performed on 80 individuals undergoing shoulder arthroscopy. Patients received interscalene brachial plexus block using 30 ml of bupivacaine 0.5% with 1:100,000 epinephrine and clonidine 75 mcg. Patients were randomly assigned to receive either dexamethasone (8 mg or 0.9% NaCl as an placebo) to the mixture. After injection, patients recorded pain scores and analgesic consumption in a diary and commented the time at which they perceived that the sensory block from the interscalene brachial plexus block resolved. This was based on pain recovery of sensation and strength in the arm. Variables measured included demographic, preoperative and postoperative pain scores, and duration of analgesia. Results. Dexamethasone prolonged median sensory (114 vs. 885 min, P < 0.0001) and motor (1874 vs. 827 min, P < 0.0001) block compared with the control. At 24 h, the dexamethasone group had lower median verbal analogue scale scores compared with control (8.0 vs. 6.0, P < 0.01). The two groups had similar median pain scores (10 vs. 8.0, dexamethasone vs. control, respectively). The opioid requirement in postoperative analgesia was lower in the dexamethasone group than in the control group for the first 24 h, and similar thereafter. Median patient satisfaction scores were not significantly different between the two groups at 48 h (5.0 vs. 5.0, dexamethasone vs. control, respectively).

Conclusion. This addition of dexamethasone to a bupivacaine-clonidine—clonidine ultrasound-brachial plexus block prolongs sensory block and reduces opioid use.

For J Anesthesiol 20102:236–268

Keywords: interscalene, analgesia, duration of analgesia, clonidine, randomized, placebo-controlled.

Received 1 June 2008 Revised 1 September 2009 Accepted 1 November 2009

Introduction
Regional anesthesia has gained much popularity in current anesthetic practice. Improving duration of local

Addition of epinephrine prolongs duration of subcutaneous infiltration of local anesthetics.
The Effect of Single Low-Dose Dexamethasone on Blood Glucose Concentrations in the Perioperative Period: A Randomized, Placebo-Controlled Investigation In Gynecologic Surgical Patients

Murphy, Glenn S. MD†, Szolcsányi, Joseph W. MD†, Avram, Michael J. PhD†, Greenberg, Steven B. MD†,
Shoar, Torin MD†; Vender, Jeffrey S. MD†, Gray, Jayla BA†; Landry, Elizabeth BA†

Anesthesiology & Analgesia
June 2014 Volume 118 Issue 6 p 1204-1212
doi: 10.1213/ANZ.0b013e3182a39d41
Ambulatory Anesthesiology: Research Report

It is OK.....
Emend (Aprepitant) PDNV

- A new class of antiemetics is born -- NK-1 receptor antagonists
- Does not interfere with other antiemetics
- No dosage adjustments for hepatic or renal compromise
- Does not effect QT segments
- Use in caution with CYP3A4 (warfarin) drugs; this is typically related to a three day course in chemo-related treatments
- Decreases efficacy of hormonal contraceptives
- Anesthesia is a single dose; 40-80mgs

- Expensive single 80mg dose is $125
Emend (Aprepitant)

- This is a additional adjunct treatment to those refractory to PONV

- Most side effects are related to prolonged and high doses with little evidence that any effects are related to a single anesthesia dose

- Top adverse experiences in patients with general anesthesia were;
  - Anemia, bradycardia, flatulence, hypotension, pruritus, pyrexia

- Expensive ; Expensive; Expensive; Expensive

- Two additional NK-1 Drugs: Casopitant, Rolapitant
Rolapitant

VARUBI is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting.

The recommended dosage is 180 mg Rolapitant administered approximately 1 to 2 hours prior to the start of chemotherapy.

Administer in combination with dexamethasone and a 5-HT3 receptor antagonist,
Akynzeo
Akynzeo, a combination product of netupitant and palonosetron

Each capsule contains 300 mg of netupitant, and palonosetron hydrochloride equivalent.
Hypoxia triggers cortical afferents which triggers the vomiting center which leads to the act of vomiting.
Supplemental perioperative oxygen improves postop outcomes

$\text{FO}_2$ of 0.8 doubles subcut $\text{O}_2$ tension & halves postop wound infection rate

Supplemental $\text{O}_2 \downarrow$ PONV after laparoscopies & laparotomies

_Curr Opin Anesthesiol_ 2006;19:11-18
Salivex
Ajulemic acid
Nabilone
Marinol
Cannadur
Cannabis

As of 2013; 23 controlled studies looking at Cannabinoids for pain management
MARINOL should not be used if you are

- allergic to dronabinol or any of its ingredients,
  - including marijuana and sesame oil

- Most patients respond to 5 mg three or four times daily.

- Marinol has been shown to provide increased pain relief when taken in combination with opioid pain relievers, according to ClinicalTrials.gov. The active ingredient in Marinol, THC, is believed to bind with pain receptors to reduce the transmission of pain through the spinal cord and brain.
Life Long Learning = Better Patient Care!

**Purpose**

This study will compare two different drug regimens on all hospitalized nursing home residents, for the prevention of post-operative nausea and vomiting (PONV).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and Vomiting</td>
<td>UTRG UNIVERSITY</td>
</tr>
</tbody>
</table>

**Study Type**: Interventions

**Study Design**: Allocation: Randomized

End-point: Classification: Efficacy Study

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Primary Purpose</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT29F87E22</td>
<td>UTRG UNIVERSITY</td>
<td>UTRG UNIVERSITY</td>
</tr>
</tbody>
</table>

**Control**: Prevention of postoperative nausea and vomiting in surgical patients

Resources have been provided by NHLBI.

MedCalc Plus related topics: Nausea and Vomiting

---

**Prevention of nausea and vomiting following breast surgery**

**Authors**: [Provide author names and affiliations]

**Abstract**

**Background**: The purpose of this study was to determine the rate of nausea and vomiting in women following breast surgery (PONV) under general anaesthesia (GA), before and after the introduction of a standard atracurium-propanolol (AC) regime.

**Methods**: We performed a retrospective review of patients undergoing breast surgery at our institution from January 2008 to February 2010. Patients were randomized to receive either AC or lignocaine (LA) premedication. Data was collected from medical records regarding demographics, 194 anaesthetic variables, and postoperative nausea and vomiting (PONV). Data was stratified by sex and age, and the incidence of nausea and vomiting and postoperative nausea and vomiting (PONV) was calculated for both groups.

**Results**: The incidence of PONV was 45% in the AC group and 55% in the LA group. The majority of nausea and vomiting occurred within the first 24 hours after surgery. The incidence of nausea and vomiting was significantly lower in the AC group (P < 0.05).

**Conclusion**: Postoperative nausea and vomiting following breast surgery is a significant problem, and the use of AC significantly reduces the incidence of PONV.
Role of Cannabinoids in Pain Management

Ethan B. Russo and Andrea G. Hohmann

Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I-III clinical trials.

and their role in inflammation. The opium poppy (Papaver somniferum) provided the prototypical narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (Cannabis sativa) prompted the isolation of Δ9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body’s own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endogenous system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (Capsicum annuum etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

The Endocannabinoid System
Olanzapine as an antiemetic: is an atypical antipsychotic that belongs to the thienobenzodiazepine class.

Olanzapine cost:

Rapidly disintegrating tab 5mg: ~ $1.00
Rapidly disintegrating tab 10mg: ~ $1.15
Tab 5mg: $0.10
Tab 10mg: $0.20
IM injection: $25.25

We only have a very small amount of information about the use of olanzapine IV, and none of it in the periop period...............

Most Studies looked at it as compared to Zofran...............
A new 5HT-3 receptor antagonist

Aloxi binds with both the serotonin site but also a allosteric binding site; this action increases the overall affinity for aloxi by triggering a conformational change. This change also causes a receptor internalization and induces a prolonged inhibition of serotonin binding to the cell surface receptors.

What is cool about it??  40 hour plasma half-life
Small single dose --- 0.075 mg single dose

Easy to remember dose timing -- before induction of anesthesia in preop over 10 seconds

NO information for Peds or OB
these pediatric patients was comparable to the prevention of vomiting in patients 4 years of age and older.

**Postoperative Nausea and Vomiting:** **Prevention of Postoperative Nausea and Vomiting:**

**Adult Studies:** Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/cisatracurium and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving 554 patients. ZOFTRAN Injection (4 mg) IV, given over 2 to 5 minutes was significantly more effective than placebo. The results of these studies are summarized in Table 8.

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Ondansetron 4 mg IV</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emetic episodes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>136</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Treatment response over 24-h postoperative period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Emetic episodes</td>
<td>103 (76%)</td>
<td>64 (46%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 Emetic episode</td>
<td>13 (10%)</td>
<td>17 (12%)</td>
<td></td>
</tr>
<tr>
<td>More than 1 emetic episode/rescued</td>
<td>20 (15%)</td>
<td>58 (42%)</td>
<td></td>
</tr>
<tr>
<td>Nausea assessments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>134</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>No nausea over 24-h postoperative period</td>
<td>56 (42%)</td>
<td>39 (29%)</td>
<td></td>
</tr>
</tbody>
</table>
Anesthesia and Analgesia 2016; 122:656

Meta-Analysis of studies from 1974-2014

Drastically reduced PONV, especially with preop and small dose 30 minutes before extubation.
Clinical Research Article

The antiemetic effect of midazolam or/and ondansetron added to intravenous patient controlled analgesia in patients of pelviscopic surgery

Dae Seong Kim, Gil Ho Ki, Hyun Kang, Chong Wha Baek, Young Hun Jung, Young Cheol Woo, Jin Yum Kim, and Sun Dyon Park

Department of Anesthesiology and Pain Medicine, College of Medicine, Chung-Ang University, Seoul, Korea

Background: We made a comparative study on the antiemetic effect of midazolam and ondansetron added to intravenous patient-controlled analgesia (PCA) using fentanyl with gynecologic patients undergoing pelviscopic surgery.

Methods: The PCA using 20 μg/kg of fentanyl was started in all groups postoperatively. A dose of 16 mg of ondansetron was added to the PCA of group O (n = 30). A dose of 5 mg of midazolam was added to the PCA of group M (n = 30). While 16 mg of ondansetron and 5 mg of midazolam were added to the PCA of group MO (n = 30). Total volume of the PCA was 60 ml, and the PCA system was programmed to deliver 0.5 ml/h of continuous doses and a 0.5 ml bolus on demand, with a 15 minutes lockout interval. The incidence of postoperative nausea and vomiting (PONV), sedation score, visual analog scale (VAS) for pain, and rescue drug dose for PONV were investigated at the postanesthesia care unit (PACU), 6 hours, and 24 hours after recovery.

Results: The incidence of PONV in group MO was significantly lower than in group O at PACU, 24 hours after recovery (P < 0.05). The sedation score and VAS pain score showed no differences among all groups.
The last 30 minutes Versed

Non-Pharmacologic Methods for PONV

- Acupuncture—really exciting information!

- Acupressure
  - over “P6” point of wrist (3cm prox. to distal wrist crease, between the tendons of palmaris longus and flexor carpi radialis)
  - over K-K9 acupuncture point (middle phalanx of 4th finger) applied bilaterally

- Alcohol Pad—Quese Ease!

---

September 2013; Anesthesia and Analgesia: Aromatherapy as Treatment for Postoperative Nausea: A Randomized Trial
Hunt, Ronald MD*; Dienemann, Jacqueline PhD, RN†; Norton, H. James PhD‡; Hartley, Wendy MSN, RN§; Hudgens, Amanda BSN, RN‖; Stern, Thomas MD¶; Divine, George PhD#
The BEST treatment of choice for beta-blocker overdose is?

A. Glucagon  
B. Methylene Blue  
C. Esmolol  
D. Vasopressin
Life Long Learning = Better Patient Care!

Glucagon

- Glucagon enhances the formation of cAMP.

- Glucagon is used to increase myocardial contractility and heart rate in the setting of beta-blocker toxicity.

- Glucagon stimulates catecholamine release and has been used as a diagnostic tool in pheochromocytoma.

- Dose:
  - 1-5 mg IV slowly
  - Infusion: 25–75 mcg/min

Dosing source: *A Practical Approach to Cardiac Anesthesia* by Frederick A. Hensley, Glenn P. Gravlee, Donald E. Martin

Glucagon must be reconstituted immediately prior to administration.
Hypotensive Thought Pattern

- What is your order for treating Hypotension????

  - 0 fluids
  - 1 and 2; Neo and ephedrine
  - 3 methylene blue
  - 4 epi chip shots (5-10mcg)—Guy Weinberg, Paper
  - 5 vasopressin

- What is 6 for you?

  - ?? Glucagon
Hemodynamic Effects of Methylene Blue

Methylene blue, a commonly used tissue marker, is normally hemodynamically inert.

However, for a variety of clinical scenarios associated with an inflammatory response, methylene blue results in increases of systemic blood pressure, systemic vascular resistance (SVR), and myocardial contractility.

The application of methylene blue’s effects is also being studied in the management of numerous clinical scenarios, including:

- vasoplegia
- anaphylactic shock
- septic shock
- hypotension from ACE-Is/ARBs
- hemodialysis hypotension
- cardiogenic shock
Dosing of Vasopressin

**Intraoperative hypotension**
- Dilute with 19 mL NS in a 20 cc syringe to create a concentration of 1 unit/mL.
- Administer 0.5 – 1 unit to treat hypotension in an adult.

**Septic Shock**
- Exogenous vasopressin has been used in patients with septic shock in several studies. AVP infusion (0.01–0.04 U/min) increased peripheral vascular resistance and arterial blood pressure within minutes of application. No increase in pulmonary vascular resistance or pulmonary artery pressure was reported in patients treated with low-dose vasopressin (0.04 U/min), nor were cardiac complications or changes in electrolyte, blood and urine osmolality, or metabolic variables.
Shortage


Par Sterile Products introduced Vasostrict injection in November 2014. This is the only FDA-approved vasopressin injection.

Fresenius Kabi will discontinue distributing vasopressin on March 15, 2015. A letter is available regarding this discontinuation.

Available Products Vasostrict Injection, Par Sterile Products 20 units/mL, 1 mL multi-dose vial, 25 count (NDC 42023-0164-25)

New Pain Drugs

- Ofirmev
- Caldolor
- Sufentanil Patch
- Nucynta
- Remoxy
- Mexiletine

- Antidote: Entereg
  - (almivopam)
CDC Statement – Worst EVER?

A 'civil war' over pain medication separates the medical community

"There's a civil war in the pain community," said Dr. Daniel B. Carr, president of the American Academy of Pain Medicine. "One group believes the primary goal of pain treatment is curtailting opioid prescribing. The other group looks at the disability, the human suffering, the expense of chronic pain."

The Issues With the CDC Guidelines on Opioids for Chronic Pain, According to AAPM's Director

Dr Twillman extensively emphasized the fact that these CDC guidelines are expert-based and not evidence-based. In addition, most of these experts are strongly biased, as indicated by their affiliations to, for example, anti-opioid advocacy groups.
**Multimodal Approach to Acute Pain Management**

1. **Mild Pain**
   - Acetaminophen, NSAIDs, or COXIBs
   - Local/regional anesthesia

2. **Moderate Pain**
   - Low doses of opioids
   - Acetaminophen, NSAIDs, or COXIBs
   - Local/regional anesthesia

3. **Severe Pain**
   - Higher doses of opioids
   - Acetaminophen, NSAIDs, or COXIBs
   - Local/regional anesthesia

---

Modified from Crews et al., 2002

Life Long Learning = Better Patient Care!

We Must Start to Think Differently!

Multi-Modal Synergy Pre-emptive
Life Long Learning = Better Patient Care!

Receptors

Mu (µ) Receptor Activation

Proposed Mechanism: COX-1, COX-2 & COX-3

How Caffeine Works
OFIRMEV $10.00/1000mg

- IV acetaminophen injection: Cadence Pharm
  - (Cadence was bought out) (price spike)

- Minimum dosing interval is every 4 hours

- Administer over 15 min…..well….?????
  - www.ofirmev.com

- Do not exceed max daily doses.. Adult is 4 grams per day
- Pediatric is dosed at 15mg/kg with max of 75 mg/kg/day

CHEAPPPPPPPP----Not any more… ???

- Regional Anesthesia Pain Management 2015 discusses that the purchase by Mallickrodt increased the price by 285%, costing the healthcare system nearly $2.78 Million in inflation costs.
Figure 1 - Acetaminophen metabolism

Conjugation

- Glucuronide (nontoxic)
- Acetaminophen
- Sulfate (nontoxic)

Conjugation

- P-450 2E1

NAPQI (toxic)

- NAC

Glutathione

Cysteine and mercapturic acid conjugates (nontoxic)
Life Long Learning = Better Patient Care!
OFIRMEV

• Liver issues is big

• Contraindicated in patients with liver failure/hepatic injury or with known hypersensitivity to acetaminophen…

• What about ETOH?

• Common side effects are: N/V; HA: insomnia; constipation, pruritus and agitation and atelectasis

• Using this drug may mask post surgical fever when used for post-operative pain.
COX-3: the Acetaminophen Target Finally Revealed

It has been known for years that non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and acetaminophen, provide relief from fever, pain, and inflammation through their actions on cyclooxygenase (COX) enzymes. Four COX isoforms, COX-1 and -2, were first identified in the early 1990's as the catalysts for an important step in prostaglandin biosynthesis. Although both enzymes have similar functions, their temporal and spatial expression patterns are very different. COX-1 is constitutively expressed in many somatic cell types and is considered a "housekeeping" enzyme with roles in such processes as vascular homeostasis and gastrointestinal protection. In contrast, COX-2 expression is primarily induced by factors such as endotoxins, cytokines, and growth factors. COX-2 is expressed at sites of inflammation and produces prostaglandins that mediate inflammatory and pain sensation responses. COX-2 involvement in inflammation, pain, and a variety of diseases has inspired researchers to investigate the actions of NSAIDs on these enzymes. Although many advances have been made over the last 10 years in understanding the pain relief and anti-inflammatory mechanisms of aspirin, ibuprofen, and the new COX-2 inhibitors, the mechanism of acetaminophen action has remained elusive.

Finally, identification of a new isozyme, COX-3, suggests that it is the target for acetaminophen. COX-3 was discovered by Northern analysis of canine cerebral cortex RNA using a COX-1 cDNA probe. The COX-1 probe unexpectedly illuminated a band at 2.0 kb, labeling a transcript later confirmed to be COX-3, an alternate splice variant of COX-1 in which intron 1 is retained (Figure 1). Interestingly, intron 1 is not only present in canine, human, and murine versions of COX-3, but it is conserved in length and sequence in those species as well. While COX-3 retains all of the important catalytic and structural features of COX-1 and -2, it is likely that intron 1 is responsible for the deviant enzymatic properties of COX-3 perhaps via subtle alterations in structure, glycosylation state, and/or expression.

Thus far, little is known about the temporal regulation of COX-3 expression. However, it has been known for decades that acetaminophen inhibits COX activity in canine brain.
Ibuprofen-Caldolor $10

- Think about Ketorolac. Actions and side effects
- Big differences… Less action on Cox 1 and more Cox 2 action..
- What does this mean? Less bleeding. More pain control can give anytime during the surgery… better now that we can give per-op

- 400mg/4ml or 800mg/8ml
- Dilute and administer over 30 minutes
- 400mg-800mg Over 30 min repeat every 6 hours PRN*
- Fluids “well hydrated prior to use”
Meloxicam IV/IM is a proprietary, Phase III-ready, long-acting COX-2 NSAID used to target moderate to severe acute pain. Meloxicam IV/IM is a nonsteroidal anti-inflammatory drug... In five phase II studies treating more than 700 patients with acute pain, meloxicam IV/IM demonstrated positive effect on treating rapid onset of pain relief and” time to peak” analgesic effect, 18 to 24 hour duration of pain relief as well as favorable tolerability.
Sufentanil $3.52/50mcg

- 5 - 10X more potent than fentanyl
- Sufentanil 0.0035 mg = fentanyl 0.05 mg
- Safe therapeutic index: 25,211
- Dose: .025 - 30 µg/kg
- Analgesic dose: 0.1 - 0.4 µg/kg IV
- Maintenance dose: 1µg/kg followed by 0.25-0.5 µg/kg/hr

- High dose: 10 - 30 µg/kg

- New PATCH coming out from Durrect Pharm....
Sufentanil tablets dispensed sublingually with a handheld PCA device (15mcg) or via single-dose applicator (30mcg) from a healthcare professional are in late-stage development for treatment moderate to severe acute pain.

When administered sublingually, sufentanil’s fast onset of analgesia, noninvasive route of delivery and favorable patient satisfaction ratings make it a potential alternative to IM or IV dosing.

The type and frequency of adverse events observed in the studies were typical of opioids in a post-operative setting with reports of nausea, vomiting and somnolence more common in the active drug cohorts.

DSUVIA-Sublingual Sufentanil

DSUVIA

Treatment for Pain

AcelRx Pharmaceuticals Provides Guidance on 2017 Milestones for ARX-04, now known as DSUVIA in the United States, for the Treatment of Moderate-to-Severe Acute Pain

About AcelRx Pharmaceuticals, Inc.

AcelRx Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of moderate to severe acute pain. An NDA for DSUVIA (sufentanil sublingual tablet, 30 mcg), known as ARX-04 outside the United States, with a proposed indication for the treatment of moderate-to-severe acute pain in medically supervised settings, was recently submitted to the FDA for review.
Fentanyl Patch

- Transdermal Patch

- Technology changing for delivery

- On Demand? : Fentanyl iontophoretic transdermal system provides a 40 mcg dose of fentanyl per activation on-demand

- Other fentanyl thoughts:
  - BUCCAL TABLET; BUCCAL SOLUBLE FILM; SUBLINGUAL NASAL SPRAY; SUBLINGUAL SPRAY
Insys Therapeutics, Inc.

Subsys® (fentanyl sublingual spray) 100, 200, 400, 600, 800, 1200, 1600 mcg


Life Long Learning = Better Patient Care!

[Effect of dexmedetomidine alone for postoperative analgesia after laparoscopic cholecystectomy].
[Article in Chinese; Abstract available in Chinese from the publisher]
Chen XH, Wang ZJ, Xiang QM, Zheng JW.
Recro Pharm Dex-IN

Recro’s Dex-IN, an intranasal form of dexmedetomidine, which has been tested as an analgesic drug for post-operative pain. Last year the company’s lead drug passed a Phase Ib trial that demonstrated its proof of concept in providing effective pain relief. However, in September Recro Pharma halted a trial of its lead product candidate Dex-IN.

The company decided to stop the trial because it does not believe the study would achieve “statistical significance” in its current design. Recro Pharma has an upcoming interim analysis of ongoing Post Op Day 1 Phase II trial for Dex-IN, and depending on clinical success, the possibility for two proprietary compounds to enter Phase III by year end.
Gabapentin is typically well tolerated in the correct doses:

- Doses range 300-1200 mg single dose for anesthesia: max dose is 1200 mg TID or max of 3600 mg/day

- Higher the dose (smaller the patient) more side effects (keep in mind excretion i.e., renal failure)

- Typically:
  - Somnolence
  - Dizziness
  - Fatigue
  - Impaired concentration

- Typically single small doses (300-600) little problems
- Keep in mind Half life of 5-7 hrs
Use of preoperative gabapentin significantly reduces postoperative opioid consumption: a meta-analysis.

Abstract

OBJECTIVE: Effective preoperative pain management is crucial in the care of surgical patients. Opioids, which are commonly used in managing postoperative pain, have a potential for tolerance and addiction, along with sedating side effects. Gabapentin's use as a multimodal analgesic regimen to treat neuropathic pain has been documented as having favorable side effects. This meta-analysis examined the use of preoperative gabapentin and its impact on postoperative opioid consumption.

MATERIALS AND METHODS: A comprehensive literature search was conducted to identify randomized controlled trials that evaluated preoperative gabapentin on postoperative opioid consumption. The subsequent meta-analysis cumulated opioid consumption following the surgery and monitored vomiting, somnolence, and nausea.

RESULTS: A total of 1,753 patients involved in 17 randomized controlled trials formed the final analysis in this study. Postoperative opioid consumption was reduced when using gabapentin within the initial 24 hours following surgery (standard mean difference, 1.26; 95% confidence interval, 0.95 to 1.57; P < 0.001). There was a significant reduction in vomiting, somnolence, and tracheal consumption (P < 0.05). While a significant increase in postoperative somnolence incidence was observed (relative risk, 1.30; 95% confidence interval, 1.10 to 1.54; P < 0.05), there was no significant effect on postoperative vomiting and nausea.

CONCLUSION: The administration of preoperative gabapentin reduced the consumption of opioids during the initial 24 hours following surgery. The reduction in postoperative opioids with preoperative gabapentin increased postoperative somnolence, but no significant differences were observed in nausea and vomiting incidence. The results from this study demonstrate the gabapentin's efficacy in neuropathic pain, ataxia, and diabetic pain. Gabapentin is an effective analgesic agent, and clinicians should consider its use in multimodal treatment plan among patients undergoing elective surgery.
Gabapentin not just for pain!
Microcron Technology
Drugs---IROKO Pharm

ZORVOLEX is the first low dose FDA-approved NSAID developed using proprietary SoluMatrix Fine Particle Technology™.

ZORVOLEX contains diclofenac as submicron particles that are approximately 20 times smaller than their original size. The reduction in particle size provides an increased surface area, leading to faster dissolution.

ZORVOLEX was developed to align with recommendations from FDA and other professional medical organizations that NSAIDs be used at the lowest effective dose for the shortest possible duration consistent with individual patient treatment goals. For more information, visit www.zorvolex.com.
Hospira, Inc. (NYSE: HSP), the world's leading provider of injectable drugs and infusion technologies, and a global leader in biosimilars, has received approval from the U.S. Food and Drug Administration (FDA) for Dyloject™ (diclofenac sodium) Injection, a proprietary nonsteroidal anti-inflammatory drug (NSAID) analgesic. Dyloject is indicated for use in adults for the management of mild to moderate pain and for the management of moderate to severe pain alone or in combination with opioid analgesics.

“While not a replacement for opioids, Dyloject is [an] injectable therapy option that can be administered more conveniently in a small-volume, intravenous bolus over 15 seconds as opposed to other injectable non-opioid analgesics that are formulated in large volumes or require dilution prior to administration and typically require an infusion of 15 to 30 minutes to administer the full dose,”
Tramadol (1-3 mg/kg) Single Pre-Operative Dose
Tramadol Infusion for Postthoracotomy Pain Relief: A Placebo-Controlled Comparison with Epidural Morphine


Epidural tramadol via intraoperatively placed catheter as a standalone analgesic after spinal fusion procedure: An analysis of efficacy and cost.


Combined Ketamine-Tramadol Subcutaneous Wound Infiltration for Multimodal Postoperative Analgesia: A Double-Blinded, Randomized Controlled Trial after Renal Surgery.

Khajavi MR¹, Navardi M¹, Shariat Moharari R¹, Pourfakhr P¹, Khalili N², Etezadi E¹, Imani F¹.
Capsaicin (Zostrix)

- Is a new Receptor Born? **TRPV 1**
- Selectively stimulates unmyleninated C fibers afferent neurons and cause release of substance P
- This continued release leads to depletion of substance P and decrease in pain
- Patch and PO
- PO is chili-peppers or Herbal 40,000 H.U.
- PO is also in pure form under trials
- Could be a benefit? Heart burn? Burning sensation?
Clonidine produces a dose-dependent impairment of baroreflex-mediated thermoregulatory responses to positive end-expiratory pressure in anaesthetized humans

Clonidine was clinically evaluated to suppress postoperative shivering in 60 patients who had undergone anesthesia for general, thoracic and vascular surgery. The study was carried out in double blind conditions with comparison of two doses (75 and 150 micrograms) of clonidine.

D3forME (Vitamin D3)
Catapres (clonidine)
Transderm (scopolamine)
Nicoderm (nicotine)

**Exelon (rivastigmine)  possible muscle relaxant interaction  ###**

Lidoderm (lidocaine)
Duragesis (fentanyl)
Fortesta, Axiron (testosterone)
Nitrodur (nitroglycerin)

Combipatch (estradiol, norethindrone) ? procoagulant
Alora, Menostar, Vivelle-dot, Estraderm (estradiol) ? procoagulant

Butrans (Buprenorphine) antagonizes opioids (mixed agonist/antagonist). Remove 4 days before surgery if need for significant doses of opioids postop

Emsam (selegiline = MAOI drug!) for severe depression or Parkinson’s, may need to continue as long as providers
A Drug used for the treatment of Alzheimer's and is a cholinesterase inhibitor. Complete action is unknown!

Rivastigmine, an acetyl cholinesterase inhibitor, may be administered orally or as a transdermal patch for treatment of Alzheimer's disease and may interfere with neuromuscular blocking drugs.


Recent article:

**Nano anesthesia: A Novel, Intravenous Approach to Ankle Block in the Rat by Magnet-Directed Concentration of Ropivacaine-Associated Nanoparticles**

*Anesthesia and Analgesia: April 2014*
Exparel

• EXPAREL is a local analgesic that utilizes bupivacaine in combination with the proven product delivery platform, DepoFoam®. A single intraoperative injection given at the close of surgery delivers postsurgical pain control with reduced opioid requirements for up to 72 hours.

• Following its release from the DepoFoam® particles, the rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

A pivotal soft tissue trial of EXPAREL versus placebo, patients experienced a 30% reduction in cumulative pain scores and a 45% reduction in opioid consumption.
DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20203

PUBLIC HEALTH SERVICE

TRANSMITTED BY FACSIMILE

Dave Stack
President and CEO
Pacora Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany NJ 07054

RE: NDA # 022496
EXPAREL® (bupivacaine liposome injectable suspension)
MAW 68

WARNING LETTER

Dear Mr. Stack:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed educational technique flashcards (EXP-AP-0124-201209 & EXP-AP-0134-201210) (administration guides) and a journal ad (EXP-AP-0039-201302) for EXPAREL® (bupivacaine liposome injectable suspension) (Exparel) submitted by Pacora Pharmaceuticals, Inc. (Pacora) under cover of Form FDA-2253. The journal ad was also submitted as a complaint to the OPDP Bad Ad Program. The administration guides provide evidence that Exparel is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for use, which renders Exparel misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. See 21 U.S.C. 355(a), 352(f), 331(a), (c), 21 CFR 201.3(m), 201.100; 201.115; 201.128. In addition, the journal ad is false or misleading because it includes the following false statement of fact: The third administration guide is attached.
Potential for Wrong Route Errors with Exparel

There is a dangerous potential for errors in the administration of two “look-alike” medications that are or will be common in anesthesia practice in this country: propofol and the new bupivacaine liposomal suspension Exparel, not meant for IV administration. Both are milky white suspensions, and because propofol has been the only such medication for many years, a real potential for error exists.

Exparel is a local anesthetic that is injected into a surgical wound during a surgical procedure to produce postsurgical analgesia. It is not intended for systemic use. When prepared in syringes, these products essentially look identical. If Exparel is accidentally administered intravenously instead of propofol, toxic liposomal concentrations might result, and cardiac conductivity and susceptibility may be depressed, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest.

Propofol is used as an anesthetic during surgical procedures and as a sedative during procedures or for patients undergoing mechanical ventilation. Thus, Exparel and propofol may be used in similar healthcare settings.
Life Long Learning = Better Patient Care!

Exparel
Posidur

- New product just like Exparel

- Except Clear…. Could this be trouble?
• 20% lipid solution

• 1.5 ml/kg over 1 minute

• Follow immediately by a infusion at rate of 0.25ml/kg/min (17.5 ml/min for a 70 kg adult)

• Repeat dose if no improvement – and double the infusion rate

• Max of 10 ml/kg???

• www.lipidrescue.org

• ACLS-----limit epi----Weinberg work!

• What about Propofol? (Propofol is 1%)
Other Things to Remember!

• Ask the question.... What about other treatments?

• What did Larry Say?
Life Long Learning = Better Patient Care!

The Saving Grace!

- Wellbutrin 7.95 gms, Lamotrigine 4 grams
- Wellbutrin 100mg/TID
- Lamotrigine 300mg/QD
Many classes of compounds bind and inhibit Na channels

- Local anesthetics
- General anesthetics
- Ca channel blockers
- $\alpha_2$ agonists
- Tricyclic antidepressants
- Substance P antagonists
- Many nerve toxins
  - Benadryl
  - Droperidol


Pre-operative Alvimopan (Entereg)

- μ-Opioid antagonist that is restricted from crossing the blood-brain barrier
- Blocks peripheral gastrointestinal side effects (e.g., ileus, constipation) without compromising CNS activity
- Oral dosing
  - Low systemic absorption
  - High μ-receptor affinity
  - Appropriate for patients with chronic pain
Mivacurium is coming back...
Gantacurium
Phase 2 complete

- Is this a new Generation being born of NMB?
- Based on amino acid pathway—**olefinic**

- This drug is chemically degraded by rapid adduction to L-cysteine and removes Chlorine
- These two routes make it unavailable to bind to acetylcholine receptor
- Does not require Liver, Kidneys, Temperature or pH
- Two exciting analogs...

- There has always been a search for the new Suxx.....
Gantacurium

- Dose: 0.5 mg/kg
- Fast acting with short duration
- Exciting new group of drugs!
- Key is: NO histamine release!
CW002

- Same pathway as Gantacurium!
- This compound Lacks Chlorine
- Dose: 0.15mg/kg
- Fast acting Intermediate duration
- Key is: NO histamine release!
CW 011

- This is the baby of this group...
- Lacks Chloride so slower to break down

- Dose: 0.10 mg/kg
- Fast acting more intermediate duration

- Key is: NO histamine release!
L-Cysteine

Dissolved in concentration of 200mg/ml

• Antidote for New class of Muscle relaxants
  • Olefinic isoquinolone Diester NMB
  • Only works with new group of NMB’s
Cysteine

Human Studies: IV administration of exogenous L-Cysteine induced faster recovery.

Dose in Studies: 5-50mg/kg
• (average dose is 10mg/kg)

Compared to Edrophonium reversal with atropine.
Did not need to give antimuscarinics agent.
Reversed in 1 minute

There are risks…High doses: (added to TPN) but 1-1.5 grams/kg can cause neuro defects reported in infants
FDA News Release

FDA approves Bridion to reverse effects of neuromuscular blocking drugs used during surgery

First drug approved in new class of medications:

For Immediate Release

December 15, 2015

The U.S. Food and Drug Administration today approved Unison (sugammadex) injection to reverse the effects of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide, which are used during certain types of surgery in adults.

Rocuronium bromide and vecuronium bromide are neuromuscular blocking drugs that cause temporary paralysis by interfering with the transmission of nerve impulses to the muscle and are used to paralyze the vocal cords when patients require an artificial airway or breathing tube for surgery, a process called tracheal intubation. They can also be used to prevent patients from moving during surgery while they are receiving general anesthesia. Neuromuscular blocking drugs are also sometimes used to prevent the body from breathing automatically when a patient has to be placed on a ventilator.

"Unison provides a new treatment option that may help patients recover sooner from medications used for intubation or ventilation during surgery," said Sharon Hestrin MD, director of the Division of Anesthesia, Analgesics and Antibiotic Products in the
The Development and Regulatory History of Sugammadex In the United States

by Glenn Murphy, MD

The Neuromuscular Research Group at Corgent Medicines, Inc in 2012, showed that sugammadex was effective in blocking neuromuscular transmission for 6 hours after a single injection. This was a significant advancement for the treatment of neuromuscular block. Since then, it has been approved in Europe, Australia, and Japan. In the United States, however, the process has been delayed due to regulatory hurdles.

Sugammadex is a derivative of gamma-trimethylindolenine, which is the neurotransmitter released at the neuromuscular junction. It is a selective and reversible blocker of the neuromuscular junction, which is used to reverse the effects of neuromuscular blocking agents. Sugammadex is unique in that it can be administered intravenously, which allows for rapid reversal of neuromuscular blockade.

In the United States, the FDA has been cautious in approving the use of sugammadex due to concerns about its safety and efficacy. The FDA has required extensive clinical trials to prove the safety and effectiveness of sugammadex.

One of the key concerns is the potential for sugammadex to cause adverse effects, such as respiratory depression. The FDA has required that sugammadex be used only in the hospital setting, where respiratory support can be readily available.

In conclusion, the development and regulatory history of sugammadex is a testament to the challenges of bringing a new medication to market. The FDA's cautious approach is necessary to ensure the safety and effectiveness of new medications, but it can also delay the availability of these medications to patients in need.
Cyclodextrins are poly saccharide compounds that were analyzed as scavenging molecules for toxins and additives for food materials.
Beta Cyclodextrins were developed as vehicles for long acting drugs.

They have been tried as solubilizing agents for various drugs like **Propofol, bupivacaine, sufentanil**
Sugammadex--Bridion

- Forms a very tight water soluble complex with steroidal NDMR
  - i.e. ROC > VEC > PANC

- It is biologically inactive, does not bind to plasma proteins
- Does not rely on renal excretion

- _WE_ have always mis-used muscle relaxants (first reported 1979)

- IV administration results in rapid removal of free drug from the plasma. This action creates a concentration gradient favoring the movement of the NDMR molecules from the NMJ back into the plasma, where they are encapsulated by free Sugammadex molecules.
Life Long Learning = Better Patient Care!

Sugammadex

- Does not affect SUXX or benzylisoquinolininiums;
- If after using Sugammadex and paralysis needs to be achieved consider using these drugs

- SIDE EFFECTS: hypotension; coughing (was from a study when given to awake patients) vomiting, nausea, dry mouth, decreased temperature

- Is traditional Neuromuscular function monitoring needed?
Cost of Sugammadex

- 2mg/kg dose: 140mg, one 2mL vial = $84.93
- 4mg/kg dose: 280mg, one 5mL vial = $155.55
- 16mg/kg dose: 1120mg, two 5mL vials and one 2mL vial = $396.03
- Caveats
  - Uncontracted prices from distributor
  - Patient cost usually approximately 3x this cost

Dose examples: ROC 1.2mg.kg administered and three minutes later 16mg/kg of Sugammadex given, this provides faster onset/offset profile than suxx

Will this change the face of anesthesia??
Life Long Learning = Better Patient Care!

- Sugammadex
  - Recent FDA Approval
  - Soon available as 200mg/2mL and 500mg/5mL vials
- Calabadian
  - Gantacurium Paradigm

Source: Full Prescribing Information, Bridion® (Sugammadex). 2015, Merck Sharp & Dohme Corp.

Fig. 5. (A) Current Radiograph crystal structure of a rocuronium molecule and a sugammadex molecule. (B) Synopsis encapsulation of rocuronium molecule (blue) by a sugammadex molecule (green) at 1:1 ratio. (From Cameron KS, Clark JK, Cooper A, et al. Modified gammacyclodextrins and their rocuronium complexes. Org Lett 2002;4:3403–6 ©American Chemical Society; with permission.)
Sugammadex - FDA Saga

2014 Lit review identified 15 cases of hypersensitivity reactions from sugammadex.

All within 5 minutes of administration.
Most common reactions rash and anaphylaxis.

11 patients skin tested, 10 positive
Use of Sugammadex

- Binds Roc > Vec >> Panc
- Dose Depends on Depth – Single Bolus
  - If 2 TOF twitches returned, 2mg/kg
  - If 1-2 PTC and 0 TOF twitches, 4mg/kg
  - If reversal needed as soon as 3 mins after 1.2mg/kg *rocuronium* dose, 16mg/kg
- Confirm reversal
- Time = 1.5-3 minutes (mean)
Sugammadex – Adverse Reactions

- Serious but rare:
  - Anaphylaxis
  - Bradycardia

- > 10%
  - Nausea, Vomiting, Pain, Hypotension, Headache

- Signs of emergence (moving, sucking, chewing)

- Large meta-analysis with > 1500 patients = no significant difference in side effects compared with neostigmine with less residual paralysis
In response to the FDA's requests, 4 additional studies were conducted examining the impact of sugammadex on coagulation. These investigations demonstrated a small increase in PT and aPTT that occurred within minutes of administration, but resolved within an hour.

In addition, in a large study of patients undergoing hip or knee replacement surgery, no increase in bleeding or transfusion requirements was observed in patients randomized to receive sugammadex.
Sugammadex - Bleeding

- Increases PTT, PT/INR up to 25% for up to 1h in healthy volunteers

- In a study of patients with major lower extremity orthopedics surgery, PTT and PT/INR increases < 10% were noted (did NOT require transfusion)

- No difference in bleeding, anemia incidence

- Concomitant thromboprophylaxis in this study
Cardiac

In order to address concerns related to cardiac arrhythmias, an analysis of phase 2 and 3 clinical studies was conducted, as well as an analysis of post-marketing data.

These study findings indicated that QTc was not prolonged in patients given sugammadex. The studies also indicated that arrhythmias did not occur with greater frequency with sugammadex compared to neostigmine, although bradycardia can occur with both agents.
Sugammadex – Not For Use In

- Children < 18
  - Some rat studies show possible decreased bone development in childhood
- Severe renal impairment (renal excretion)
  - GFR < 30
- Elderly patients exhibit slower recovery
Sugammadex - Bleeding

- Increases PTT, PT/INR up to 25% for up to 1h in healthy volunteers

- In a study of patients with major lower extremity orthopedics surgery, PTT and PT/INR increases < 10% were noted

- No difference in bleeding, anemia incidence

- Concomitant thromboprophylaxis in this study
Sugammadex – Drug Interactions

- Toremifene (SERM) may prolong NMBD recovery
- Other drugs could displace rocuronium
- Physically incompatible with: ondansetron, ranitidine, verapamil

Source: Full Prescribing Information, Bridion® (Sugammadex). 2015, Merck Sharpe and Dohme Corp.
FDA also warned about the potential for marked bradycardia, and that some of these cases have resulted in cardiac arrest, often within minutes of giving the drug.

Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade, and physicians should give anticholinergic agents, such as atropine, if they observe clinically significant bradycardia, the agency said.

Physicians should also advise women using hormonal contraceptives that the drug may temporarily reduce contraceptive efficacy, so they should use an alternative method of birth control for a period of time after getting the drug. The most common adverse reactions with sugammadex included vomiting, hypotension, pain, headache, and nausea.
Recurarization Bottom Line

• (Except in magnesium case) No clinically significant recurarization has been reported when sugammadex is used as labeled according to manufacturer recommendations

• Recurarization can be seen if an inadequate dose is used!!
7.3 Interaction Potentially Affecting the Efficacy of Hormonal Contraceptives

*In vitro* binding studies indicate that BRIDION may bind to progestogen, thereby decreasing progestogen exposure. Therefore, the administration of a bolus dose of BRIDION is considered to be equivalent to missing dose(s) of oral contraceptives containing an estrogen or progestogen. If an oral contraceptive is taken on the same day that BRIDION is administered, the patient must use an additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days.

In case of non-oral hormonal contraceptives, the patient must use an additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days.
Always Aware

Sugammadex and Hormonal Birth Control Interaction: Identifying and Educating Affected Patients Automatically through Health Link

Sugammadex is a medication indicated for the rapid reversal of neuromuscular blockade induced by rocuronium and Vecuronium. It was recently added to the formulary and is restricted to use in the OR and ED. Sugammadex interacts with hormonal birth control, both oral and non-oral formulations, possibly resulting in temporary loss of efficacy of the birth control for up to seven days.

Beginning September 13, 2016 documentation of sugammadex administration by the provider will generate an automatic educational message for women of reproductive potential who are between the ages of 10 and 60 years old. The message informs them that they received sugammadex. It also provides information about the nature of the interaction and the need for back-up birth control for seven days. Condoms and spermicides are recommended.
Life Long Learning = Better Patient Care!

Sugammadex
Life Long Learning = Better Patient Care!

Preoperative Melatonin and Its Effects on Induction and Emergence in Children Undergoing Anesthesia and Surgery

Antidote to Factor X inhibitors

Portola Pharmaceuticals (Nasdaq:PTLA) today announced that **andexanet alfa**, a U.S. Food and Drug Administration (FDA)-designated breakthrough therapy, has been granted orphan drug designation by the FDA's Office of Orphan Products Development for reversing the anticoagulant effect of direct or indirect Factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event or who require urgent or emergent surgery. Currently, there is no approved antidote for these patients.

**Praxbind (idarucizumab)** for use in patients who are taking the anticoagulant Pradaxa (dabigatran) during emergency situations when there is a need to reverse Pradaxa’s blood-thinning effects.

Trial included 123 patients taking Pradaxa who received Praxbind due to uncontrolled bleeding or because they required emergency surgery. In this ongoing trial, based on laboratory testing, the anticoagulant effect of Pradaxa was fully reversed in 89 percent of patients within four hours of receiving Praxbind. In this patient trial, the most common side effects were low potassium (hypokalemia), confusion, constipation, fever and pneumonia.
"Another tool to distinguish us from the CRNA"
The Ultrasound Probe in the Hands of the Anesthesiologist: A Powerful New Tool for Airway Management

MICHAEL SELTZ KRISTENSEN, MD
Head of Section for Anesthesia for ENT Head, Neck, and Maxillofacial Surgery, Rigshospitalet, University Hospital of Copenhagen, Denmark

WENDY H.L. TEOH, MBBS, FANZCA
Department of Women’s Anaesthesia, KK Women’s and Children’s Hospital Singapore, Adjunct Assistant Professor, Duke University-NUS Graduate Medical School, Singapore
Others that might impact Anesthesia

- JM-1232 New hypnotic nonbenzo from Japan
- PF0-713 Variant of Propofol
- AZD-3043 Nonbarb hypnotic

**Just FDA approved:**

*Idarucizumab to reverse pradaxa*

*Factor X concentrate*
Life Long Learning = Better Patient Care!
Can I be excused?
... my brain is full!
Thank you!

Email me for the articles: pstrube3000@yahoo.com